Global Vaccine Action Plan

Monitoring, Evaluation & Accountability

Secretariat Annual Report 2016

Bill & Melinda Gates foundation · Gavi The Vaccine Alliance · unicef · World Health Organization

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Acronyms and Abbreviations

AEFI	adverse events following immunization
ANC1	first antenatal visit
AFP	acute flaccid paralysis
aP	a-cellular pertussis
AVAREF	African Vaccine Regulatory Forum
BCG	Bacille Calmette–Guérin (vaccine)
BMGF	Bill & Melinda Gates Foundation
bNAbs	broadly neutralizing antibodies
CI	confidence interval
CCI	Composite Coverage Index
CFDA	China Food and Drug Administration
CMV	cytomegalovirus
cMYP	comprehensive multi-year plan
COIA	Commission on Information and Accountability for Women's and Children's Health
CRS	congenital rubella syndrome
CSO	civil society organization
CTC	controlled temperature chain
cVDPV	circulating vaccine-derived poliovirus
DCVRN	Developing Countries Vaccine Regulators Network
DHS	Demographic and Health Survey
DoV	Decade of Vaccines
DTP	diphtheria–tetanus–pertussis (vaccine)
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
EQA	external quality assessment
EWEC	Every Woman Every Child
FDA	(US) Food and Drug Administration
Gavi	Global Alliance on Vaccines and Immunisation
GACVS	Global Advisory Committee on Vaccine Safety
GPEI	Global Polio Eradication Initiative
GNI	gross national income
GVAP	Global Vaccine Action Plan
GVIRF	Global Vaccine and Immunization Research Forum
GVSI	Global Vaccine Safety Initiative
HA	haemagglutinin
HEAT	Health Equity Assessment Toolkit
HepB	Hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	human papillomavirus
HSS	health system strengthening
IAVI	International AIDS Vaccine Initiative
IB-VPD	invasive bacterial vaccine-preventable disease
ICTRP	International Clinical Trials Registry Platform
iERG	independent Expert Review Group
IHR	International Health Regulations
IPAC	Immunization Practices Advisory Committee
IPV	inactivated polio vaccine
iTAG	independent Technical Advisory Group
IVB	Immunization, Vaccines and Biologicals Department (WHO)
JRF	(WHO-UNICEF) joint reporting form
KANCO	Kenya AIDS NGOs Consortium
LAIV	live attenuated influenza vaccine
LQA–CS	lot quality assurance – cluster sampling
M&E/A	monitoring and evaluation/accountability
M&RI	Measles and Rubella Initiative

MenAfriVac	serogroup A meningococcal conjugate vaccine
MCV	measles-containing vaccine
MDG	Millennium Development Goal
MICS	Multiple Indicator Cluster Surveys
MR	measles–rubella
MMR	measles–mumps–rubella
MNT	maternal and neonatal tetanus
MNTE	maternal and neonatal tetanus elimination
MSF	Médecins Sans Frontières
Mtb	*Mycobacterium tuberculosis*
NGO	nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NITAG	National Immunization Technical Advisory Group
NRA	national regulatory authority
NVC	National Verification Committee
OECD	Organisation for Economic Co-operation and Development
OPV	oral polio vaccine
ORS	oral rehydration salts
PATH	Program for Appropriate Technology in Health
PAB	protected at birth (against neonatal tetanus)
PAHO	Pan American Health Organization
PCV	pneumococcal conjugate vaccine
PDVAC	Product Development for Vaccines Advisory Committee
PMNCH	Partnership for Maternal, Neonatal and Child Health
PQS	performance, quality and safety
QC	quality control
R&D	research and development
RCV	rubella-containing vaccine
RV	rotavirus vaccine
RSV	respiratory syncytial virus
RVC	Regional Verification Commission
SAGE	Strategic Advisory Group of Experts (on immunization)
SDG	Sustainable Development Goal
SHA	Systems of Health Accounts
SIA	supplementary immunization activity
SO	(GVAP) Strategic Objective
TAG	Technical Advisory Group
TPP	target product profile
TT	tetanus toxoid
TTCV	tetanus toxoid-containing vaccines
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNICEF-SD	United Nations Children's Fund Supply Division
V3P	Vaccine Product, Price and Procurement (project)
VFC	(United States CDC) Vaccines for Children Fund
VPD	vaccine-preventable disease
VPPAG	Vaccine Presentation and Packaging Advisory Group
VSV	vesiculostomatitis virus
VVM	vaccine vial monitor
VVM/TI	vaccine vial monitor with threshold indicator
WAP	weighted average price
WG	working group
WHA	World Health Assembly
WHO	World Health Organization
wP	whole-cell pertussis
WPV	wild poliovirus
WUENIC	WHO-UNICEF Estimates of National Immunization Coverage

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Introduction

The Global Vaccine Action Plan and process for monitoring progress

The Global Vaccine Action Plan (GVAP) is a framework adopted by all the World Health Organization (WHO) Member States at the Sixty-fifth World Health Assembly in May 2012 to achieve the vision of the Decade of Vaccines (DoV) 2011–2020 of "a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases".[1] The GVAP's mission is to "improve health by extending by 2020 and beyond the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live".

The GVAP has articulated five goals and six strategic objectives to achieve this mission, as shown in Table 1. The Sixty-fifth World Health Assembly requested the WHO Director-General to monitor progress and report annually, using an accountability framework, in order to guide immunization discussions and future actions.[2] In response, the DoV partners developed a Monitoring & Evaluation/Accountability (M&E/A) Framework that identifies specific indicators to measure progress for each goal and strategic objective. The DoV partners also agreed to a process for an annual independent review of progress.

Table 1: The GVAP Monitoring and Evaluation/Accountability Framework: goals, strategic objectives and indicators to evaluate progress

Goal/Strategic Objective	Indicators
GOALS	
1. Achieve a world free of poliomyelitis	1.1 Interrupt wild poliovirus transmission globally
	1.2 Certification of poliomyelitis eradication
2. Meet global and regional elimination targets	2.1 Neonatal tetanus elimination
	2.2 Measles elimination
	2.3 Rubella/Congenital rubella syndrome (CRS) elimination
3. Meet vaccination coverage targets in every region, country and community	3.1 By 2015, reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria–tetanus–pertussis-containing (DTP) vaccines
	3.2 By 2020, reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended
4. Develop and introduce new and improved vaccines and technologies	4.1 Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases **Note:** this indicator is included in the "Research and development" section
	4.2 Licensure and launch of at least one platform delivery technology **Note:** this indicator is included in the "Research and development" section
	4.3 Number of low-income and middle-income countries that have introduced one or more new or underutilized vaccines **Note:** this indicator is included in the "Immunization coverage" section
5. Exceed the Millennium Development Goal 4 target for reducing child mortality and integration indicators	5.1 Reduce under-five mortality rate
	5.2 Integration of health care interventions and immunization activities

[1] The GVAP can be found at: http://www.who.int/immunization/global_vaccine_action_plan/en/.
[2] Resolution WHA65.17, available at: http://apps.who.int/gb/or/e/e_wha65r1.html.

Goal/Strategic Objective	Indicators
STRATEGIC OBJECTIVES (SOs)	
1. Ensuring country ownership of immunization	1.1 Increasing domestic expenditures for immunization per person targeted
	Note: this indicator is included in the "Sustainable financing and supply for immunization" section
	1.2 Presence of an independent technical advisory group that meets the defined criteria
2. Demand for immunization	2.1 Percentage of countries that have assessed the level of hesitancy in vaccination at a national or subnational level.
	2.2 Reasons for vaccine hesitancy
3. The benefits of immunization are equitably extended to all people	3.1 Percentage of districts with 80% or greater coverage with three doses of diphtheria-tetanus-pertussis-containing vaccine
	Note: this indicator is included in the narrative of "Immunization coverage" section
	3.2 Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s)
	Note: this indicator is included in "Immunization coverage" section
4. Strong immunization systems are an integral part of a well-functioning health system	4.1 Dropout rates between first dose (DTP1) and third dose (DTP3) of diphtheria–tetanus–pertussis-containing vaccines
	Note: this indicator is included in the "Immunization coverage" section
	4.2 Sustained coverage of diphtheria-tetanus-pertussis-containing vaccines 90% or greater for three or more years
	Note: this indicator is included in the narrative of the "Immunization coverage" section
	4.3 Immunization coverage data assessed as high quality by WHO and the United Nations Children's Fund (UNICEF)
	Note: This indicator is no longer monitored.
	4.4 Number of Member States with case-based surveillance for vaccine-preventable diseases: invasive bacterial vaccine-preventable diseases and rotavirus
5. Stockout and access to sustained supply of vaccines of assured quality	5.1 Percentage of doses of vaccine used worldwide that are of assured quality
	Note: this indicator is included in the "Sustainable financing and supply for immunization" section
	5.2 Number of countries reporting a national-level stockout of at least one vaccine for at least one month
6. Country, regional and global research and development innovations maximize the benefits of immunization	6.1 Progress towards development of HIV, TB and malaria vaccines
	6.2 Progress towards a universal influenza vaccine (protecting against drift and shift variants)
	6.3 Progress towards institutional and technical capacity to carry out vaccine clinical trials
	6.4 Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8°C range
	6.5 Number of vaccine delivery technologies (devices and equipment) that have received WHO prequalification against the 2010 baseline
	Note: All these indicators are included in the "Research and development" section

Goal/Strategic Objective	Indicators
SUSTAINABLE FINANCING AND SUPPLY FOR IMMUNIZATION	
Access to sustainable financing and supply for immunization (in response to the 2015 World Health Assembly resolution WHA68.6, on sustained access to affordable vaccines)	• Vaccine prices • Immunization financing (SO1.1) • Vaccines shortages • Technology transfer • Vaccines research and development • prequalification • NRA strengthening and in-country registration process improvements • Percentage of doses of vaccine used worldwide that are of assured quality (SO5.1) • Number of vaccine delivery technologies (devices and equipment) that have received WHO prequalification (SO6.5) • **Note:** All these indicators are now included in the "Sustainable financing and supply for immunization" section

This report, prepared by the Secretariat for the Decade of Vaccines Global Vaccine Action Plan, serves as the basis for the independent review. As was the case in previous years, this report reviews progress against each of the indicators in the GVAP Monitoring and Evaluation/ Accountability Framework. In addition it contains a narrative report on trends in vaccine prices, short updates on tracking resources and commitments to immunization, and independent voluntary submissions from various partners on the activities they conducted under the GVAP umbrella.

Updates to the GVAP Secretariat report 2016

This report includes a few new features from the 2015 edition, as outlined below.

1. The report does not strictly follow the structure of the GVAP, but rather considers linked indicators relating to specific areas together, even though they reflect different indicators. As an example, all results relating to immunization coverage are compiled into one section of the report, even though they come under separate goals or strategic objectives. Grouping results in this way also meets the request from the Strategic Advisory Group of Experts (SAGE) on immunization that certain original indicators be considered as part of the overall report on progress with immunization coverage, rather than as independent indicators.
2. The same applies to several indicators (vaccine prices, immunization financing) that have been gathered in the section "Sustainable financing and supply for immunization". This is done to detail the activities initiated in response to the World Health Assembly (WHA) resolution 68.6[3] in 2015.
3. A new indicator on vaccine safety has been included following the request from the SAGE DoV working group (WG).
4. The indicator for integration of health care interventions and immunization activities has been revised following the requests by the SAGE DoV WG.
5. Progress on the GVAP research and development indicators, which are to be reported biennially, is included in this 2016 report.
6. Civil society organizations (represented by the "GAVI CSOs Constituency") were specifically invited to submit reports focusing on their efforts to improve ownership, leadership and accountability from national and subnational authorities. They also provided their annual general reports on the implementation of the GVAP. Those pieces are all included in the independent submissions from the GVAP CSOs constituency section.
7. The report also contains independent submissions by various partners (technical partners, donors, etc.).

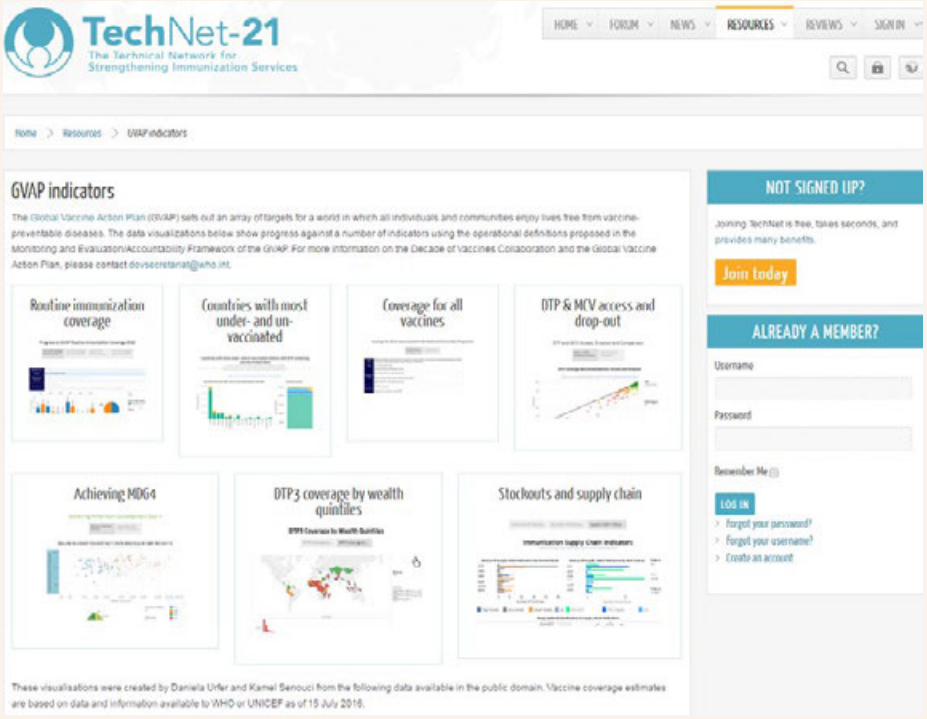
[3] http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf#page=27

Data Visualization of GVAP Indicators

Please note that for several indicators, the GVAP Secretariat has provided interactive maps and graphs that will help the reader to better understand and explore the data.

To access these interactive figures/dashboard please use the Technet21 platform:

http://www.technet-21.org/en/resources/gvap-indicators



When looking at the data, please hover over the dots, bars and countries; change the year; use the filters; use zoom, etc. to view additional information in the background.

For example, for the graph showing the relationship between DTP1 and DTP3, by filtering by region and then hovering over the circles, one can see which country the circles represent.

I

Monitoring results: goals, strategic objectives and indicators

1. DISEASE ELIMINATION

GOAL 1: Achieve a world free of poliomyelitis (indicators G1.1 and G1.2)

Highlights

The Global Polio Eradication Initiative (GPEI) is making strong progress on several fronts.

- It has been two years since Nigeria (July 2014) and the African continent (August 2014) have detected the circulation of wild poliovirus (WPV).
- Since August 2014, wild poliovirus has been circulating in only two countries – Afghanistan and Pakistan.
- In April 2016, in a globally synchronized effort, 155 countries ceased using type 2 oral polio vaccine (OPV), switching from tOPV to bOPV. This was an important step in the polio endgame – a prelude to the time, after full eradication, when all oral poliovirus can be stopped.
- Given the failure in Afghanistan and Pakistan, the GPEI's 2013–18 Strategic Plan to stop polio has been extended to run until the end of 2019 at an additional cost of US$ 1.5 billion.
- A shortfall in the global supply of inactivated polio vaccine (IPV) represents a constraint to the programme.
- In 2015 more countries were affected by circulating vaccine-derived poliovirus (cVDPV) outbreaks than by WPV, giving the former a greater precedence and illustrating how important the trivalent to bivalent OPV switch will be in 2016.

G1.1: INTERUPT WILD POLIOVIRUS TRANSMISSION GLOBALLY

TARGET: 2014

G1.2: CERTIFICATION OF POLIOMYELITIS ERADICATION

TARGET: 2018

For the definition of each indicator, description of data sources, comments on data quality, description of results, narrative and highlights please refer to the documents listed in Box 1.

Box 1: Descriptions of indicators, results, data sources and highlights

1. For context, see the Global Polio Eradication Initiative Status Reports 2015 (June and December), available at: http://www.polioeradication.org/Resourcelibrary/Strategyandwork/Annualreports.aspx
2. To review the real-time updates on polio cases worldwide, see: http://www.polioeradication.org/Dataandmonitoring.aspx
3. To review the October 2015 report of the Independent Monitoring Board of the Global Polio Eradication Initiative, please visit: http://www.polioeradication.org/Aboutus/Governance/IndependentMonitoringBoard/Reports.aspx

Progress towards the achievement of polio eradication goals and interim milestones is intensively monitored by several bodies, including the Independent Monitoring Board of the GPEI, which reviews progress on a quarterly basis and issues a report after each meeting. Below are excerpts from WHO, GPEI and Independent Monitoring Board documents that summarize progress towards this goal and the corrective actions that are being taken, as well as recommendations for future actions.

Interruption of wild poliovirus transmission

In 2015 74 cases of paralytic poliomyelitis due to wild poliovirus were reported globally, compared to 359 cases in 2014. All the cases in 2015 were reported from Afghanistan and Pakistan and were caused by wild poliovirus type 1. On 20 September 2015, the Global Commission for the Certification of Poliomyelitis Eradication declared the global eradication of wild poliovirus type 2. Wild poliovirus type 3 has not been detected since November 2012.

Endemic countries – Afghanistan and Pakistan

Owing to continued cross-border transmission, Afghanistan and Pakistan continue to be treated as a single epidemiological block. In Pakistan, 54 cases were reported in 2015, compared to 306 in 2014. In Afghanistan, 20 cases were reported, compared to 28 in 2014. In Pakistan and Afghanistan, the interruption of wild poliovirus transmission depends on reaching all missed children, filling chronic gaps in strategy implementation and being able to vaccinate children

in infected areas that have been difficult to access due to insecurity. The remaining reservoirs of wild poliovirus are the Khyber-Peshawar-Nangarhar and Quetta-Kandahar corridors, linking Pakistan with Afghanistan, and Karachi in Pakistan. These are now the focus of attention for targeted, high-quality immunization activities.

In Pakistan, the number of polio cases continues to decline. A national emergency action plan for the disease is being overseen directly by the office of the prime minister. Emergency operations centres at federal and provincial levels ensure almost real-time monitoring of activities, implementation of corrective action and increased accountability and ownership at all levels. Most importantly, the national plan focuses on identifying chronically missed children, the reasons why they are missed and implementing area-specific approaches to overcome these challenges. As a result, innovative strategies are being implemented, operational weaknesses of the programme are being increasingly addressed and access continues to improve in previously inaccessible areas. Nevertheless, Pakistan in 2015 accounted for 73% of all wild poliovirus cases worldwide. Vaccination coverage gaps remain in Karachi, Peshawar-Khyber corridor and parts of the Quetta block with evidence of continued transmission.

In Afghanistan, the number of polio cases continues to decline steadily, for example in the southern region. However, transmission continues along corridors in the east and south, as evidenced by detection of wild poliovirus in children with acute flaccid paralysis (AFP) and in environmental samples. Although programmes are being improved in order to reduce the number of children missed in accessible areas, the deteriorating security situation is a concern, reducing access particularly in eastern and northern regions.
A temporary suspension of vaccination by local leaders in the southern region was resolved by highlighting the importance of maintaining neutrality in public health efforts. A national emergency action plan is being implemented, all efforts to identify and address gaps are being closely tracked, and the country is developing innovative strategies to reach children wherever and whenever feasible, including with a strong focus on border areas. Table 1.1 shows the number of AFP cases in 2015 by WHO region.

Table 1.1: AFP/polio case count in 2015, by WHO region

WHO region	AFP cases reported	Non-polio AFP rate	AFP cases with adequate specimen (%)	Wild poliovirus confirmed cases	cVDPV confirmed cases
African Region	25 684	6.29	95	0	18
Region of the Americas	1 796	0.75	78	0	0
South-East Asia Region	51 014	9.29	89	0	2
European Region	1 620	1.03	88	0	2
Eastern Mediterranean Region	13 196	6.15	92	74	2
Western Pacific Region	6 523	1.76	90	0	8

Source: WHO; data as of 28 June 2016.

Recently-endemic countries – Nigeria

In Nigeria, no cases due to wild poliovirus type 1 have occurred since 24 July 2014; as a result, Nigeria was officially removed from the list of endemic countries on 25 September 2015. With large populations in remote, hard-to-reach areas, as well as regional insecurity, success in Nigeria was thanks to renewed political commitment and attention to detail at every level of the programme.

International spread of wild poliovirus

Episodes of international spread of poliovirus continued in 2015 with both Afghanistan and Pakistan exporting virus across their shared border. Minimizing the risk and consequences of new international spread of polioviruses requires the following: full implementation of the eradication strategies in the remaining infected areas; comprehensive application of the temporary recommendations issued by the WHO Director-General under the International Health Regulations (IHR 2005);

and heightened surveillance globally to facilitate a rapid response to new cases.

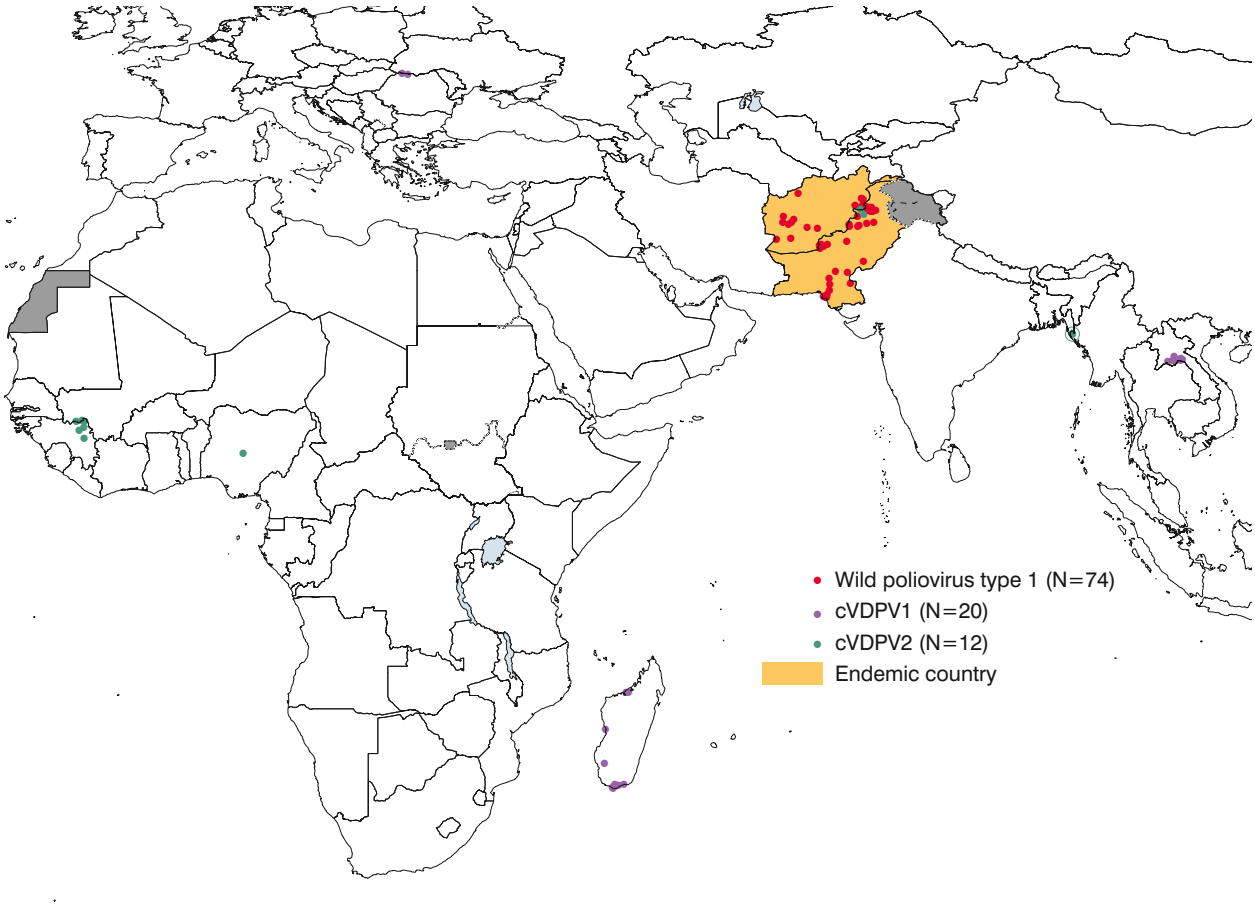
At its meeting on 10 November 2015, the IHR Emergency Committee noted with concern the current outbreaks due to circulating vaccine-derived poliovirus (cVDPV) types 1 and 2 and the emergence of such strains in three WHO regions in 2015, particularly at this stage of the Polio Endgame. The Committee recommended extending the temporary recommendations to countries affected by such outbreaks, which are shown in Table 1.2 and Figure 1.1 (previously, the recommendations had been limited to countries affected by wild poliovirus).

Table 1.2: Breakdown of confirmed WPV and cVDPV cases in 2015, by country

Country	WPV1	cVDPV type 1	cVDPV type 2
Afghanistan	20		
Pakistan	54		2
Lao People's Democratic Republic		8	
Madagascar		10	
Ukraine		2	
Guinea			7
Myanmar			2
Nigeria			1

Source: WHO; data as of June 2016.

Figure 1.1: Remaining wild poliovirus cases and cVDPV[a] cases[b] worldwide, 2015



[a] cVDPV is associated with ≥ 2 AFP cases or non-household contacts. VDPV2 cases with ≥ 6 (≥ 10 for type 1) nucleotides different from Sabin poliovirus type 1 are reported here.

[b] Excludes viruses detected from environmental surveillance.

Source: WHO data; June 2016.

Vaccine-Derived Poliovirus Outbreaks

Circulating vaccine-derived polioviruses type 1

In 2015 in Madagascar, 10 new cases of a circulating vaccine-derived poliovirus type 1 were reported, genetically linked to isolates of the same strain first detected in 2014. In Ukraine, two cases were reported, with onset of paralysis on 30 June 2015 and 7 July 2015. In the Lao People's Democratic Republic, 7 cases were reported, with the onset of paralysis for the first case occurring on 7 September 2015. Two more cases there have been reported to date in 2016.

In Madagascar, national efforts continue to be intensified to stop the prolonged circulation of the virus. In the Lao People's Democratic Republic, a comprehensive outbreak response was launched immediately after confirmation of the first reported case. In Ukraine, an outbreak response commenced on 21 October 2015 after a delay of several weeks.

Circulating vaccine-derived polioviruses type 2

In Nigeria, one case of disease due to cVDPV2 was reported, with onset of paralysis on 16 May 2015, related to a strain first isolated from environmental samples in August 2014. In Guinea, four cases due to cVDPV2 were detected, related to a strain last detected in the country in August 2014. The onset of paralysis in the first case

occurred on 20 July 2015. Two cases were also reported in Pakistan in February 2015. In Myanmar, two cases due to cVDPV2 were detected. The onset of paralysis was recorded in one case on 5 October 2015; the other case was assigned retrospectively with onset of paralysis in the same village in April 2015.

In Nigeria, the outbreak response is part of the national emergency action plan, overseen by the office of the president. In Guinea and border areas of Mali, outbreak response was initiated within two weeks of confirmation of the outbreak. In Myanmar, outbreak response was initiated in November, with two campaigns focusing on larger populations in December 2015. A strain isolated from a case with onset of paralysis in April 2015 detected in South Sudan is being managed as a circulating strain (the genetic linkage was uncertain, therefore the case was classified as an ambiguous VDPV; however the response was managed as a cVDPV based on the detection of known cVDPV2 cases several months earlier). Response activities are ongoing and the strain has not been detected since April 2016. The emergence of vaccine-derived poliovirus occurs only when routine immunization coverage is low, highlighting the importance of strengthening routine immunization systems.

Withdrawal of the type 2 component in oral poliovirus vaccine

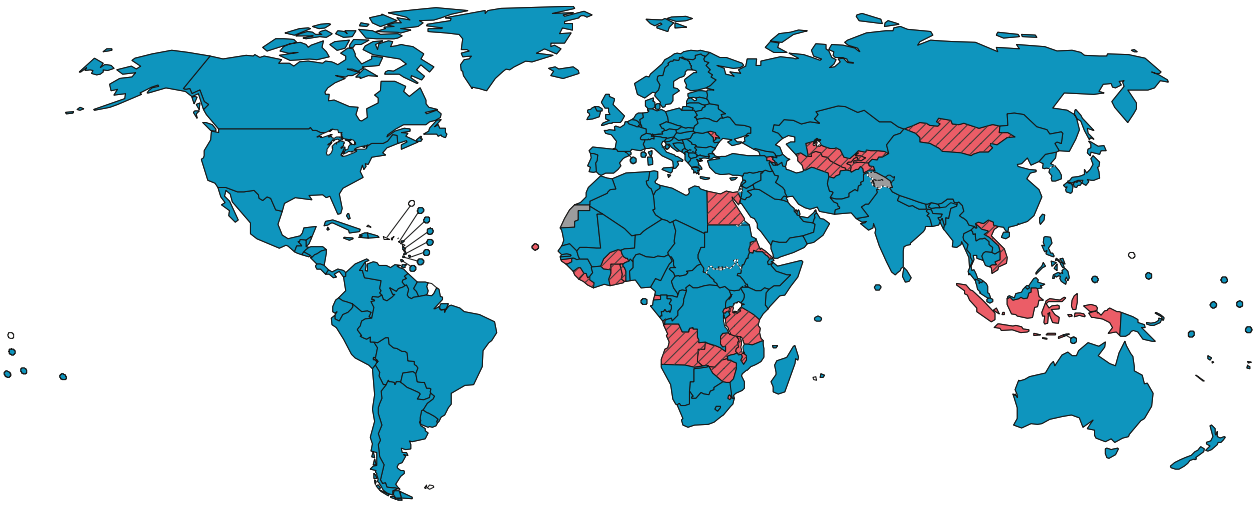
On 20 September 2015, the Global Commission for the Certification of Poliomyelitis Eradication declared that wild poliovirus type 2 has been eradicated, with the last detected case occurring in 1999. On 20 October 2015, SAGE reviewed the situation of type 2 vaccine-derived polioviruses and progress towards global readiness for the coordinated, phased removal of oral polio vaccines. Subsequently, the global switch from trivalent OPV to bivalent OPV was conducted between 17 April and 1 May 2016. As of the start of May 2016, all 155 targeted countries and territories are no longer using the trivalent oral polio vaccine (tOPV), and have replaced it with bivalent OPV (bOPV).

Global vaccine supply to prepare for the trivalent to bivalent oral polio vaccine switch

To prepare for the switch to bivalent oral polio vaccine, all Member States have committed themselves to introduce at least one dose of inactivated poliovirus vaccine into their routine immunization programmes. The level of commitment from countries to meet this goal has been exceptional. SAGE noted the reduction in inactivated polio vaccine supply due to technical difficulties manufacturers have encountered in scaling-up production. Due to this, SAGE advised the following: prioritization of the use of inactivated poliovirus vaccine (i.e. introduction of vaccine in the higher-risk tier 1 and 2 countries before the switch); maintaining stocks of inactivated poliovirus vaccine and monovalent type 2 oral polio vaccine for response to a type 2 poliovirus outbreak after withdrawal of oral polio vaccine type 2; and minimizing the period of delay in inactivated poliovirus vaccine supply and the number of countries affected by it (currently only lower-risk tier 3 and 4 countries are affected by the delay). As of 1 July 2016, 168 (87%) Member States (including partial introduction in India) have introduced IPV (Figure 1.2). Six (3%) additional Member States[4] have committed formally to introduce it by July 2016. Twenty countries[5] (10%) have delayed the introduction to December 2017.

[4] Armenia, Cabo Verde, Equatorial Guinea, Guinea-Bissau, Indonesia, Swaziland.
[5] Angola, Burkina Faso, Egypt, Eritrea, Ghana, Kyrgyzstan, Liberia, Malawi, Mongolia, Republic of Moldova, Rwanda, Sierra Leone, Tajikistan, Togo, Turkmenistan, United Republic of Tanzania, Uzbekistan, Viet Nam, Zambia, Zimbabwe.

Figure 1.2: Countries using IPV vaccine to date and countries having made a formal decision to introduce



* As of 1 July 2016; data includes partial introduction in India. Introduced to date: Afghanistan, Albania, Algeria, Andorra, Antigua and Barbuda, Argentina, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Benin, Bhutan, Bolivia (Plurinational State of), Bosnia and Herzegovina, Botswana, Brazil, Brunei Darussalam, Bulgaria, Burundi, Cambodia, Cameroon, Canada, Central African Republic, Chad, Chile, China, Colombia, Comoros, Congo, Cook Islands, Costa Rica, Cote d'Ivoire, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Democratic People's Republic of Korea, Democratic Republic of the Congo, Djibouti, Dominica, Dominican Republic, Ecuador, El Salvador, Estonia, Ethiopia, Fiji, Finland, France, Gabon, Gambia, Georgia, Germany, Greece, Grenada, Guatemala, Guinea, Guyana, Haiti, Honduras, Hungary, Iceland, India, Iran (Islamic Republic of), Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Kiribati, Kuwait, Lao People's Democratic Republic, Latvia, Lebanon, Lesotho, Libya, Lithuania, Luxembourg, Madagascar, Malaysia, Maldives, Mali, Malta, Marshall Islands, Mauritania, Mauritius, Mexico, Micronesia (Federated States of), Monaco, Montenegro, Morocco, Mozambique, Myanmar, Namibia, Nauru, Nepal, Netherlands, New Zealand, Nicaragua, Niger, Nigeria, Niue, Norway, Oman, Pakistan, Palau, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Republic of Korea, Romania, Russian Federation, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Samoa, San Marino, Sao Tome and Principe, Saudi Arabia, Senegal, Serbia, Seychelles, Singapore, Slovakia, Slovenia, Solomon Islands, Somalia, South Africa, South Sudan, Spain, Sri Lanka, Sudan, Suriname, Sweden, Switzerland, Syrian Arab Republic, Thailand, The former Yugoslav Republic of Macedonia, Timor-Leste, Tonga, Trinidad and Tobago, Tunisia, Turkey, Tuvalu, Uganda, Ukraine, United Arab Emirates, the United Kingdom USA, Uruguay, Vanuatu, Venezuela (Bolivarian Republic of), Yemen.

GPEI continues to monitor closely the global supply of inactivated poliovirus vaccine, and tries to minimize the number of countries affected (in terms of delays in introduction and/or stock-out of inactivated poliovirus vaccine). The difficulties in supply have been aggravated by further production delays in the first quarter of 2016. In this context, the Global Polio Eradication Initiative is exploring with WHO regions and Member States the feasibility of instituting dose-sparing strategies, such as using intradermal administration of fractional-dose inactivated poliovirus vaccine (one-fifth of a full dose). In April 2016, to promote dose-sparing, SAGE encouraged countries to evaluate the cost–benefits, trade-offs and programmatic feasibility associated with providing IPV in a 2-dose fractional intradermal dose schedule (e.g. at 6 and 14 weeks) in lieu of a single intramuscular dose at 14 weeks. As of March 2016, some Member States have already committed to using fractional-doses. India in particular is participating in this effort, which should enable the country to maximize and optimize its available vaccine supply (potentially by as much as five times), thereby ensuring that the national vaccine supply for 2016 and 2017 can be fully met. Studies have shown that two fractional doses offer better protection to children than a single full dose *(1)*.

Strengthening routine immunization

GPEI has started a joint programme of work with the Gavi Alliance and other partners to support efforts to strengthen routine immunization in 10 "focus" countries with significant polio resources. Six of these countries[6] have developed annual national immunization plans that build on polio assets to improve broader immunization goals, resulting in as much as a 22% reduction in unimmunized children in some areas in 2014 compared with 2013 *(2)*. Polio staff in these countries spend as much as 50% of their time on broader immunization and public health issues.

Containment

There was some progress on efforts to contain poliovirus type 2 in 2015, in line with the *WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use* (GAPIII) *(3)*. As of 11 February 2016, 115 Member States reported they had no wild poliovirus type 2 or vaccine-derived poliovirus type 2, 12 reported they did, 26 were completing reports, with the remainder yet to complete their reports on the destruction or planned retention of wild poliovirus type 2 or vaccine-derived poliovirus type 2 materials, in designated "poliovirus-essential" facilities, with the simultaneous nomination of a national containment authority in countries hosting such facilities. By the end of July 2016, three months after the switch, countries are expected to complete the second part of phase I, and report on the destruction or planned retention of all Sabin type 2 poliovirus materials following the same approach. In phase II (the poliovirus type 2 containment period that started in 2016) Member States hosting poliovirus-essential facilities (vaccine production, research and repositories) are expected to certify these facilities have appropriately implemented the containment requirements described in GAPIII. The GVAP Secretariat is supporting Member States to rapidly accelerate efforts in order to complete phase I and implement the Global Vaccine Action Plan.

Post-polio eradication transition planning

Planning for the post-polio eradication transition is the fourth objective of the current GPEI Strategic Plan. When the GPEI's work to eradicate polio is complete, it will leave behind the legacy of a polio-free world for all future generations, the most sustainable contribution that can be made by a public health programme. There also exists an opportunity for other health goals to make use of the existing polio infrastructure and the lessons learned in the polio eradication programme.

To date, the GPEI's work towards polio transition planning has focused on raising awareness of the urgency in beginning the planning process and developing transition guidelines and other tools and guidance to assist country and regional planning processes.

In April 2016, GPEI completed a critical budget planning exercise covering the 2016–2019 period, setting out the budget decrease foreseen for the next four years. This provides the basis to plan human resource management accordingly, and seek alternative sources of funding where necessary. GPEI is now developing a plan detailing its overarching strategic approach for the next phase of transition planning. The plan sets out three workstreams to deliver the transition planning objectives.

a. Support the development of a transition plan in each of 16 priority countries.

To the greatest extent possible, the planning process is driven at country level and led by governments. In the 16 countries that have the greatest GPEI-funded assets, GPEI is supporting the government and working with current and new partners to develop a transition plan. Each plan will cover a specified time period and should be aligned or integrated with the country's comprehensive multi-year plan (cMYP) for immunization, other relevant plans and the overall health sector plan. GPEI has developed and issued transition guidelines to assist countries with their planning process. GPEI is now supporting countries in applying these guidelines, particularly emphasizing a high-quality process of mapping country needs and GPEI assets, as the basis for subsequent planning and engagement of a broad range of stakeholders in the planning process, including donors. The goal is for 14 of the 16 priority countries to have developed a transition plan by the end of 2016. The other two countries –

[6] Chad, Democratic Republic of the Congo, Ethiopia, India, Nigeria, Pakistan

Afghanistan and Pakistan – will develop plans after polio transmission is interrupted.

b. Facilitate the development of a global transition plan.

GPEI has assets at regional and global levels – principally in its headquarters and the regional offices of its partner agencies. Also, some assets that are based in countries might need to remain part of regional, global, or other supranational programmes or organizations – in one or more of their funding, direct management, and coordination activities. A global plan will therefore need to be developed in tandem with the country transition plans.

c. Document and disseminate the lessons of polio eradication.

It is critical to document the lessons learned from polio eradication, as one of the largest ever global health initiatives. GPEI will document and disseminate lessons learned from polio eradication in multiple media forums.

Update for 2016

After more than two years without wild poliovirus in Nigeria, the government reported on 11 August 2016 that two children have been paralysed by the disease in the northern Borno state.

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GOAL 2:
Achieve maternal and neonatal tetanus elimination (Indicator G2.1)

Highlights

- The GVAP target for 2015 was not achieved – only 19 of the 40 Member States required to meet the GVAP milestone for 2015 had achieved elimination since 2010 – maternal and neonatal tetanus (MNT) continued to be a public health problem in 21 Member States at the end of 2015.
- The remaining 21 countries have developed their MNT elimination plans of action as part of comprehensive multi-year planning.
- A total of 38 of the 59 priority Member States (64%) had achieved MNT elimination as of December 2015.
- One of the headline stories of 2015 was India's achievement of MNT elimination. This was the result of successful strategies to improve access to tetanus toxoid (TT) vaccination and health systems strengthening, which increased access to health service delivery in general, including antenatal care and institutional delivery.
- Levels of coverage of antenatal care and skilled attendance at birth from the most recent surveys are presented in the GVAP Secretariat report 2014. These very important aspects of MNT elimination rely heavily on the performance of the health systems and often progress slowly unless there is a concerted effort by governments, as seen in China and India.

DEFINITION OF INDICATOR	An incidence of < 1 case of neonatal tetanus per 1000 live births per year in all districts or similar administrative units of a country (please refer to *GVAP Secretariat Report 2013 (1)* for more information); the neonatal tetanus indicator acts as a proxy for maternal tetanus To monitor sustainability of elimination, the routine Expanded Programme on Immunization (EPI), reproductive health and surveillance data will be used, as sustainability is directly linked to health system strengthening with a focus on routine delivery of immunization, antenatal care (ANC), clean delivery, clean cord care practices and surveillance activities Note that the guidelines that will provide an opportunity to periodically review and monitor the elimination status are being finalized, and will offer a menu of options for the countries to choose and adapt based on the findings from the risk analysis
TARGET	(From 2010 baseline, with 40 countries still to achieve elimination): • 10 countries eliminated neonatal tetanus (NT) by 2012 • 22 countries eliminated NT by 2013 • 36 countries eliminated NT by 2014 • 40 countries eliminated NT by 2015
DATA SOURCES	• WHO-UNICEF joint reporting forms (JRF) • Country health management information system reports • Country disease surveillance reports • Immunization coverage survey reports • Multiple Indicator Cluster Survey (MICS) reports, Demographic and Health Survey (DHS) reports and any other reports of immunization and reproductive health programme reviews • Reports of maternal and neonatal tetanus elimination (MNTE) validation surveys

Introduction and background

Tetanus is an acute, potentially fatal disease caused by a neurotoxin produced by the bacterium *Clostridium tetani* that is commonly found in the soil and in the intestinal tracts of animals and humans. As such, the disease cannot be eradicated. Maternal and neonatal tetanus (MNT) are forms of generalized tetanus affecting mothers during pregnancy, due to unclean abortion or delivery, and infants during the first month of life. Neonatal tetanus infection begins when *C. tetani* spores are introduced into the umbilical tissue during delivery. The organisms produce a neurotoxin at the site of the umbilical cord wound which passes into the blood stream of the newborn infant and then into the central nervous system. This results in motor neuron hyperactivity, hypertonia and muscle spasms. Death occurs as a result of paralysis of the respiratory muscles and/or inability to feed.

The global estimate of neonatal tetanus deaths declined from over 780 000 in 1988 to 49 000 in 2013 *(2)* due to the implementation of recommended strategies by countries. The main activities implemented include TT vaccination (including campaigns in high-risk districts), improvement in clean delivery and clean cord care practices and integration with antenatal care services. For example, China and India focused on strengthening their health systems through promoting institutional delivery including use of incentives such as maternity waiting homes, cash grants and provision of free services to the mother and newborn child within the first week of birth. And Ethiopia and Malawi placed more community-based health workers in antenatal care services who also advocate for other health interventions such as immunization and improvement in clean delivery practices. The Democratic Republic of Congo is another example of proactive prevention – 89% ANC, 80% skilled attendants at birth and 82% reported TT2+ coverage, with currently only 14 out of its 516 districts being at high risk for MNT.

At the global level, the development of guidelines for sustaining MNT elimination is completed, and is awaiting a review by the SAGE WG on MNTE and broader tetanus prevention before its finalization and dissemination. This will provide a menu of options to countries on appropriate responses that may be required following periodic desk reviews of MNT risk indicators.

Results

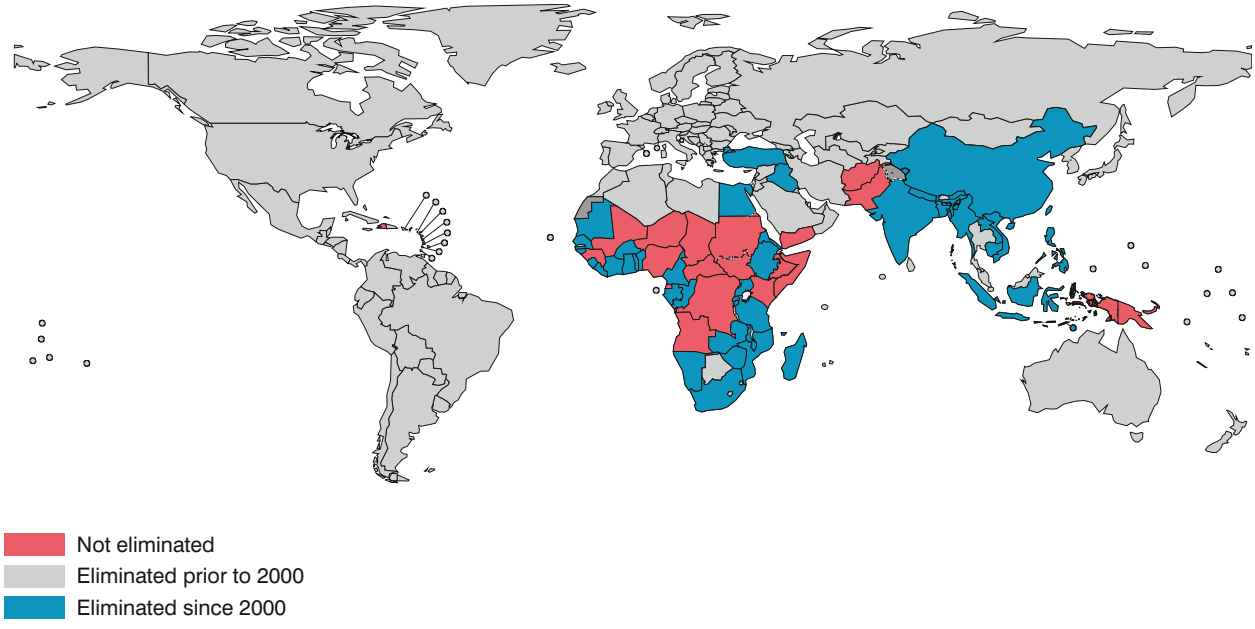
- In 2012, six Member States – Burkina Faso, Cameroon, China, Guinea Bissau, Timor-Leste and the United Republic of Tanzania – were validated as having eliminated MNT. With four Member States validated in 2011 (Ghana, Liberia, Senegal and Uganda) in addition to Ethiopia (excluding Somali region) and the third of the four phases in Indonesia, the milestone for achieving elimination in ten additional countries between 2010 and 2012 was thus met.
- In 2013, five additional Member States (Cote d'Ivoire, Gabon, Iraq, Lao People's Democratic Republic and Sierra Leone) and three additional states in India (Delhi, Mizoram and Uttarakhand) achieved elimination (bringing the total number of states that achieved elimination in India to 18 out of 35 at the time).
- In 2014, Madagascar attained MNT elimination as well as 12 additional states of India[7].
- In 2015, three Member States (Cambodia, India and Mauritania) and 16 of 17 regions of the Philippines achieved elimination.

As of December 2015, a total of 38[8] out of the 59 priority Member States (64%) have achieved MNT elimination (see Figure 1.3). Since 2010, the total number of countries that achieved elimination is 19 of the 40 required to meet the GVAP milestone for 2015. It is envisaged that almost all of the remaining 21 Member States will achieve elimination by the DoV target of 2020 if the implementation challenges are addressed.

[7] Andaman & Nicobar Islands, Arunachal Pradesh, Assam, Bihar, Chhattisgarh, Daman & Diu, Jharkhand, Madhya Pradesh, Odisha, Rajasthan, Tripura, Uttar Pradesh.

[8] Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, China, Comoros, Congo, Côte d'Ivoire, Egypt, Eritrea, Gabon, Ghana, Guinea Bissau, India, Iraq, Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Mauritania, Mozambique, Myanmar, Namibia, Nepal, Rwanda, Senegal, Sierra Leone, South Africa, Timor-Leste, Togo, Turkey, Uganda, United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.

Figure 1.3: Member States with validated elimination of maternal and neonatal tetanus (as of December 2015)[a]

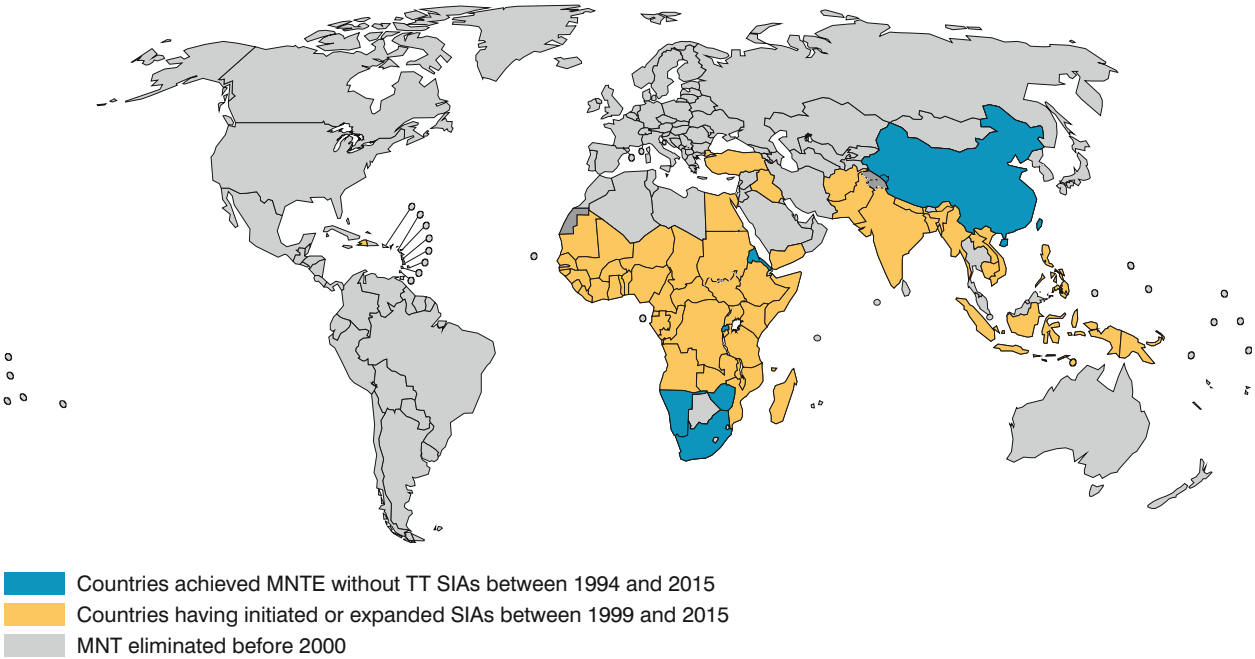


[a] This includes Ethiopia (except Somali region), 30 of 34 provinces in Indonesia and 16 of 17 regions in the Philippines.

Source: WHO/UNICEF database, July 2016.

In addition, TT supplementary vaccination campaigns targeting women of reproductive age (15–49 years) were conducted in nine Member States[9] in 2015, raising to 52 the total number of countries that have implemented TT SIAs from 1999 to 2015 (Figure 1.4). Figure 1.5 shows the cumulative number of women or reproductive age receiving at least 2 doses of TT during supplementary immunization activities (SIAs).

Figure 1.4: The 52 Member States that implemented TT SIAs between 1999 and 2015



Source: WHO/UNICEF database, July 2016.

[9] Angola, Chad, Ethiopia, Haiti, Indonesia, Mali, Pakistan, South Sudan, Sudan.

Discussion

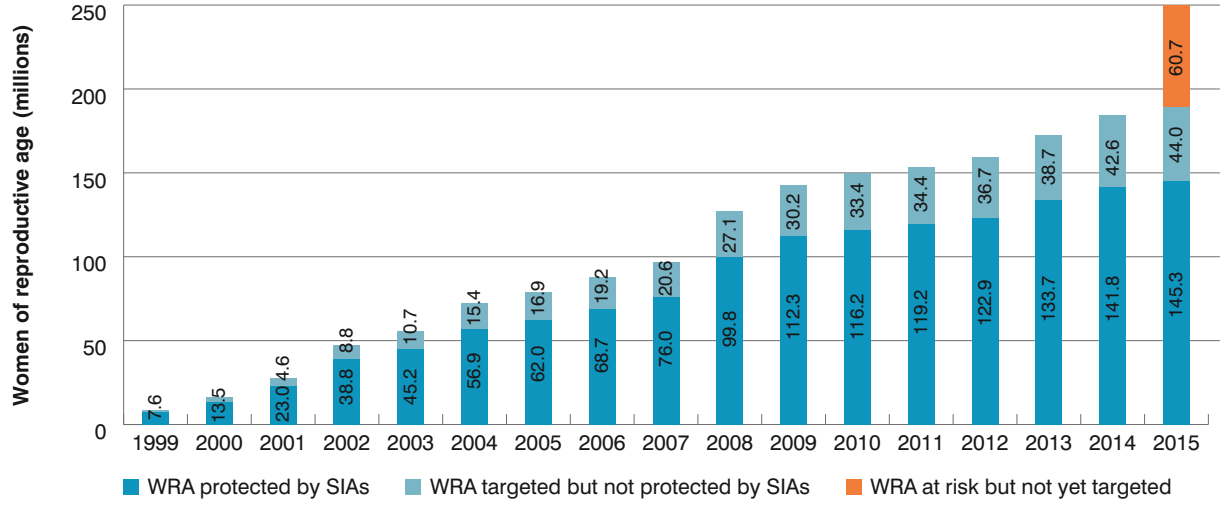
Areas requiring focus in order to maintain progress towards the attainment of MNTE in all countries

The SAGE WG on MNTE and broader tetanus prevention set up in September 2015 is expected to provide the much needed orientation on where to focus to ensure that the remaining priority countries attain elimination, but also to ensure that all countries that have achieved elimination receive the necessary guidance to sustain their elimination status. The issue of gender and geographic inequity in access to TTCV is also to be addressed, as well as the US$ 135 million (inclusive of TT Uniject cost of US$ 37 million) funding gap that is a serious challenge to the global goal for achieving MNTE. Figure 1.6 shows that lack of funding makes it difficult to conduct the SIAs that will help to achieve MNTE and reach the unreached women. Ownership and contributions by national governments have proven instrumental in the achievements to date, as has funding by private sector contributions (e.g. Kiwanis International, Procter & Gamble) and UNICEF national committees. To maintain the momentum, it is now time for individual and collaborative fundraising efforts by all MNTE partners to tap bilateral and multilateral donors.

TT Uniject is needed for use particularly in the 10 countries[10] where there are serious issues with accessing high-risk populations, primarily due to geographical difficulties and/or security challenges. The use of TT Uniject by lay health workers after brief training in Afghanistan, Ghana, Mali, Pakistan and Somalia in the past has led to coverage levels of at least 80% for TT3 (unpublished country reports), and an assessment of the experiences of the use by the Program for Appropriate Technology in Health (PATH) found that the vaccine was correctly administered, safe injection technics were applied and no side-effects were reported (Unpublished data from a presentation from BASICS II, for the WHO TechNet Consultation 22–25 March 2003, Antalya, Turkey).

More effective integration between EPI and ANC as well as with other elimination efforts is required to address inequities, for example through the implementation of initiatives such as the Reaching Every Child approach or the Mother & Child Health Days implemented in the most underserved communities. A package of interventions can be integrated into this effort. WHO recommends at least four ANC visits to give adequate opportunity for a pregnant woman to be assessed, and to receive all her doses of TTCV based on her tetanus vaccination status, besides delivery of other high-impact lifesaving interventions *(3)*.

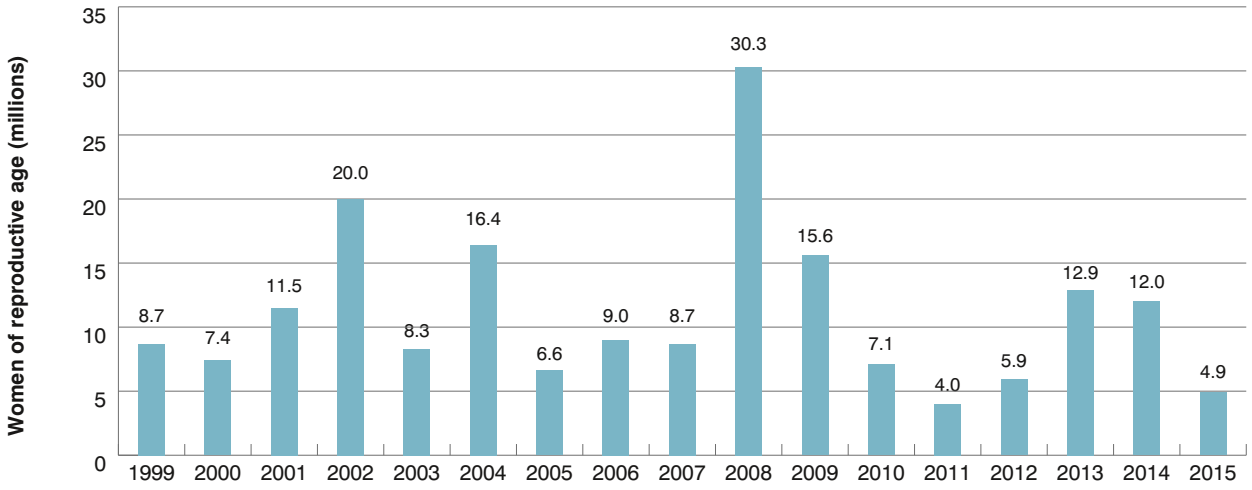
Figure 1.5: Cumulative number of women of reproductive age protected with at least 2 doses of TT during SIAs/year



Source: WHO/UNICEF MNTE Database, as of 17 March 2016. Data for 2015 are provisional.

[10] Afghanistan, Central Africa Republic, Chad, Mali, Nigeria, Pakistan, Somalia, Sudan, South Sudan, Yemen.

Figure 1.6: Trend in women of reproductive age targeted with TT SIAs – extent of activities dependent on availability of funds



Source: WHO/UNICEF MNTE database, as of 1 July 2016. Data for 2015 are provisional.

Update for 2016

- Three additional countries (Equatorial Guinea, Indonesia and the Niger) have been validated as having eliminated MNT between January and July 2016.
- Pre-validation assessments are being planned for the Democratic Republic of Congo, Ethiopia and Haiti later in 2016.

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GOAL 2: Achieve measles elimination (Indicator G2.2)

Highlights

- In 2015, 40% and 24% of Member States reached the measles-containing vaccine 1 (MCV1) and MCV2 coverage target of at least 95%. The global MCV1 and MCV2 coverage levels were 85% and 61%, respectively – both short of the programme targets.
- Since 2010, global measles incidence has decreased by 21%, but is still substantially higher than the global 2015 target of fewer than five cases per million population. The rate of decline in measles deaths has plateaued, however, and the target of a 95% mortality reduction by the end of 2015 was not reached.
- In decreasing order, the following six large Member States had the highest number of susceptible infants in 2015 and accounted for over two thirds of the global measles mortality burden in 2015: India, Nigeria, Pakistan, Indonesia, Ethiopia and the Democratic Republic of the Congo.
- Much stronger country ownership, additional financial and human resources and increased political commitment to measles elimination goals will be needed to get back on track towards elimination worldwide.
- An external midterm review of the Global Measles and Rubella Strategic Plan 2012–2020 is under way currently and the findings will be available in mid-October 2016.

DEFINITION OF INDICATOR	Framework for verification of measles elimination *(1)* lists the following. • Measles eradication: worldwide interruption of measles virus transmission in the presence of a surveillance system that meets specified performance indicators • Measles elimination: the absence of endemic measles transmission in a defined geographical area (e.g. region or country) for ≥ 12 months in the presence of a well-performing surveillance system **Note:** Verification of measles elimination takes place after 36 months of interrupted endemic measles virus transmission
TARGET	• Measles elimination goals by WHO region *(3)* · Americas: eliminated in 2002 (2 years after the 2000 goal) · Western Pacific Region: elimination by 2012 · European Region: elimination by 2015 · Eastern Mediterranean Region: elimination by 2015 · African Region: elimination by 2020 · South-East Asia Region: elimination by 2020
DATA SOURCES	• Joint Reporting Forms (JRFs) for disease incidence and WHO-UNICEF Estimates of National Immunization Coverage (WUENIC) data for coverage rates • Progress reports of the regional verification commissions: from the Regions of the Americas, Europe and the Western Pacific for outbreak data and status of countries with regard to elimination as of 31 December 2014
COMMENTS ON DATA QUALITY	• JRFs and WUENIC data are subject to the same limitations as all other data submitted via the JRFs, as described in the 2015 GVAP Secretariat report *(2)* • Regional verification commission reports are only available from three regions: European Region, Region of the Americas and the Western Pacific Region (note that commissions will only verify elimination if data quality standards are met)

Background and progress

The impact of the measles vaccine on global public health has been tremendous. Before 1963, most of the world's population had been infected with measles virus by their 15th birthday, resulting in an estimated 100 million cases and more than 2 million deaths annually *(4)*. By 2000, four decades of steadily increasing use of the vaccine had led to a dramatic reduction in the number of cases to just over half a million annually. In 2002, the Region of the Americas stopped endemic transmission of measles (i.e. measles was eliminated from the region) and sustained the elimination for more than a decade. Since the sixty-third World Health Assembly in 2010 endorsed three global measles targets for 2015 as milestones towards global eradication of measles,[11] however, progress has been slow.

Between 2010 and 2015, global routine measles vaccine coverage stagnated at 85% – well below the 2015 target of ≥ 90%; Table 1.3). Three of the six WHO regions have sustained MCV1 coverage above 90% (the Regions of the Americas, Europe and the Western Pacific), one region achieved coverage between 80 and 90% (South-East Asia Region) and two regions achieved coverage below 80% (African Region and Eastern Mediterranean Region). The number of Member States achieving the global MCV1 coverage target at the national level has decreased in 2015 as compared to 2010; 122 Member States achieved the MCV1 national coverage target of ≥ 90% in 2010 but only 119 achieved the target in 2015[12] (Table 1.3 and Figure 1.7).

While the reported incidence of measles has decreased by 21% globally since 2010 (from 50 cases per million population in 2010 to 39.8 in 2015), only one region achieved the global target of fewer than five cases per million population (Region of the Americas; Table 1.3 and Figure 1.8). And since 2010, seven fewer Member States have met the global target.

Between 2000 and 2014, estimated measles deaths decreased by 79% (from 546 800 to 114 900) and all regions reported substantial reductions in estimated measles mortality. However, progress since 2010 has been too slow (from 69% mortality reduction in 2010 to 79% in 2014), meaning that the target of 95% mortality reduction was not achieved by the end of 2015.

By 2015, 160 Member States (82%) had introduced a second dose of MCV, an increase from 154 (79%) in 2014 and 136 (70%) in 2010. MCV2 coverage globally was 61% (compared to 39% in 2010) (Figure 1.9). Among those 160 countries, 65 provide MCV2 to infants aged under 2 years and have reported coverage both for MCV1 and MCV2. In these 65 countries,[13] the difference between MCV1 and MCV2 coverage decreased from 16% in 2014 to 12% in 2015 (87% MCV1 compared to 75% MCV2). This highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and the inability to interrupt measles virus transmission. Given these gaps in coverage and population immunity, it is not surprising that outbreaks continue to threaten elimination goals in all six WHO regions. Such gaps also highlight the need for SIAs.

Many countries regularly supplement routine efforts through the use of SIAs. SIAs vaccinated approximately 223 million children in 32 Member States in 2014 and an additional 136 million children in 50 Member States in 2015. Among 63 countries that conducted SIAs between 2014 and 2015, based on administrative data, 52% (33 Member States) were able to reach the target of 95% national coverage. Of the six countries that did post-campaign coverage surveys, two countries (Côte d'Ivoire and Timor-Leste) achieved 95% coverage while in Afghanistan, Nigeria, Sierra Leone and Yemen, coverage was 92%, 84%, 69%, and 91%, respectively.

Regional review

At least ten countries in the African Region had documented measles outbreaks, with large outbreaks in 2015 in Ethiopia, the Democratic Republic of the Congo and Nigeria. Outbreaks are mainly the result of stagnating MCV1 coverage levels and the poor quality of SIAs in many countries. Funding gaps also led to countries limiting the age ranges covered by SIAs (where a wider age range is indicated because of an increasing susceptibility in older age groups) and delaying MCV2 and rubella-containing vaccine (RCV) introduction owing to uncertainty about future financial commitments.

In the Region of the Americas, 423 cases were reported in 2015, mostly related to two outbreaks in Brazil (214 cases), Canada (195 cases) and the United States of America (which did not report any figures in the WHO-UNICEF JRF). More than 80% of reported cases in Brazil and Canada were unvaccinated. With the achievement of one year without endemic measles transmission in Brazil on 6 July 2016, the RVC has reviewed the national report and verified that outbreak interruption has been achieved. As a whole, the region has witnessed high routine MCV1 coverage since 2012 (2012: 94%, 2013: 92%, 2014: 93% and 2015: 94%) with

[11] The global milestones endorsed are to: 1) exceed 90% coverage with the first dose of MCV nationally and exceed 80% vaccination coverage in every district or equivalent administrative unit; 2) reduce annual measles incidence to fewer than five cases per million and maintain that level; 3) reduce measles mortality by 95% or more in comparison with 2000 estimates.

[12] It should be noted that the 90% MVC1 coverage target for 2015 is a milestone towards elimination. In order to achieve the regional elimination targets, vaccination coverage needs to be > 95% for two doses of MCV administered through routine immunization or routine immunization and SIAs. To prevent measles outbreaks, this high level of coverage needs to be achieved uniformly across all districts and across people in all age groups born since the introduction of measles vaccine.

[13] Countries that had introduced MCV2 in 2015 were excluded from this comparison.

heterogeneous coverage at the subnational level where many municipalities have less than 80% coverage. To this end, eight of 11 countries of the Americas had conducted high-quality follow-up campaigns in 2012–2015 (achieving MCV1 coverage > 90%) in order to reduce the pool of susceptible individuals for measles and rubella.

The Eastern Mediterranean Region has seen a downward trend in reported measles cases since 2012 (with total numbers of confirmed cases in 2012, 2013, 2014 and 2015 of 34 504, 20 884, 18 080[14] and 21 335, respectively). A large outbreak of measles in Egypt in 2015 (N=5431) was caused by inadequate coverage in high-risk areas. Iraq experienced a measles outbreak between 2013 and early 2015. However, measles cases there decreased following a national measles SIA in late August 2015. The majority of the reported outbreaks in the Eastern Mediterranean Region affect children under 10 years of age, indicating poor implementation of routine vaccination and poor quality of SIAs.

In the European Region, measles outbreaks affected primarily Bosnia and Herzegovina, Kyrgyzstan and Germany in 2015 (n=25 424) 61% more cases than in 2014 (n=14 176). The majority of the reported cases in 2015 were either unvaccinated or had unknown vaccination status. More than half of those affected were 15 years of age or older but it has to be noted that age distribution was known for only 35% of confirmed cases.

In 2015, measles continued to circulate widely in most countries of the South-East Asia Region (except the Democratic People's Republic of Korea and the Maldives). Bhutan reported 11 cases in 2015, which were later shown to be attributed to multiple independent importations. While the completeness and quality of investigations of suspect cases varied among countries, it is clear that the main cause of continued measles cases was underutilization of measles vaccine. Of the 29 109 cases reported in the region, India continued to report the most confirmed and linked cases (25 488), followed by Nepal *(1599)* and Sri Lanka *(1568)*; Indonesia did not report incidence data in the JRF for 2015 or 2014. Despite this, by the end of 2015 regional coverage with MCV1 had increased to 85% and with MCV2 to 71%. By February 2016 all Member States in the region introduced two-dose MCV into their routine immunization programme.

Measles incidence (per million population) in the Western Pacific Region increased 28% from 27.6 in 2010 to 35.4 in 2015. This is largely the result of endemic transmission in China (N=42 361) and an outbreak in Mongolia (N=20 359), which had no cases during the previous four years. The region is witnessing increased infection and transmission of measles virus among people outside the target group of current immunization strategies for measles elimination (i.e. infants aged < 8 months, adolescents and adults). However, this increase masks the low incidence achieved in 2012 (5.9 per million population) and the peak incidence in 2014 (48.3 per million population) of confirmed cases (71.6 per million population using compatible cases for 2014 as per Table 1.3).

These events illustrate the need for sustained efforts to raise immunization coverage levels and maintain them even in areas where elimination-level control has previously been attained. Every opportunity to address systemic bottlenecks and to increase routine immunization coverage should be seized. The introduction of a routine second dose of MCV and SIAs provide such opportunities. For example, SIAs have been shown to contribute to strengthening the routine immunization programme through improving several aspects including health-worker skills and knowledge, social mobilization, cold chain and logistics and integration of other public health interventions (5, 6).

The establishment of Regional Verification Commissions (RVCs) for measles elimination and their corresponding National Verification Committees (NVCs) has helped to refine the understanding of the barriers to elimination and build stronger national commitment to achieving elimination goals (Table 1.4).

The Region of the Americas has the longest standing RVC. As of December 2015, 98% of its Member States were verified as having achieved measles elimination (Table 1.5). On 6 July 2016, Brazil achieved one year without endemic measles cases, and their national report was reviewed, discussed and approved during a recent RVC meeting, declaring that the measles outbreak interruption has been achieved. The RVC will meet at PAHO-HQ on 4–5 August to assess whether the evidences submitted by the NVCs of all countries and Subregional Verification Committees, are accepted to declare the Americas as free of measles.

At the Western Pacific Region RVC meeting in 2015 (Table 1.6), Australia, Brunei Darussalam, Cambodia, Japan, Mongolia and the Republic of Korea were verified as having achieved or sustained measles elimination based on a verification-standard epidemiological surveillance system supported by accredited laboratories.

In the European Region (Table 1.7), 50 of 53 Member States have established NVCs and at the RVC meeting in October 2015, 21 of the Member States (40%) were documented to have interrupted endemic measles transmission for more than 36 months.

[14] 2014 cases were revised down from 19 099 to 18 080 due to revised JRFs from Egypt and Somalia that became available after the cut-off for the 2015 Secretariat report.

In the Eastern Mediterranean Region, a regional verification guide was drafted but no RVC has yet been established. However, NVCs were established in 15 of 22 Member States. Three countries in the region (Bahrain, Oman and Palestine) are ready for verification, as they have reported few or zero cases for the past three years in the presence of nationwide measles case-based surveillance and high coverage for both MCV1 and MCV2.

The South-East Asian Region has recently established an RVC, and its first meeting is scheduled for August 2016. All countries in the region drafted (and some adopted) national plans of action to achieve the goal of measles elimination by 2020.

Compared to 2014, there has been some progress in terms of the number of regions with RVCs and significant progress in the number of Member States that have established NVCs, particularly in the South-East Asian Region. A total of 137 Member States (71%) are covered by NVCs, a Subregional Verification Committee or a joint Subregional Verification Committee. As yet, there is no RVC in the African Region.

In decreasing order, the following six Member States had the highest number of susceptible infants in 2015: India, Nigeria, Pakistan, Indonesia, Ethiopia and the Democratic Republic of the Congo (Figure 1.10). Those countries accounted for more than two thirds of the measles mortality burden as estimated in 2014 (latest available data).

For these countries, one could highlight the importance of strengthening health systems to achieve higher immunization coverage. Routine MCV1 coverage in these countries has either shown little progress or has declined since 2010, and the reported measles incidence remains high. In addition, discrepancies between administrative data and survey data on immunization coverage, particularly for SIAs, remain an issue (e.g. in 2015, Nigeria reported a 100% coverage rate for an SIA through administrative data, whereas it reported 84% coverage through the SIA coverage evaluation survey).

Conclusion

Although in 2015 some improvement was seen in MCV2 immunization coverage and a small reduction was reported in measles incidence (compared to 2010), based on current trends and programme performance, the 2015 global targets (as well as regional elimination targets in the five WHO regions where measles is still endemic) were not achieved.

Measles is a highly infectious disease, and its elimination requires very high and homogeneous population immunity and a high-quality surveillance system. Without a robust routine programme, elimination is very difficult to achieve and cannot be sustained. For Member States that are now at < 90% coverage nationally, reaching ≥ 95% coverage will require substantial additional investments over a sustained period. The gap between MCV1 and MCV2 coverage highlights the missed opportunities and routine system weaknesses that contribute to suboptimal population immunity and the inability to interrupt measles virus transmission. In 2015, SAGE reaffirmed its previous assessment that the 2015 global measles control milestones as well as regional measles and rubella elimination goals are off-track (except in the Americas). SAGE supported the conduct of a midterm review of the global measles and rubella strategic plan to better understand why targets are being missed and propose measures to accelerate progress.

Table 1.3: Number of measles cases and incidence by WHO region, 2013–2015 and baseline 2010

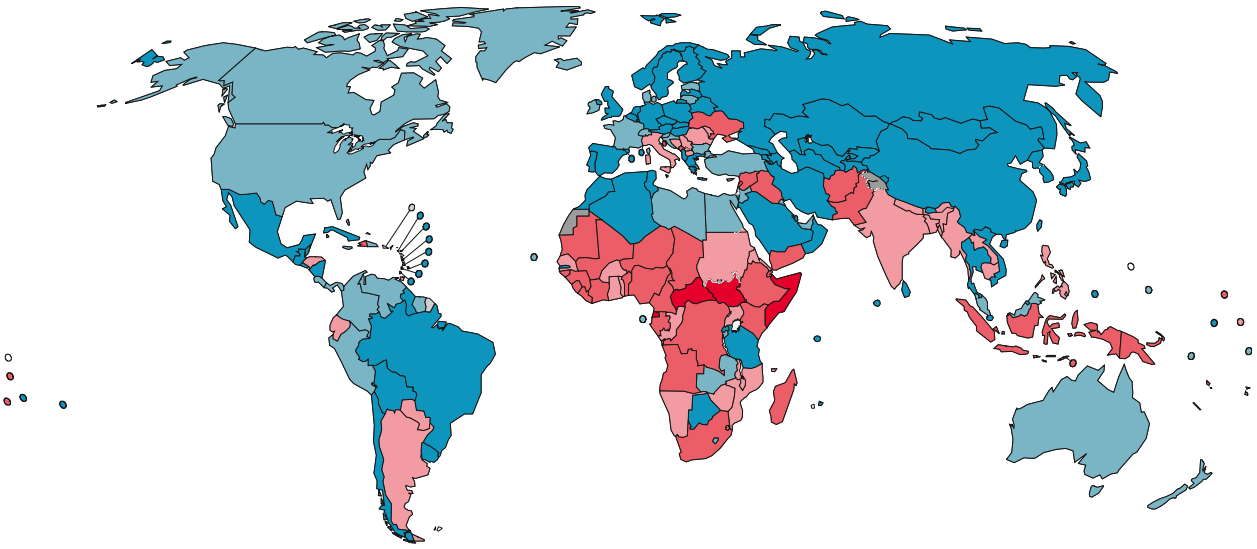
WHO region	MCV1 national coverage (%)					Percentage of Member States reporting measles in their JRF[a]				Measles incidence per million population					Percentage of Member States with incidence less than five per million population				
	2015	2014	2013	2010	% change 2010–2015	2015	2014	2013	2010	2015	2014	2013	2010	% change 2010–2015	2015	2014	2013	2010	% change 2010–2015
African Region	74	72	71	73	+1.4	98	100	100	98	115.3	76.7	182.5	233.0	-51	51	51	53	30	+71
Region of the Americas[b]	94	93	92	92	+1.1	97	100	97	100	0.6	2.0	0.5	0.3	+100	94	97	97	100	-6
Eastern Mediterranean Region	76	76	76	81	-6.6	95	90	86	100	33.5	28.9	34.7	17.5	+91	38	24	24	38	0
European Region	94	94	95	93	+1.1	77	77	87	98	36.3	19.2	33.6	34.2	-6	53	45	58	68	-22
South-East Asia Region	85	85	84	83	+2.4	91	81	100	100	17.4	17.9	16.0	29.9	-42	45	45	45	36	+25
Western Pacific Region	96	97	97	96	0	59	63	74	93	35.4	71.6	17.5	27.6	+28	33	22	48	63	-47
Total	**85**	**84**	**84**	**85**	**0**	**86**	**87**	**91**	**97**	**39.3**	**39.8**	**40.2**	**50.0**	**-21**	**55**	**51**	**58**	**59**	**-6**

[a] List of Member States not reporting JRF measles data: Albania, Andorra, Cook Islands, Fiji, Finland, Greece, Indonesia, Kiribati, Libya, Marshall Islands, Mauritius, Monaco, Montenegro, Nauru, Netherlands, Niue, Oman, Poland, Portugal, Samoa, San Marino, Singapore, Solomon Islands, Turkey, Tuvalu, Ukraine, USA. (NB: Turkey, Ukraine and Tuvalu submitted their JRF after 24 June 2016, the deadline for submission into the GVAP report).

[b] For the Region of the Americas, the incidence columns refers to suspected/confirmed measles cases.

Source: JRF (as of 24 June 2016) and WHO-UNICEF estimates, 1980–2015, July 2016 revision.

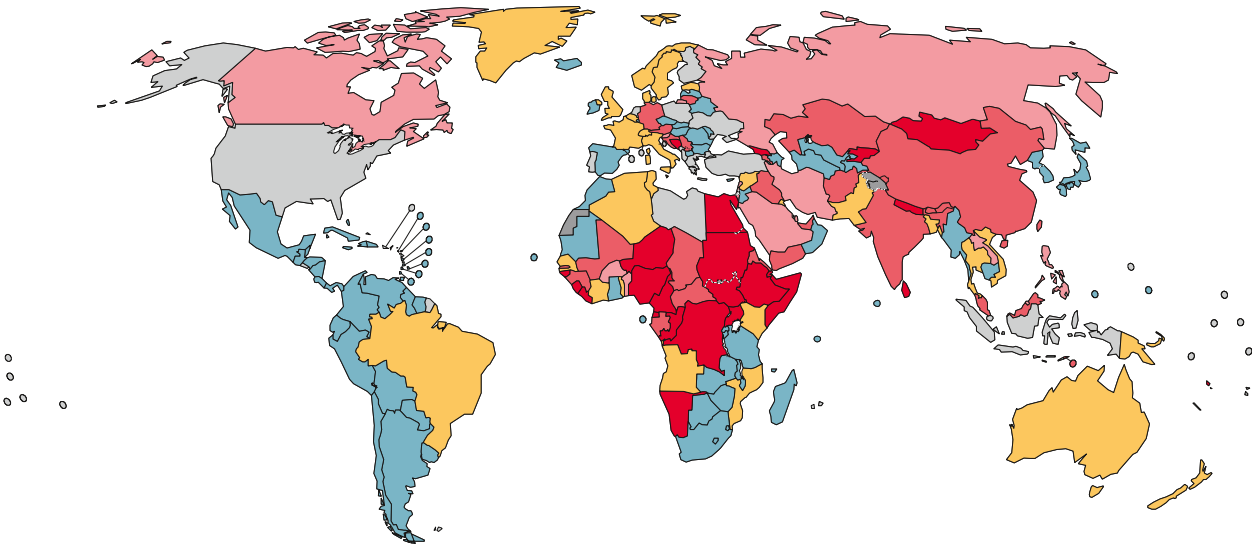
Figure 1.7: Immunization coverage (%) with MCV1 in infants per country, 2015



<50% *(4 countries or 2%)*
50–79% *(38 countries or 20%)*
80–89% *(33 countries or 17%)*
90–94% *(40 countries or 21%)*
≥95% *(79 countries or 40%)*
Not available
Not applicable

Source: WHO-UNICEF coverage estimates, 2016 revision.

Figure 1.8: Reported measles incidence rate[a] per country, 2015

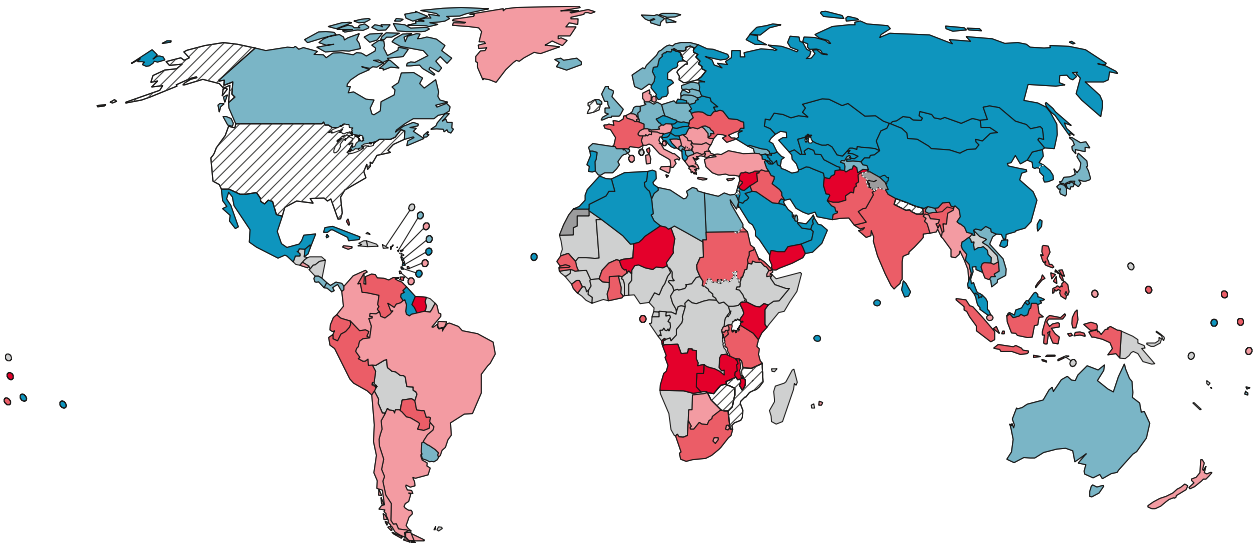


<1 (*78 countries or 40%*)
>1 to <5 (*28 countries or 14%*)
>5 to <10 (*13 countries or 7%*)
>10 to <50 (*23 countries or 12%*)
≥ 50 (*24 countries or 13%*)
Not available/No data reported to WHO Headquarters (*28 countries or 14%*)
Not applicable

[a] Per million population

Source: JRF data as of 24 June 2016.

Figure 1.9: Immunization coverage with routine MCV2 by national schedule for infants, 2015



Source: WHO-UNICEF coverage estimates, 2016 revision.

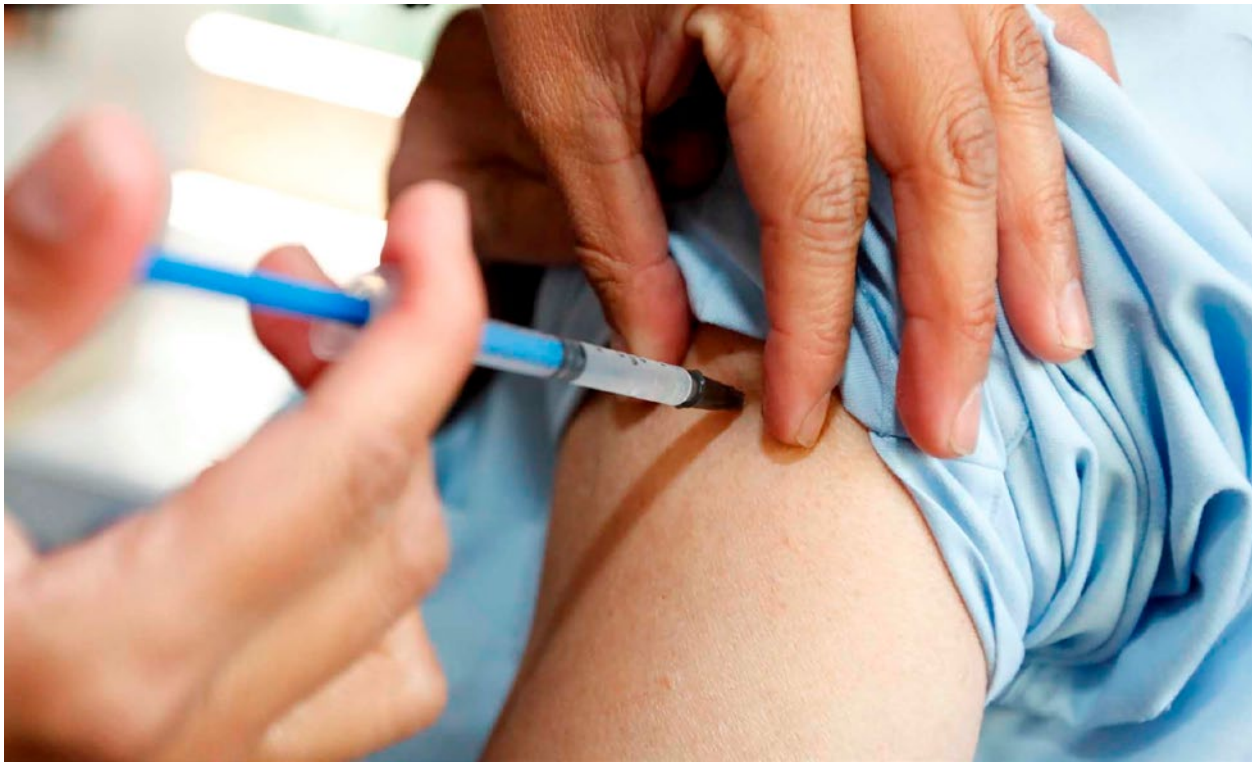


Table 1.4: Progress towards measles elimination, by WHO region (as of 31 December 2015)

WHO region	Target year for measles elimination in region	RVC established	Regional measles elimination verification report provided in 2015 by RVC for 2013/2014 data	Member States that have established an NVC n (% of total)	Established NVCs that submitted annual status reports n (% of total)[a]	Member States that were verified free of endemic measles based on 2015 reporting n (% of total)[b]
African Region	2020	No	No	None	Not applicable	Not applicable
Region of the Americas[e]	2000	Yes	Verification reports sent in 2013 (with 2002-2011 data)	24 (100)	24 (100)	43/44 (98)
Eastern Mediterranean Region	2020	No	No	15 (68)	Not applicable	Not applicable
European Region	2015	Yes	Yes (for 2014)	50 (94)	50 (100)	32 (60)[c]
South-East Asia Region	2020	Yes	No, first meeting in August 2016	10 (91)	Not applicable	Not applicable
Western Pacific Region	2012	Yes	Yes (for 2014)	27[d] (100)	17 (100)[d]	6 (22)

[a] Percentage is out of the total number of established NVCs, not the total number of Member States.

[b] Percentage is out of the total number of Member States, not the total number of established NVCs.

[c] Twenty-one of these countries were verified as having been free of endemic measles for 36 months or longer, and the other 11 were documented to have interrupted endemic measles transmission for at least 12 months (see Table 1.7).

[d] 13 Pacific island countries formed one joint Subregional Verification Committee (they are: Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Samoa, Solomon Islands, Tonga, Tuvalu and Vanuatu). China, Hong Kong SAR and China, Macao SAR established their own Committees in addition to the Chinese NVC. There are a total of 16 NVCs and 1 Subregional Verification Committee for the 27 Member States in the Western Pacific Region.

[e] Countries in the Americas are not providing National Verification Committee reports annually as both measles and rubella have been eliminated. In 2016, 22 of 24 NVCs submitted (for the second time) verification reports with 2012-2015 data. The RVC will meet in August 2016 to review these reports and assess the feasibility of declaring the Americas free of measles.

Table 1.5: Progress towards measles elimination in the Region of the Americas (as of 31 December 2015)

Status according to Pan American Health Organization (PAHO) Region definitions[a]	Number of countries/ territories (% of total)	Countries/territories
Measles elimination verified	43 (98)	34 countries + 6 overseas territories of the United Kingdom + 3 Dutch autonomous territories
Interrupted endemic transmission for ≥ 12 months but < 36 months	1 (2)	Brazil

[a] Pan American Health Organization (PAHO) Region definitions:

- Measles elimination verified: Verify interruption of endemic measles, rubella and congenital rubella syndrome cases in all countries of the Americas for a period of at least 3 years from the last known endemic case, in the presence of high-quality surveillance.
- Interrupted endemic transmission for ≥ 12 months: Absence of endemic measles transmission for a period equal or greater than 12 months, in the presence of a well-performing surveillance system. The RVC will meet in August 2016 to assess if the Americas can be declared free of measles.

Table 1.6: Progress towards measles elimination in the Western Pacific Region (as of 31 December 2015)

Status according to Western Pacific Region definitions[a]	Number of countries (% of total)	Countries
Elimination verified	6 (22)	Australia, Brunei Darussalam, Cambodia, Japan, Mongolia, Republic of Korea
Possibly ready for verification, but additional data required	2 (7)	New Zealand, Singapore
Does not yet fulfil the criteria for verified elimination	19 (71)	China[b], Lao People's Democratic Republic, Malaysia, Pacific islands subregion (Cook Islands, Fiji, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu), Papua New Guinea, Philippines, Viet Nam

[a] Western Pacific Region definitions:

- Elimination verified: The interruption of endemic measles virus transmission for ≥ 36 months in the presence of verification-standard surveillance and genotyping evidence that supports the interruption of endemic measles virus transmission. Australia, Macao (China), Mongolia and the Republic of Korea were verified again in March 2015 (as well as in March 2014) as having interrupted measles virus transmission for more than 3 + 1 years. Brunei Darussalam, Cambodia and Japan were verified in March 2015 as having interrupted measles virus transmission for more than 3 years. Note: As the next RVC meeting will be held in September 2016, the measles outbreak in Mongolia that started in March 2015 and lasted until June 2016 has not yet been discussed by the RVC.
- Possibly ready for verification, additional data required: After reviewing the first reports prepared by the NVCs, the RVC determined that interruption may have been achieved, but more detailed epidemiological data were needed to verify measles elimination.
- Endemic transmission: The existence of continuous transmission of indigenous or imported measles virus that persists for ≥ 12 months in the nation.

[b] Data apply to all parts of China excluding China, Hong Kong SAR and China, Macao SAR. Elimination has been verified for China, Macao SAR. China, Hong Kong SAR may be ready for verification of elimination, but additional data are needed.

Table 1.7: Progress towards measles elimination in the European Region (as of 31 December 2015)

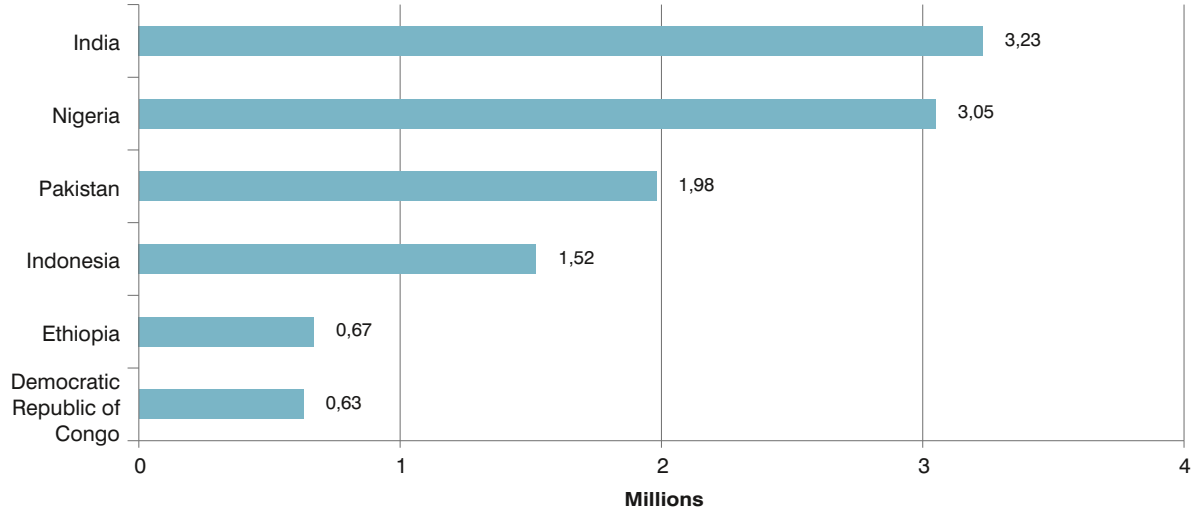
Status using European Region definitions[a]	Number of Member States (% of total)	Member States
Interrupted endemic transmission for ≥ 36 months	21 (40)	Andorra, Armenia, Azerbaijan, Belarus, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Hungary, Israel, Latvia, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Slovenia, Sweden, Turkmenistan
Interrupted endemic transmission for ≥ 12 months but < 36 months	11 (21)	Croatia, Denmark, Greece, Iceland, Lithuania, Montenegro, Republic of Moldova, Spain, Tajikistan, United Kingdom of Great Britain and Northern Ireland, Uzbekistan
Endemic transmission[b]	18 (34)	Austria, Belgium, Bosnia and Herzegovina, France, Georgia, Germany, Ireland, Italy, Kazakhstan, Kyrgyzstan, Poland, Romania, Russian Federation, Serbia, Switzerland, The former Yugoslav Republic of Macedonia, Turkey, Ukraine
No report submitted	3 (6)	Albania, Monaco, San Marino

[a] European Region definitions:

- Interrupted endemic transmission for ≥ 36 months: Absence of endemic measles transmission from 2012–2014 in the presence of a well-performing surveillance system.
- Interrupted endemic transmission for ≥ 12 months but < 36 months: Absence of endemic measles transmission at least in 2015 in the presence of a well-performing surveillance system.
- Endemic transmission: Continuous transmission of indigenous or imported measles virus that has persisted for a period of 12 months or more in the Member State. (Note: this definition differs from that stated in the WHO Weekly Epidemiological Record.)
- No report submitted: Not available because the country does not have a functioning NVC or it failed to submit the annual status report.

[b] Italy, Serbia, The former Yugoslav Republic of Macedonia and Ukraine submitted reports with missing documentation.

Figure 1.10: Countries with the largest numbers of infants unvaccinated with MCV1, 2015



Source: WHO-UNICEF coverage estimates, 2016 revision.

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GOAL 2: Achieve rubella and CRS elimination (Indicator G2.2)

Highlights

- The number of countries using RCV in their national programme continues to increase. As of December 2015, 149 Member States had introduced rubella vaccines into their routine immunization programme; coverage, however, varies from 12% to 94% depending on region.
- Ten member States are planning to introduce RCV in 2016.
- In April 2015, the International Expert Committee for Measles and Rubella Elimination in the Americas verified that the region had eliminated the endemic transmission of rubella and congenital rubella syndrome (CRS).
- Rubella and CRS surveillance systems are weak and cases remain underreported, particularly in Member States that have not yet introduced RCV and/or do not have rubella control or elimination goals. Hence, global rubella and CRS surveillance data do not reflect the true burden of these diseases.

DEFINITION OF INDICATOR	• Rubella and CRS elimination: The absence of endemic rubella virus transmission in a defined geographical area (e.g. region or country) for > 12 months and the absence of CRS cases associated with endemic transmission in the presence of a well-performing surveillance system **Note 1:** There may be a time lag (up to 9 months) in occurrence of CRS cases after interruption of rubella virus transmission has occurred. Evidence of the absence of continuing rubella transmission from CRS cases is needed because infants with CRS can transmit the rubella virus for up to 12 months after birth **Note 2:** Verification of rubella elimination takes place after 36 months of interrupted rubella virus transmission
TARGET	• Region of the Americas: Rubella eliminated in 2009 and the International Expert Committee for Measles and Rubella Elimination verified the Region free from rubella and CRS in April 2015 • European Region: Rubella elimination by 2015 • Western Pacific Region: Rubella elimination but no target date set • South-East Asia Region: Rubella control by 2020 • African Region: No target set • Eastern Mediterranean Region: No target set
DATA SOURCES	• WHO-UNICEF joint reporting forms (JRFs) for disease incidence and WHO-UNICEF Estimates of National Immunization Coverage (WUENIC) data for coverage rates are subject to the same limitations as all other data submitted via the JRFs, as described in the 2015 report of the GVAP Secretariat *(2)* • There are no WHO-UNICEF estimates for rubella coverage. The first dose of measles-containing vaccine (MCV1) is used as a proxy in the Member States that have introduced rubella vaccine (as all the Member States use combined vaccines for first dose of rubella except for the Russian Federation)
COMMENTS ON DATA QUALITY	• None

Background and progress

As of December 2015, 149 Member States (77%) had introduced RCV, a 59% (55 countries) increase from 2000 (Figure 1.11 and Figure 1.12). Average coverage globally has gradually increased from 35% in 2010 to 46% in 2015. However, it varies from 12% in the African Region to 94% in the European Region and Region of the Americas (Table 1.8). In 2015, an additional seven Member States introduced rubella vaccine in their routine programme.[15] Introduction of rubella vaccine is ongoing in eleven Member States,[16] and four Member States (Kenya, Mozambique, Sierra Leone, Togo) plan to introduce the vaccine in 2017.

In 2015, the global incidence of rubella was estimated to be 3.3 per million population (reported by 158 Member States; Table 1.8 and Figure 1.13). Note that the total number of Member States reporting rubella incidence to WHO has decreased dramatically in recent years, from 176 (91%) in 2012 to 158 (81%) in 2015, which in part explains the appearance that rubella incidence is decreasing (Table 1.8).

In total 120 (62%) Member States reported CRS figures for 2015 compared with 115 (59%) for 2014 (Table 10). While this is an improvement, the very low reported incidence is probably more a sign of the almost non-existent CRS surveillance systems outside the Region of the Americas and a few other Member States than a reflection of true disease burden.

Regional review

The Region of the Americas achieved rubella and CRS elimination in 2009; the last endemic rubella case was reported on 2009 in Buenos Aires, Argentina and the last endemic CRS case was reported in 2009 in Brazil. In 2015, the region was verified as having eliminated rubella and CRS.

A total of 52 Member States in the European Region use the combined measles–mumps–rubella (MMR) vaccine, and Tajikistan is using measles–rubella (MR) vaccine in a two-dose schedule. Based on JRF data, the number of rubella cases reported in the region dropped by 99% between 2013 (n=39 614) and 2015 (n=385), but the JRF data cannot be considered accurate due to underreporting. For example, most rubella cases occurred in Poland even though Poland did not reported cases on the JRF. At its October 2015 meeting, the RVC concluded that 18 countries in the region continued to have endemic transmission (with three countries not reporting). Countries that did report cases through the JRF included Kyrgyzstan (n=100), Georgia (n=100) and Germany (n=90).

The decrease in cases reported between 2014 and 2015 is primarily the result of a decrease in cases reported by Poland (which did not report cases for 2015), despite lack of a response measure to control the outbreak. The outbreak in Poland started in 2010 and was caused by aggregation of susceptible cohorts in the context of gender-specific immunization in the past, and late introduction of the two-dose MMR schedule. As indicated in its annual status update reports, Poland reported 5891 rubella cases for 2014 (it has to be noted that there is some discrepancy between annual status update and JRF data). The outbreak mostly affected adolescent/young adult men, with 37% of those affected by rubella being 15 years of age and older.

In 2014, the Regional Committee for the Western Pacific endorsed the Regional Framework for Implementation of the Global Vaccine Action Plan in the Western Pacific and its specified immunization goals, including the regional rubella elimination goal (target date to be determined). At the regional meeting of the Technical Advisory Group (TAG) in June 2015, a recommendation was made to establish 2020 as the target date for elimination of rubella in the region. The number of reported rubella cases has been declining in the Western Pacific Region since 2011 (from 76 022 in 2011 to 9398 in 2015) with the majority of cases being reported from China, Viet Nam, Japan and the Philippines. Reported CRS cases have also declined in the region (45 in 2013 and 5 in 2015) with most cases being reported from Viet Nam (n=4). CRS surveillance has not been established by some countries in the region.

The South-East Asia Region has made significant progress towards rubella and CRS control. In February 2016, eight of 11 Member States introduced RCV into their routine immunization programme. The remaining three member States (the Democratic People's Republic of Korea, India and Indonesia) have plans to introduce RCV before 2018 and preparations are ongoing. In 2015, 4119 confirmed cases of rubella were reported. India continued to report the most confirmed cases *(3252)*, followed by Nepal *(626)* and Bangladesh *(189)*, while Indonesia did not report any data in the JRF. Surveillance for CRS only started as a WHO-supported activity after the September 2013 Regional Committee resolution and all countries in the region have agreed

[15] Burkina Faso, Myanmar, Papua New Guinea, Vanuatu, Viet Nam, Yemen and Zimbabwe.
[16] Botswana, Burundi, Cameroon, the Gambia, Lesotho, Malawi, Namibia, Sao Tome and Principe, Swaziland, Timor-Leste and Zambia.

in principle to establish sentinel surveillance for CRS. Of the confirmed rubella outbreaks, 87% *(91)* were from India.

Although the Eastern Mediterranean Region has not yet set a rubella elimination goal, 13 countries (60%) have set a national target for rubella/CRS elimination and 11 countries are now implementing CRS surveillance. In 2015, 1885 confirmed cases of rubella were reported by the countries in the region. The majority of these (95%) were reported from four countries (Sudan, Pakistan, the United Arab Emirates and Yemen), two of which (Sudan and Pakistan) have not yet introduced RCV. So far, only one of the six Gavi-eligible countries in the region (i.e. Yemen) has benefited from Gavi Alliance support to conduct SIAs of RCV (completed in 2015).

The African Region does not have a rubella control or elimination target and, in 2015 reported 5302 cases of rubella. This is not surprising given the low uptake of RCV in the region. By the end of 2015, seven (15%) of the countries had introduced RCV and another five countries are planning to introduce RCV in 2016.

Conclusion

A new phase of accelerated rubella control and CRS prevention has begun, marked by the 2011 WHO position paper, which recommended a strategy consistent with rubella and CRS elimination *(3)*, the inclusion of rubella elimination in five WHO regions by 2020 as a disease control target in the Global Vaccine Action Plan *(2012)* and Gavi Alliance support for the introduction of rubella vaccine in countries meeting the eligibility criteria. However, failure to fully integrate prevention of rubella and CRS with measles elimination activities represents a major missed opportunity for immunization and integrated disease surveillance.

The key challenges to elimination are:

a. building support for additional regions to adopt elimination goals, which includes ensuring that all Member States can achieve and maintain the minimum coverage (≥ 80%) through routine services and/or in SIAs required for introduction of RCV;
b. advocating for resources and a secure vaccine supply needed to meet the European Region's elimination goal;
c. ensuring high routine coverage of RCV (because of the use of combined MR or MMR vaccines, the programmatic target for RCV1 and RCV2 coverage is ≥ 95%);
d. ensuring high-quality MR SIAs that reach at least 95% of targeted children, as verified through surveys; and
e. strengthening synergies between rubella and measles surveillance and expanding CRS surveillance.

Commitment at all levels of government as well as involvement of the private sector is needed to address these challenges. For Gavi-eligible countries, the challenge is in capitalizing on the available resources for RCV introduction while ensuring sufficient political and financial commitment to assure the sustainability of the programme.

Financial support from the Gavi Alliance and the Vaccine Alliance together with the leadership, coordination and technical expertise from the Measles & Rubella Initiative (M&RI), provide an opportunity for Member States and regions to accelerate progress in rubella control and CRS prevention. Rubella elimination has been achieved and verified in the Americas; the European Region is the next region closest to achieving rubella elimination. Substantially greater commitment and investment by Member States and the global immunization community will be required to reach the GVAP target of rubella elimination in five regions by 2020.

Table 1.8 and Table 1.9, as well as Figure 1.11, Figure 1.12, and Figure 1.13 provide data on cases of rubella and CRS.

Table 1.8: Rubella cases and incidence by WHO region, 2013–2015 and baseline (2010)

WHO region	National rubella coverage (%)				Member States reporting rubella cases (%)				Rubella incidence per million population			
	2015	2014	2013	2010	2015	2014	2013	2010	2015	2014	2013	2010
African Region	12	9	4	0	94	94	91	79	5.6	7.8	15.1	3.9
Region of the Americas[a]	94	93	92	93	97	100	97	100	0.0	0.0	0.0	0.0
Eastern Mediterranean Region	45	42	38	38	86	90	86	81	3.0	4.7	6.6	3.5
European Region	94	94	95	93	72	72	81	92	0.6	1.0	62.8	14.3
South-East Asia Region	14	12	12	3	82	91	100	82	2.6	5.0	5.5	26.1
Western Pacific Region	89	90	88	61	56	59	67	85	5.1	7.0	18.5	27.1
Total	**46**	**44**	**42**	**35**	**81**	**84**	**86**	**88**	**3.3**	**4.8**	**14.9**	**15.0**

Note: MCV1 was used as a proxy in the Member States that have introduced rubella vaccine.

[a] For the Region of the Americas, the cases and incidence columns refers to suspected/confirmed rubella cases.

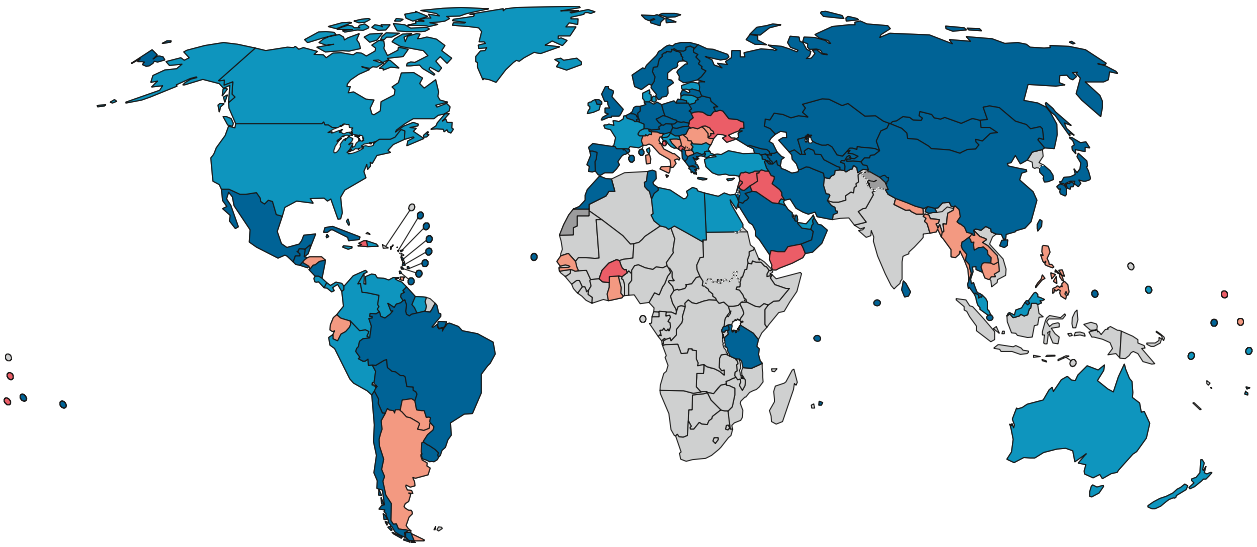
Source: JRF (as of 24 June 2016) and WHO-UNICEF estimates, 1980–2015, revision July 2016.

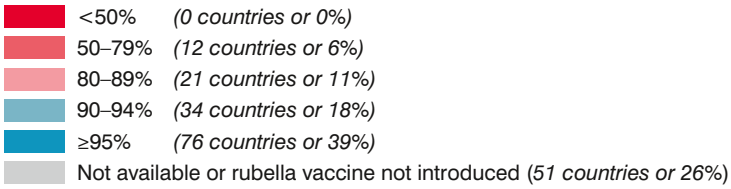
Table 1.9: CRS cases and incidence by WHO region, 2012–2015

WHO region	Member States reporting CRS cases (%)				CRS incidence per million population			
	2015	2014	2013	2010	2015	2014	2013	2010
African Region	49	36	34	32	0.28	0.08	0.03	0.13
Region of the Americas	94	100	97	100	0	0	0	0
Eastern Mediterranean Region	48	38	52	48	0	0.01	0.06	0.03
European Region	68	64	83	83	0.01	0.05	0.07	0
South-East Asia Region	64	64	55	36	0.58	0.37	0.08	0.09
Western Pacific Region	41	44	52	70	0.02	0.04	0.13	0
Total	**62**	**59**	**64**	**65**	**0.10**	**0.06**	**0.05**	**0.01**

Source: JRF (data as of 24 June 2016).

Figure 1.11: Immunization coverage with rubella-containing vaccines[a] in infants, 2015

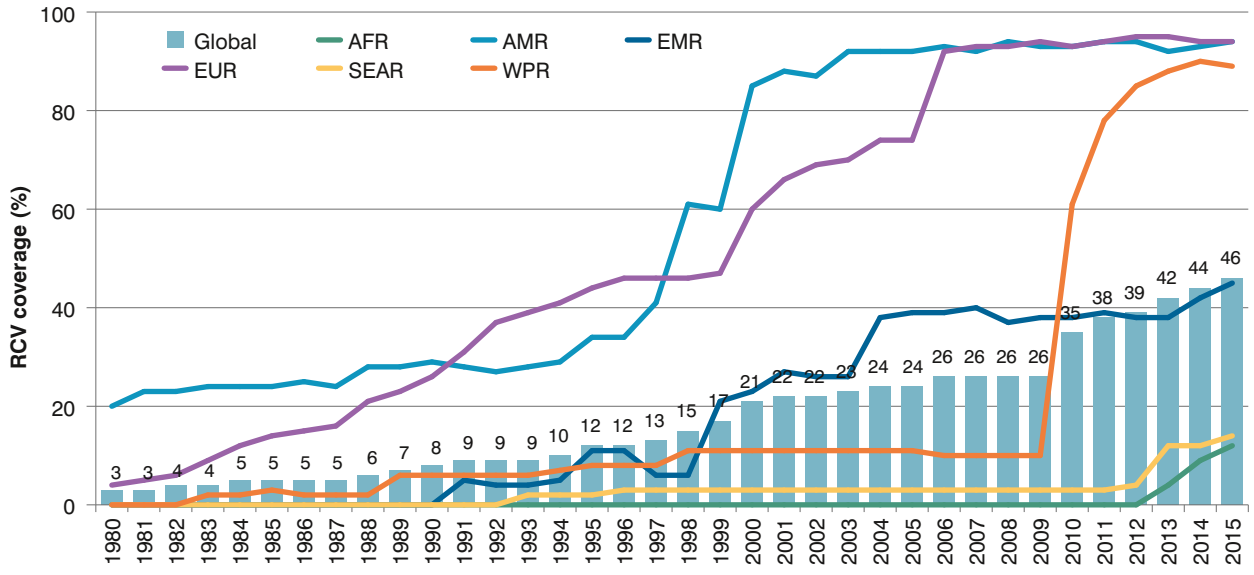




[a] Coverage estimates for the 1st dose of rubella-containing vaccine are based on WHO and UNICEF estimates of coverage of measles-containing vaccine.

Source: WHO-UNICEF coverage estimates, 2016 revision.

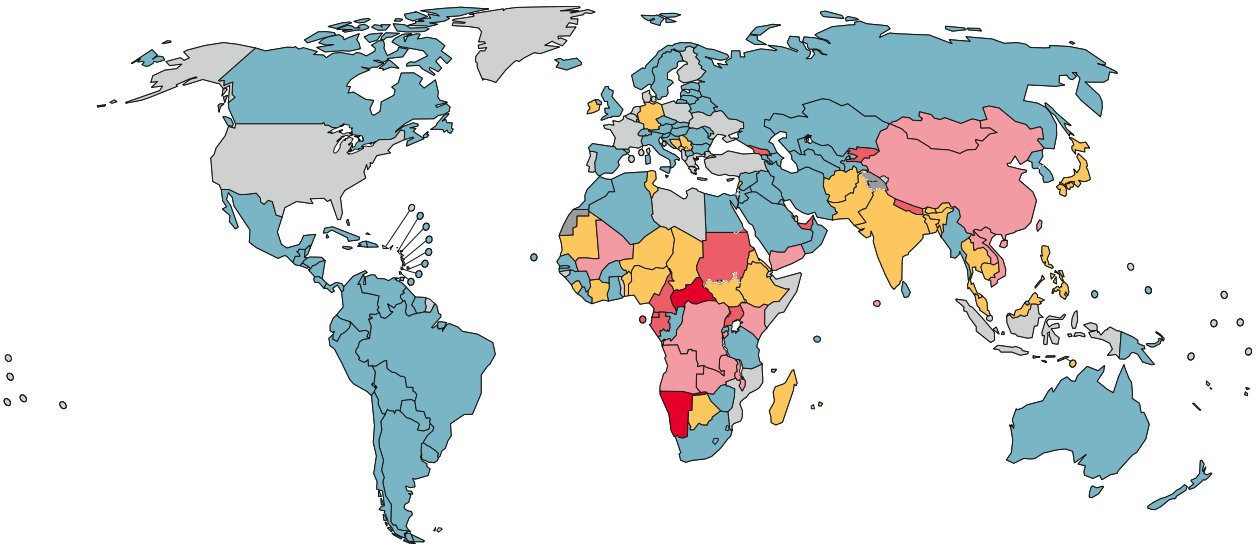
Figure 1.12: Rubella-containing vaccine coverage[a] by WHO region, 1980–2015

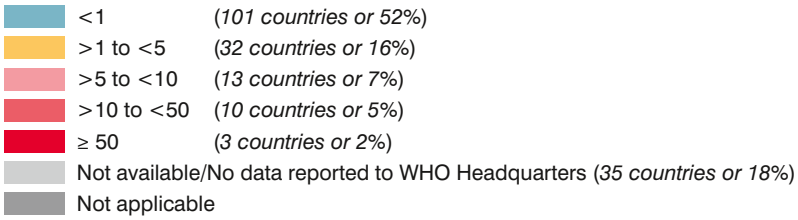


[a] Coverage estimates for the 1st dose of rubella-containing vaccine are based on WHO and UNICEF estimates of coverage of measles-containing vaccine.

Source: WHO-UNICEF coverage estimates, 2016 revision.

Figure 1.13: Reported rubella incidence rate[a] per country for 2015





[a] Per million population

Source: Joint Reporting Form as of 24 June 2016

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2. Global Vaccine Action Plan. Monitoring, evaluation & accountability: Secretariat annual report 2014. Geneva: World Health Organization; 2013 (http://www.who.int/immunization/global_vaccine_action_plan/gvap_secretariat_report_2014.pdf?ua=1, accessed 12 July 2016).
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2. IMMUNIZATION COVERAGE

Note to the reader

Progress against the GVAP goals and strategic objectives related to immunization coverage has been consolidated into a single report, as was done in the previous report on the recommendation from the SAGE Decade of Vaccines working group.

As in the previous report, and as per the SAGE working group recommendation, the data for the following indicators are no longer reported as separate indicators, but included in the overall progress with coverage:

- Indicator SO3.1: percentage of districts (or equivalent administrative units) with 80% or greater coverage with three doses of DTP
- Indicator SO4.1: DTP1-DTP3 dropout rate for national coverage
- Indicator SO4.2: 3 years sustainability of DTP3 national coverage ≥ 90%

It has to be noted that the SAGE Decade of Vaccines working group also recommended to stop monitoring Indicator SO4.3: "Immunization coverage data assessed as high quality by WHO and UNICEF" as the information provided was not relevant to quality of data provided by the countries but rather to the level of confidence of WHO and UNICEF in their own estimates. The difficulty to establish an indicator measuring the quality of the data provided by the countries also led the SAGE Decade of Vaccines working group to recommend that this be assessed at the country level using existing in-depth data quality assessment tools with partners support.

The three major sources of data for this report are:

- WHO-UNICEF Joint Reporting Form on Immunization (JRF), which collects national-level data from countries on reported cases of selected vaccine preventable diseases; recommended immunization schedules; immunization coverage; vaccine supply; and other information on the structure, policies and performance of national immunization systems;
- WHO-UNICEF Estimates of National Infant Immunization Coverage (WUENIC), which are derived from various data sources, including coverage data from the JRFs; and
- WHO Health Equity Monitor database of the Global Health Data Observatory data repository (data from DHS and MICS).

The estimates are based on data and information available to WHO or UNICEF as of 15 July 2016.

The data are available from both WHO and UNICEF web sites: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html and http://www.data.unicef.org/child-health/immunization.

An explanation of how to interpret the country profiles is also available: http://www.who.int/entity/immunization/monitoring_surveillance/routine/coverage/User_Ref_Country_Reports.pdf and http://www.childinfo.org/files/Immunization_WUENIC_guide_and_mark-up.pdf.

The GVAP assessment compares progress against indicators across time and using different country classifications. However, it has to be noted that the list of WHO Member States[17], the World Bank country classification[18] as well as the list of Gavi-eligible countries[19] have evolved over the time periods under consideration, affecting to different degrees, comparisons of indicators' results by regions, income groups and Gavi Alliance eligibility. Thus, within the GVAP 2015 report, comparisons across years were limited to the most relevant ones that were not widely impacted by these differences in classification.

Readers need to be aware as well that the entire time series of coverage estimates may be updated for certain countries based on the availability of new data that affect the coverage estimates over a period of time (e.g. a new coverage survey, an update sent by the Member States or data submitted late the previous year). Thus, the estimates of coverage for 2015 in this report may not be the same as those in the previous report. The coverage estimates for 2015 must, therefore, be compared with the 2014 estimates in the updated time series.[20, 21, 22]

For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report

[17] List of WHO Member States is available at: http://www.who.int/countries/en/
[18] World Bank country classification is available at: http://data.worldbank.org/about/country-and-lending-groups.
[19] List of Gavi-eligible countries is available at: http://www.gavi.org/support/apply/countries-eligible-for-support/.
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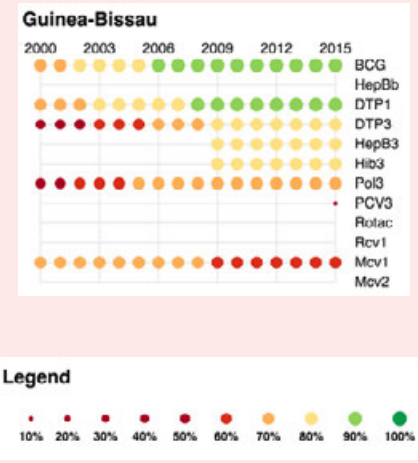
[21] Burton A, Kowalski R, Gacic-Dobo M, Karimov R, Brown D. A formal representation of the WHO and UNICEF Estimates of National Immunization Coverage: a computational logic approach. PLoS One. 2012; 7(10):e47806 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3485034/pdf/pone.0047806.pdf, accessed 12 August 2016).
[22] Brown D, Burton A, Gacic-Dobo M, Karimov R. An introduction to the grade of confidence in the WHO and UNICEF Estimates of National Immunization Coverage. The Open Public Health Journal. 2013; 6:73–76, http://www.benthamopen.com/ABSTRACT/TOPHJ-6-73, accessed August 2016).

2013, Annex 1 on "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC" (pp. 133–137), available online: http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1.

National Immunization coverage score cards 2000-2015

Please note that for all Member States, national immunization coverage rates are depicted graphically in Annex 2.1, showing the progress made by the country for individual vaccines since the year 2000.



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Visualization of GVAP indicators

Please note that for all the coverage indicators, the GVAP Secretariat has provided interactive maps and graphs that will help the reader to better understand and explore the data.

To access these interactive figures/dashboard please use the Technet21 platform:

http://www.technet-21.org/en/resources/gvap-indicators

When looking at the data, please hover over the dots, bars and countries; change the year; use the filters; use zoom, etc. to view additional information in the background.

For example, for the graph showing the relationship between DTP1 and DTP3, by filtering by region and then hovering over the circles, one can see which country the circles represent.

GVAP COVERAGE INDICATORS

Goal/Strategic Objective	Indicators
Goals	
G3 **Meet vaccination coverage targets in every region, country and community**	G3.1 Reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria–tetanus–pertussis-containing vaccines
	G3.2 Reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended
Strategic Objectives (SOs)	
SO3 **The benefits of immunization are equitably extended to all people**	SO3.1 Percentage of districts with 80% or greater coverage with three doses of diphtheria–tetanus–pertussis-containing vaccine **Included in the G3.1 coverage indicator section**
	SO3.2 Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s)
SO4 **Strong immunization systems are an integral part of a well-functioning health system**	SO4.1 Dropout rates between first dose (DTP1) and third dose (DTP3) of diphtheria–tetanus–pertussis-containing vaccines **Included in the G3.1 coverage indicator section**
	SO4.2 Sustained coverage of diphtheria–tetanus–pertussis-containing vaccines 90% or greater for three or more years **Included in the G3.1 coverage indicator section**
	SO4.3 Immunization coverage data assessed as high quality by WHO and UNICEF **This indicator is no longer monitored as recommended by the SAGE DoV WG**

GOAL 3:
Meet vaccination coverage targets in every region, country and community

Number of Member States that reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria–tetanus–pertussis-containing vaccines (Indicator G3.1)

Highlights

- A total of 126 (65%) of the Member States reached national DTP3 coverage of ≥ 90% in 2015 (the number of countries that have achieved and sustained coverage ≥ 90% over the past three years was 115).
- While WHO and UNICEF estimates showed that 126 countries had DTP3 coverage of 90% or more at the national level, only 88 of these countries reported subnational coverage data that were considered valid. Of these, only 52 countries (27%) had coverage of 80% or more in all districts and therefore are meeting the GVAP target.
- In 2015, 86% of the world's children received the required three doses of DTP – the global coverage level has been sustained above 85% since 2010. The estimated number of un- and under-vaccinated infants in 2015 was 19.4 million – the lowest reported in the past five years.
- The 68 countries that are yet to achieve the target will require innovative strategies in order to meet the GVAP goal – particularly among the six countries with less than 50% DTP3 coverage: the Central African Republic, Equatorial Guinea, Somalia, South Sudan, the Syrian Arab Republic and Ukraine.

DEFINITION OF INDICATOR	**National coverage data based on WUENIC estimates** **For district-level coverage, the data are considered valid only if the WUENIC estimates and administrative data from the JRF are the same or if the WUENIC estimates are ≥ 90%**
TARGET	**2015 in all Member States**
DATA SOURCES[23]	**WUENIC estimates** **Administrative data from country JRFs (to compare with WUENIC estimates as a check of validity)**

[23] For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).

Data availability and quality

By the end of 2015 most countries were using combination vaccines (either DTP-Hib-HepB, DTP-Hib-IPV or DTP-Hib-HepB-IPV) so the generic DTP3 term used in the report includes DTP3 alone or all DTP3-containing vaccines.

Though WUENIC data are available every year and can be used to monitor progress against achievement of target coverage at the national level, the full assessment of progress in national DTP3 coverage is limited by the availability of valid district-level coverage data. In this assessment, district-level coverage data were considered valid if WUENIC estimates are the same as the administrative coverage data reported by national authorities on the JRF, or if the WUENIC estimates of national coverage are 90% or greater.

Using this definition, 112 Member States (58%) had valid DTP3 district-level coverage estimates in 2015. Of the remaining 82 Member States, 39 have WUENIC estimates that differ from the JRF administrative data or have national coverage < 90%, and are therefore not considered valid, and 43 did not report district-level coverage. Relative to the previous years when 99 countries had valid data in 2014, there was an increase in the number of Member States that had valid DTP3 district-level coverage estimates in 2015. The number of countries that did not report district-level coverage increased from 39 to in 2014 to 43 in 2015. The number of countries with invalid district-level coverage data decreased to 39 in 2015 as compared to 56 in 2014 and 2013.

Results

National DTP3 Immunization coverage

Of the 194 Member States, 126 (65%) achieved a national DTP3 coverage rate of ≥ 90% in 2015 (Table 2.1). The distribution was uneven between regions. As compared to 2014, the rates show an increase in coverage rates in the Western Pacific Region (7%), the Region of the Americas (3%) and in the Eastern Mediterranean Region (5%). There was a coverage drop in the African Region (6%) and in the European Region (3%), respectively. Coverage levels in the South-East Asia Region remain unchanged.

Eight additional countries[24] achieved the coverage target, with DTP3 ≥ 90% in 2015. There was an increase in DTP3 coverage with ≥ 10% as compared to 2014 in the following five countries: Gabon, Haiti, Kiribati, Qatar and the Solomon Islands.

Countries such as the Congo, Dominican Republic, Ghana, Iraq, Mali, Mauritania, Panama, the Philippines, South Sudan and Swaziland have experienced recent declines in coverage (5–11%) with the Philippines reporting -19% as compared to 2014. Main causes are vaccine stock-outs, disease outbreaks or conflicts.

A total of 115 countries sustained DTP3 coverage ≥ 90% for 3 years in 2015 (Figure 2.1), which is less than in 2014 when 118 countries were able to sustain this level of coverage. National coverage data are also presented by country in Annex 2.1. Global coverage for DTP3 was 86% in 2015 (Figure 2.2). While this is 1% higher than the coverage reported in the previous report, when viewed through the updated time series, the coverage has stagnated for the past 5 years.

The total number of children unvaccinated has decreased globally from 20.6 million in 2013 to 20.0 million in 2014 and 19.4 million in 2015 (Figure 2.3), mainly though the important reduction of unvaccinated children in India (4.2 million in 2013, 3.7 million in 2014 and 3.2 million in 2015) and Nigeria (3.5 million in 2013, 3.3 million in 2014 and 2.9 million in 2015), (Figure 2.4 and Figure 2.5). The numbers show a significant downward trend in these two countries. However, the number of unvaccinated children has dramatically increased in the Philippines: from 100 000 in 2013 to 900 000 in 2015.

Countries where DTP3 is less than 90% are classified into four groups based on their DTP1 and DTP3 coverage rates (drop out) to allow recommendations adapted to their specific situation, as shown in Table 2.2 and Figure 2.6.

District-level DTP3 coverage

Among the 112 Member States with valid district-level coverage estimates in 2015, only 52 (27%) had achieved national level coverage of ≥ 90% and coverage of ≥ 80% in every district (or equivalent administrative level) (ex-GVAP Indicator G3.1; Table 2.3). This was less than the previous year, when 57 Member States (29%) reached this goal. As mentioned above, 43 countries (22%) did

[24] Bulgaria, Namibia, Paraguay, Peru, Qatar, Solomon Islands, Tuvalu and Zambia.

not provide district coverage data and 39 (20%) provided data that were considered invalid.

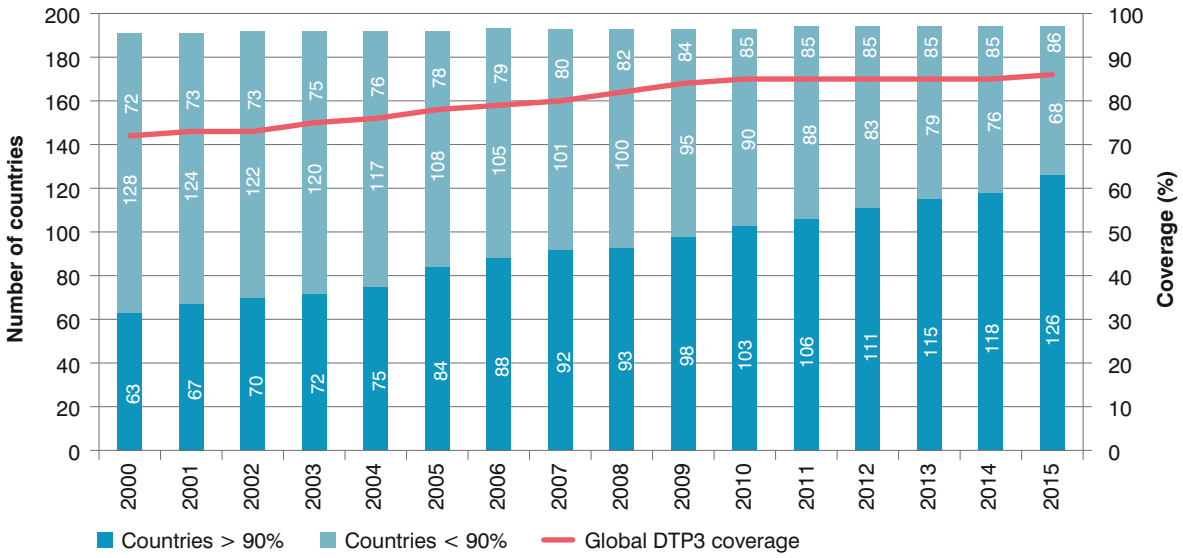
Distribution of Member States by the percentage of districts achieving the target of ≥ 80% DTP3 coverage in all districts in 2015 (GVAP Indicator ex-SO3.1) and by WHO region is described in Figure 2.7,Table 2.3 and Table 2.4. Data show that 27 (14%) countries with validated district-level coverage rates had between 80% and 99% of their districts achieving DTP3 coverage of ≥ 80% in 2015, 22 (11%) countries had between 50% and 79% of their districts achieving DTP3 coverage of ≥ 80%, while 11 (6%) countries had < 50% of districts achieving coverage of ≥ 80%. Figure 2.8 shows the numbers of unvaccinated children by country in 2015 and current DTP3 coverage.

Table 2.1: Distribution of all 194 Member States by level of national DTP3 coverage rate and region, 2015

WHO region	DTP3 ≥ 90% in 2014		DTP3 ≥ 90%		DTP3 of 70–89%		DTP3 of 50–69%		DTP3 < 50%		Total
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
African Region	19	40	16	34	19	40	9	19	3	6	47
Region of the Americas	25	71	26	74	8	23	1	3	0	0	35
Eastern Mediterranean Region	12	57	13	62	4	19	2	10	2	10	21
European region	49	92	47	89	5	9	0	0	1	2	53
South-East Asia Region	7	64	7	64	4	36	0	0	0	0	11
Western Pacific Region	15	56	17	63	6	22	4	15	0	0	27
Global	**127**	**65**	**126**	**65**	**46**	**24**	**16**	**8**	**6**	**3**	**194**

Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

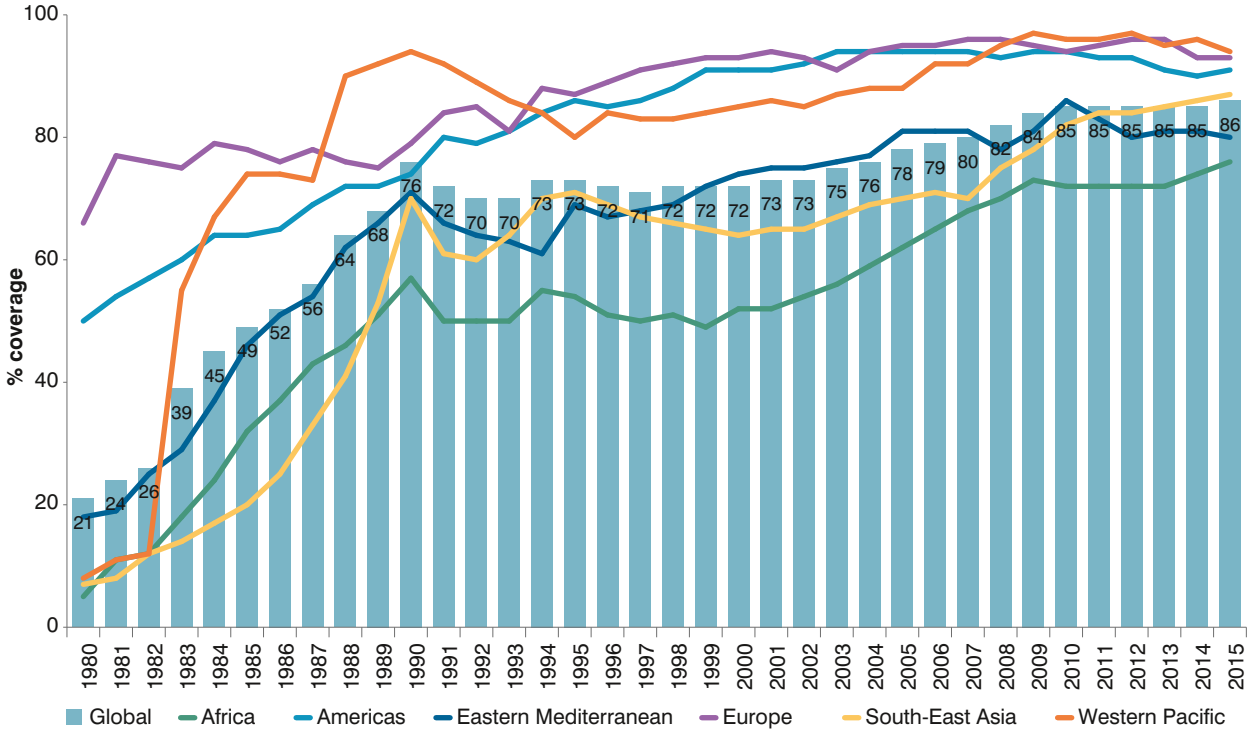
Figure 2.1: Number of countries that have reached and sustained ≥ 90% DTP3 coverage, 2000–2015 and global DTP3 coverage in 2015[a]



[a] Data in this table should be read as follows: In 2015, 126 countries had reached and sustained ≥ 90% DTP3 coverage for 1 year; 118 for 2 years, 115 countries for the past 3 years and 63 have reached and sustained it for 16 years.

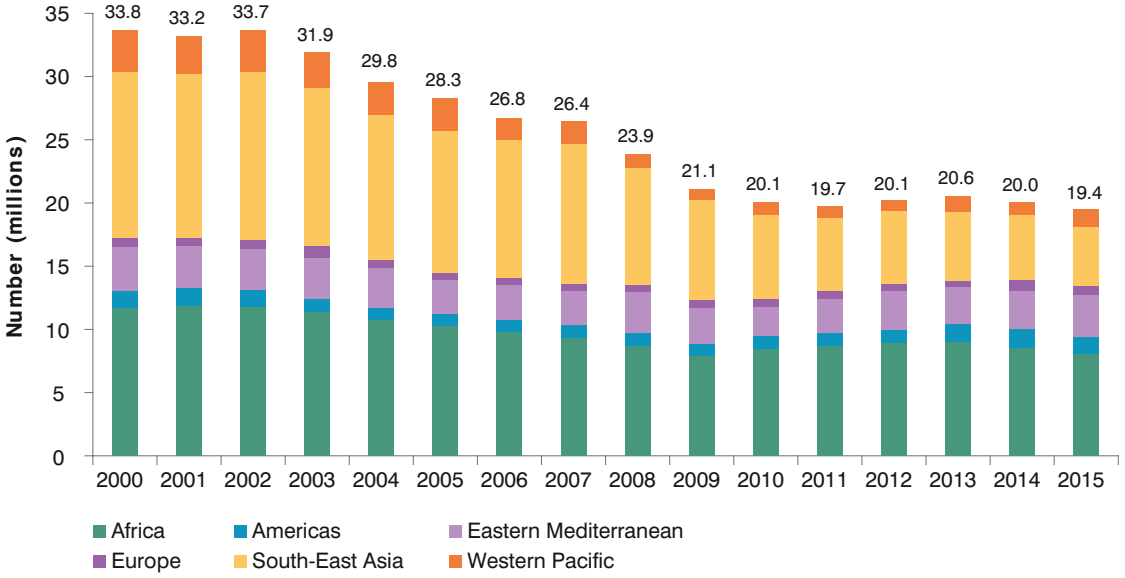
Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

Figure 2.2: Global and regional coverage with DTP3, 1980–2015



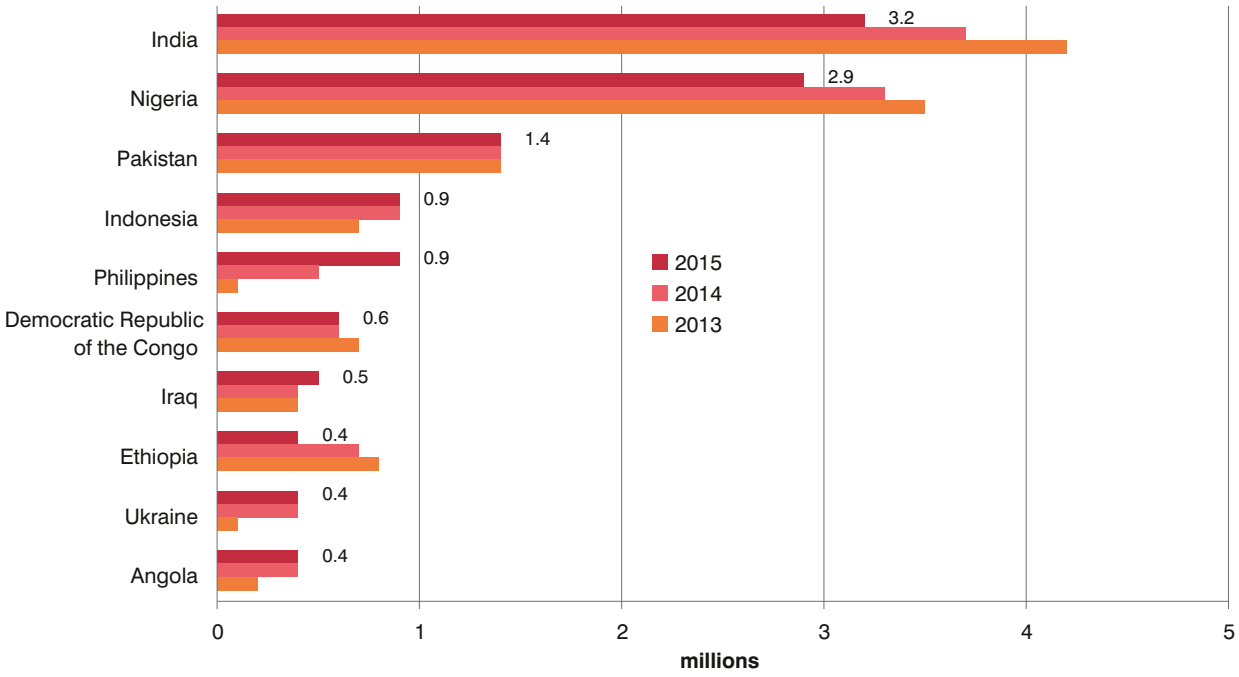
Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

Figure 2.3: Number of infants unvaccinated with DTP3 by WHO region, 2000-2015



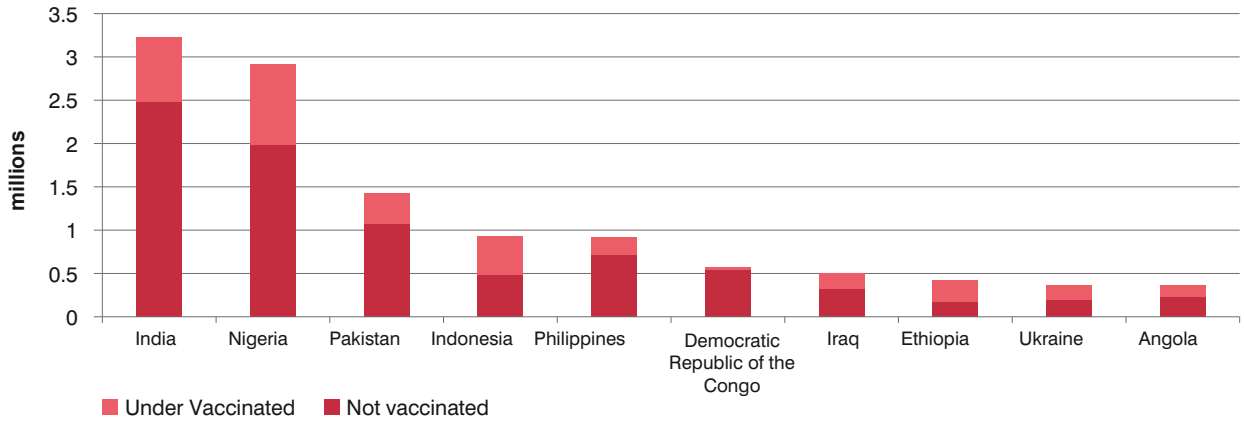
Source: WHO/UNICEF coverage estimates 2015 revision. July 2016; and *(1)*.

Figure 2.4: Countries with the most infants unvaccinated with DTP3, 2013–2015



Source: WHO/UNICEF coverage estimates 2015 revision. July 2016; and *(1)*.

Figure 2.5: Top 10 countries with most children under- and unvaccinated with DTP3, in 2015



Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

Table 2.2: Classification of Member States for which DTP3 national coverage is less than 90% into four groups based on DTP coverage, 2015

Group	Definition	Countries	Proposed strategies to increase DTP3 coverage
A	**DTP3 < 50%**	Central African Republic, Equatorial Guinea, Somalia, South Sudan, Syrian Arab Republic and Ukraine	• Most countries in this group are experiencing acute emergencies (a WHO framework for decision-making was developed in 2013 *(2)* to address immunization activities for populations affected by acute emergencies)[a] • Strengthen overall health system
B	**DTP3 of 50–89%** **DTP1 < 90%** **Drop-out ≥ 10%**	Angola, Guinea, Haiti, Iraq, Liberia, Madagascar, Mali, Mauritania, Niger, Nigeria, Papua New Guinea, Philippines, Samoa, Uganda, Vanuatu and Yemen	• Improve access through social mobilization to increase demand of the vaccine and target hard-to-reach populations • Address drop out rates by improving quality and predictability of service delivery and reducing missed opportunities
C	**DTP3 of 50–89%** **DTP1 < 90%** **Dropout < 10%**	Afghanistan, Bosnia and Herzegovina, Chad, Comoros, Congo, Democratic Republic of the Congo, Ecuador, Gabon, Honduras, Lebanon, Pakistan, Republic of Moldova, San Marino, South Africa, Timor-Leste and Tonga	• Improve access through social mobilization to increase demand of the vaccine and target hard-to-reach populations
D	**DTP3 of 50-89%** **DTP1 ≥ 90%**	Benin, Cambodia, Cameroon, Côte d'Ivoire, Djibouti, Dominican Republic, Ethiopia, Ghana, Guatemala, Guinea-Bissau, India, Indonesia, Kenya, Kiribati, Lao People's Democratic Republic, Malawi, Marshall Islands, Mexico, Micronesia (Federated States of), Montenegro, Mozambique, Myanmar, Panama, Romania, Senegal, Sierra Leone, Suriname, Togo, Venezuela, Zimbabwe	• Address drop out rates by improving quality and predictability of service delivery and reducing missed opportunities

[a] The framework recognizes that acute emergencies pose specific challenges to which guidelines developed for use in non-emergency settings may not apply. For example, acute emergencies may result in sudden changes in the burden of vaccine-preventable diseases (VPDs), either in their incidence or their case–fatality ratio, or both, as well as in an increased risk of epidemics and changes in the usual geo-distribution patterns.

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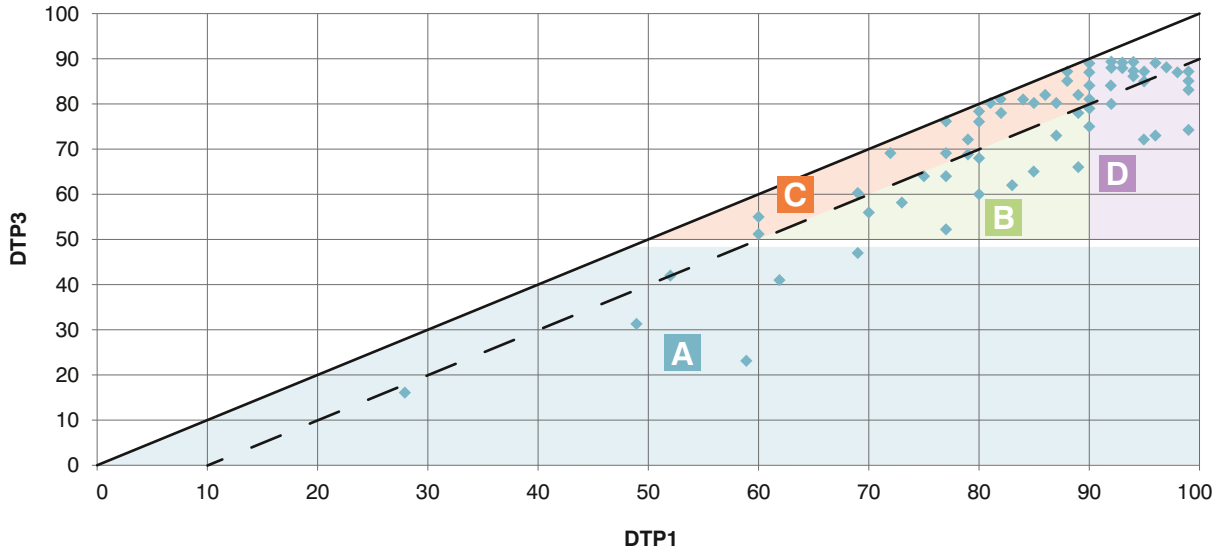
Figure 2.6: Classification of Member States for which DTP3 national coverage is less than 90% into four groups based on DTP coverage, 2015[a]



[a] Data in this table should be read as follows:
A: Countries need to strengthen overall health system (DTP3 < 50%)
B: Countries need to improve access and reduce drop-out rate (DTP1 < 90% & dropout ≥ 10%)
C: Countries need to improve access (DTP1 < 90% but drop-out rate < 10%)
D: Countries need to reduce drop-out rate (DTP1 ≥ 90% and DTP3 < 90%)

Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

Table 2.3: Distribution of Member States by national and district-level DTP3 coverage achievements and WHO region, 2015

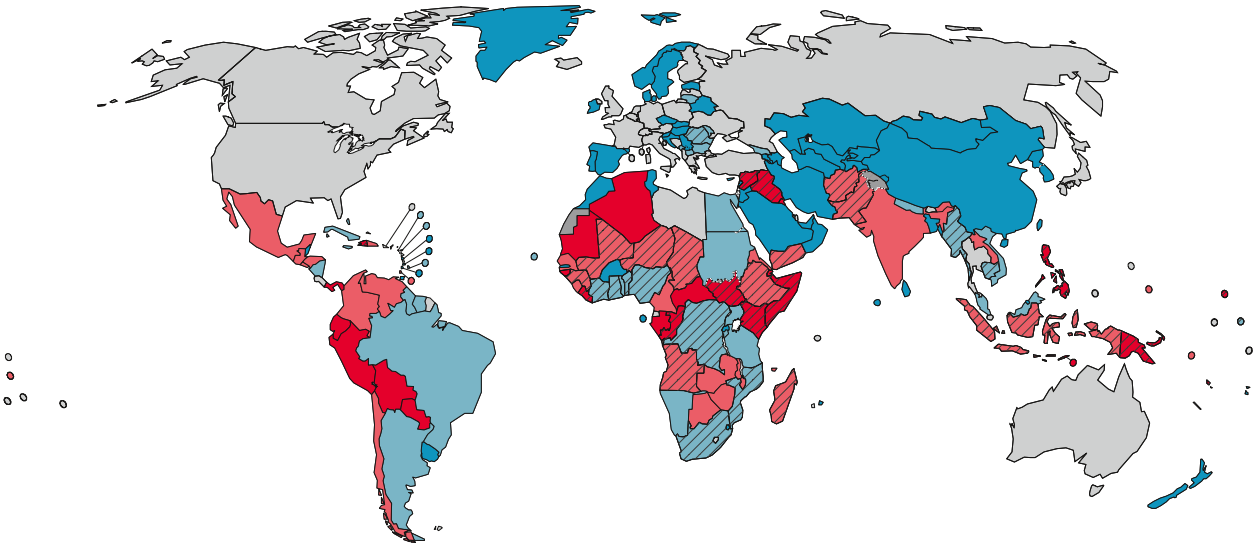
WHO region	Countries with valid DTP3 district coverage data available								DTP3 district coverage data not available		DTP3 district coverage data available but not valid		Total
	DTP3 national coverage ≥ 90% & all districts ≥ 80%		DTP3 national coverage ≥ 90% but not all districts ≥ 80%		DTP3 national coverage < 90%		Total						
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
African Region	6	13	8	17	10	21	24	51	3	6	20	43	47
Region of the Americas	6	17	17	49	8	23	31	89	3	9	1	3	35
Eastern Mediterranean Region	8	38	3	14	0	0	11	52	2	10	8	38	21
European region	22	42	4	8	2	4	28	53	24	45	1	2	53
South-East Asia Region	4	36	1	9	2	18	7	64	2	18	2	18	11
Western Pacific Region	6	22	3	11	2	7	11	41	9	33	7	26	27
Global	**52**	**27**	**36**	**19**	**24**	**12**	**112**	**58**	**43**	**22**	**39**	**20**	**194**

Table 2.4: Distribution of Member States by percentage of districts achieving ≥ 80% coverage for DTP3 in 2015, by WHO region

WHO region	Countries with valid DTP3 district coverage data available										DTP3 district coverage data not available		DTP3 district coverage data available but invalid		Total
	100% districts with DTP3 ≥ 80%		80–99% districts with DTP3 ≥ 80%		50–79% districts with DTP3 ≥ 80%		0–49% districts with DTP3 ≥ 80%		Total						
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
African Region	6	13	5	11	9	19	4	9	24	51	3	6	20	43	47
Region of the Americas	6	17	11	31	9	26	5	14	31	89	3	9	1	3	35
Eastern Mediterranean Region	8	38	2	10	0	0	1	5	11	52	2	10	8	38	21
European region	22	42	6	11	0	0	0	0	28	53	24	45	1	2	53
South-East Asia Region	4	36	1	9	1	9	1	9	7	64	2	18	2	18	11
Western Pacific Region	6	22	2	7	3	11	0	0	11	41	9	33	7	26	27
Global	**52**	**27**	**27**	**14**	**22**	**11**	**11**	**6**	**112**	**58**	**43**	**22**	**39**	**20**	**194**

Source: WHO/UNICEF coverage estimates 2015 revision. July 2016.

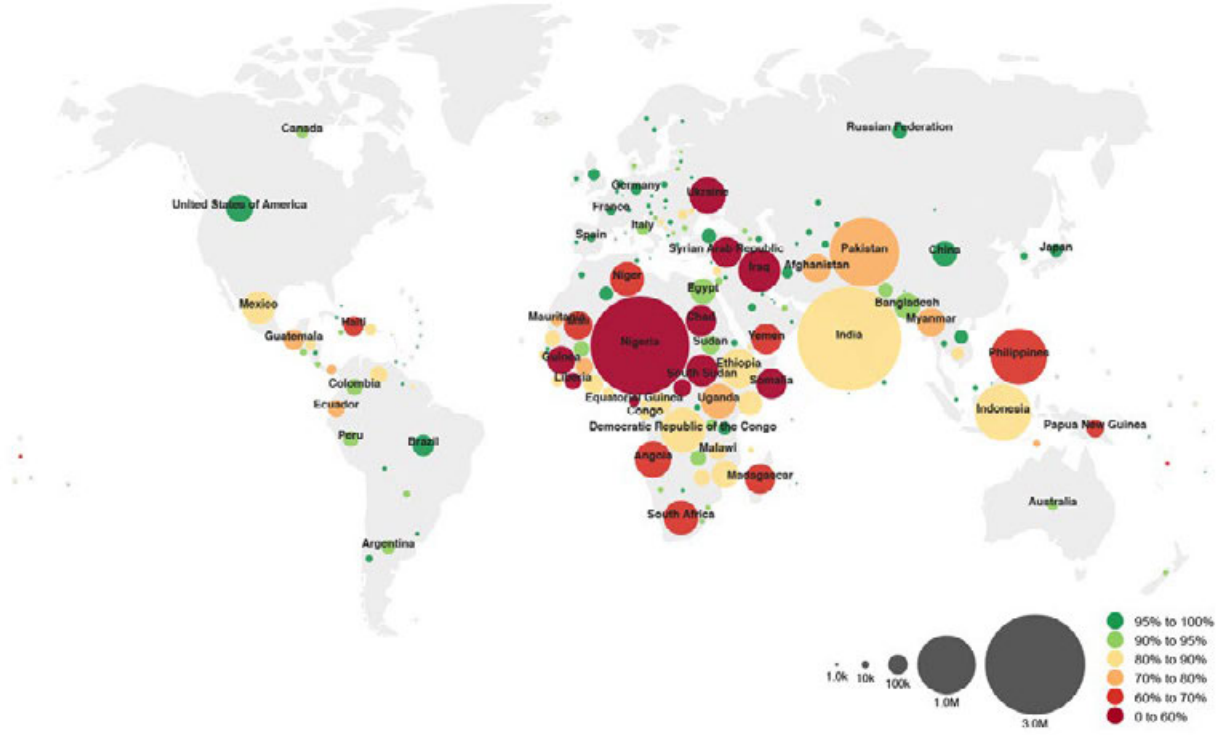
Figure 2.7: Member States by the percentage of districts with DTP3 coverage ≥ 80%, 2015



< 50% (25 Member States or 13%, 14 of which provided administrative coverage DTP3 data considered invalid)
50–79% (34 Member States or 18%, 12 of which provided administrative coverage DTP3 data considered invalid)
80–99% (39 Member States or 20%, 12 of which provided administrative coverage DTP3 data considered invalid)
All districts (53 Member States or 27%, 1 of which provided administrative coverage DTP3 data considered invalid)
Not available (43 Member States or 27%, with 1 Member States having administrative coverage DTP3 data that are invalid)
Not applicable
WHO-UNICEF (WUENIC) estimate is < 90% or differs from country's administrative coverage reported on the JFR and therefore district data are not considered valid (40 Member States or 21%)

Source: WHO/UNICEF coverage estimates, 2015 revision.

Figure 2.8: DTP3 coverage and numbers of unvaccinated children by country, 2015



Source: WHO/UNICEF coverage estimates, 2015 revision.

References

1. World population prospects: the 2015 revision. New York: United Nations, Department of Economic and Social Affairs, Population Division; 2015.

2. Vaccination in acute humanitarian emergencies: a framework for decision making. Geneva: World Health Organization; 2013 (WHO/IVB/13.07; http://apps.who.int/iris/bitstream/10665/92462/1/WHO_IVB_13.07_eng.pdf, accessed 15 August 2016).

Number of Member States that reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes (Indicator G3.2)

Highlights

- District level coverage is currently only monitored for DTP3 and not for other vaccines. Hence, the results in this section mainly relate to national level coverage.
- In 2015, 78 countries (40%) reached this target for all vaccines, while 116 did not (60%); this is less than the number of countries achieving the target in 2014 and in 2013, 43% in each of the two years
- Among the 126 countries that had achieved DTP3 ≥ 90%, 78 also achieved coverage ≥ 90% with all other vaccines in their national programmes. On the other hand, 48 MS (25% of all Member States) met DTP3 national coverage goals but failed to meet the ≥ 90% coverage targets for all vaccines in national programs, while 68 nations (35%) failed to meet both targets.
- A total of 53 Member States sustained 90% national coverage and 80% coverage in every district for all vaccines in national programmes in 2015, which is less than in 2014 when 64 countries were able to sustain this goal.

DEFINITION OF INDICATOR	Indicator includes the following vaccines: Three doses of DTP, polio and the first dose of MCV for all Member States Bacille Calmette–Guérin (BCG) vaccine for Member States where included in the schedule (i.e. not limited to high-risk populations) Three doses of HepB, Hib, pneumococcal conjugate vaccine (PCV) and rotavirus last dose (2nd or 3rd dose, depending on the vaccine) when part of the national immunization schedule National coverage data are included only for vaccines that have been introduced into the immunization schedule for at least one year before the JRF reporting year (e.g. coverage reported for the calendar year 2012 for a vaccine introduced in 2010) and in countries that have reported these data
TARGET	2020 in all Member States
DATA SOURCES[25]	WUENIC estimates Administrative data from country JRFs

Data availability and quality

It is possible to measure progress against the target for this indicator only for national-level coverage at this point, since district-level administrative data are currently available only for DTP3 and measles-containing (MCV) vaccines. For the purposes of this analysis, it should be noted that the lowest coverage rate for any one particular vaccine that is part of the national immunization programme is used to determine whether the country has met the indicator target.

[25] For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).

Results

Countries achieving national coverage of 90% or greater for all vaccines in their immunization schedule in 2015 are shown in Figure 2.9. In 2015, 78 countries (40%) reached this target for all vaccines, while 116 did not (60%); this is less than the number of countries achieving the target in 2014 and in 2013, 43% in each of the two years, as illustrated in Table 2.5.

The majority of countries achieving this goal are high-income (29 countries) and upper-middle income (26 countries). Low income and lower-middle-income countries[26] account for 21 of the 78 Member States reaching national coverage of 90% or greater for all vaccines in 2015.

It is noteworthy that nine countries[27] achieved the goal in 2015, which had not achieved it in 2014. That being said, 14 countries that had attained the coverage level in 2014 could not sustain it in 2015. In many cases, however, those Member States had only one antigen falling under the 90% threshold.[28] This could be due to a number causes, like recent introduction of a new vaccine into the national programme (PCV3 for Armenia, Bolivia (Plurinational State of); rotavirus vaccine for Estonia and the United Arab Emirates) or possibly stockouts of a specific antigen at national level: Armenia, Estonia, Ghana, Japan, Malta, Portugal, the United Kingdom and Zimbabwe. The causes should be investigated at country level.

Among the 126 countries that had achieved DTP3 ≥ 90%, 78 also achieved coverage ≥ 90% with all other vaccines in their national programme. On the other hand, 48 Member States (25%) met DTP3 national coverage goals but failed to meet the ≥ 90% coverage targets for all vaccines in national programmes, while 68 nations (35%) failed to meet both targets. A variety of causes could account for coverage of some vaccines being lower than that of DTP3. These causes are not identifiable by examining data available at the global level. Countries in this category need to examine their own data carefully to understand the underlying causes for lower coverage with one or more vaccines and take the necessary corrective actions.

National coverage data for all vaccines included in the schedule are presented in individual visualizations in Annex 2.1.

Individual vaccines' global coverage varies from one vaccine to another. If BCG, DTP1, DTP3, HepB3 and PAB, POL and MCV1 are all above 80% of global coverage; coverage for Hep B birth dose, RCV1, MCV2 and new vaccines like rotavirus, PCV and Hib remains low (Figure 2.10) since many countries are yet to introduce these vaccines in their national programme.

Table 2.5: Number of Member States that achieved ≥ 90% national coverage for all the vaccines included in their national immunization schedule[a] by WHO region, 2013–2015

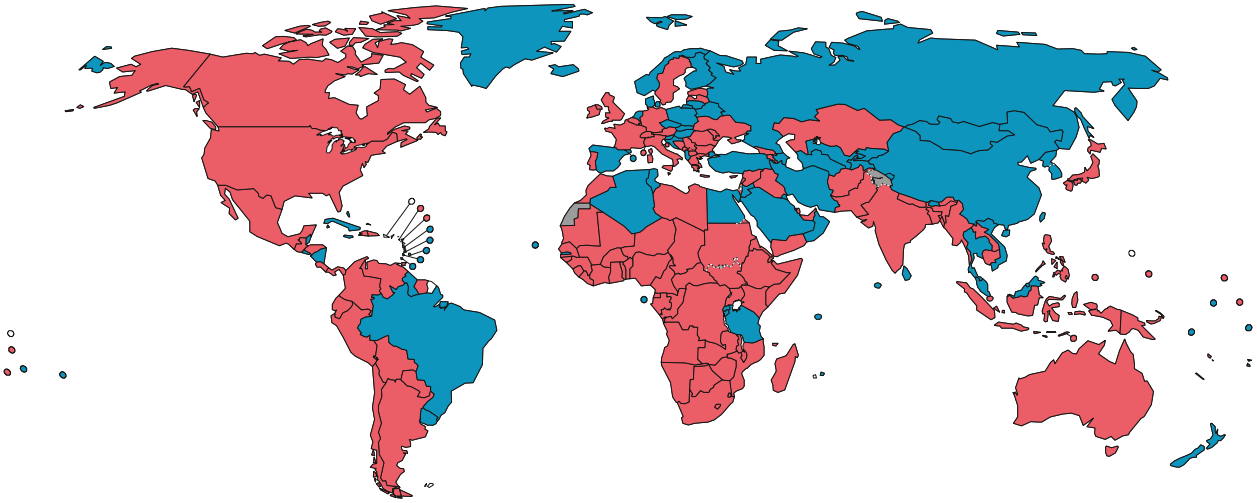
WHO region	2013		2014		2015	
	n	(%)	n	(%)	n	(%)
African Region	12	26	13	28	10	21
Region of the Americas	15	43	16	46	17	49
Eastern Mediterranean Region	11	52	9	43	9	43
European region	29	55	28	53	24	45
South-East Asia Region	5	45	5	45	5	45
Western Pacific Region	12	44	12	44	13	48
Global	**84**	**43**	**83**	**43**	**78**	**40**

[a] Schedule of infant vaccines for this indicator includes infant vaccines that are universally introduced, not infant vaccines used for risk groups and/or infant vaccines introduced in some parts of the country.

Source: WHO/UNICEF coverage estimates, 2015 revision. July 2016

[26] These terms come from the World Bank income classification. More information is available at: http://data.worldbank.org/about/country-and-lending-groups.
[27] Azerbaijan, Colombia, El Salvador, Grenada, Latvia, Morocco, Saint Lucia, Solomon Islands and Tuvalu.
[28] Antigua and Barbuda, Armenia, Bolivia (Plurinational State of), Eritrea, Estonia, Malta, Japan, Portugal and United Arab Emirates.

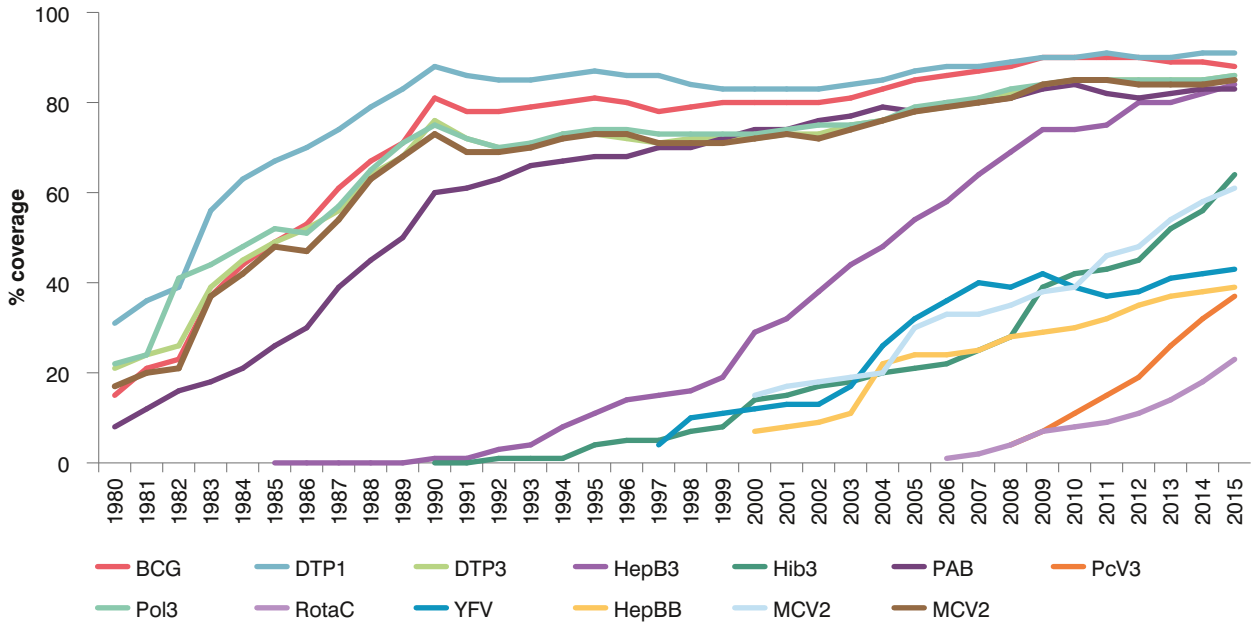
Figure 2.9: Member States that achieved national coverage of ≥ 90% for all vaccines included in the national infant immunization schedule, 2015[a]



[a] Schedule of infant vaccines for this indicator includes infant vaccines that are universally introduced, not infant vaccines used for risk groups and/or infant vaccines introduced in some parts of the country only.

Source: WHO/UNICEF coverage estimates, 2015 revision. July 2016.

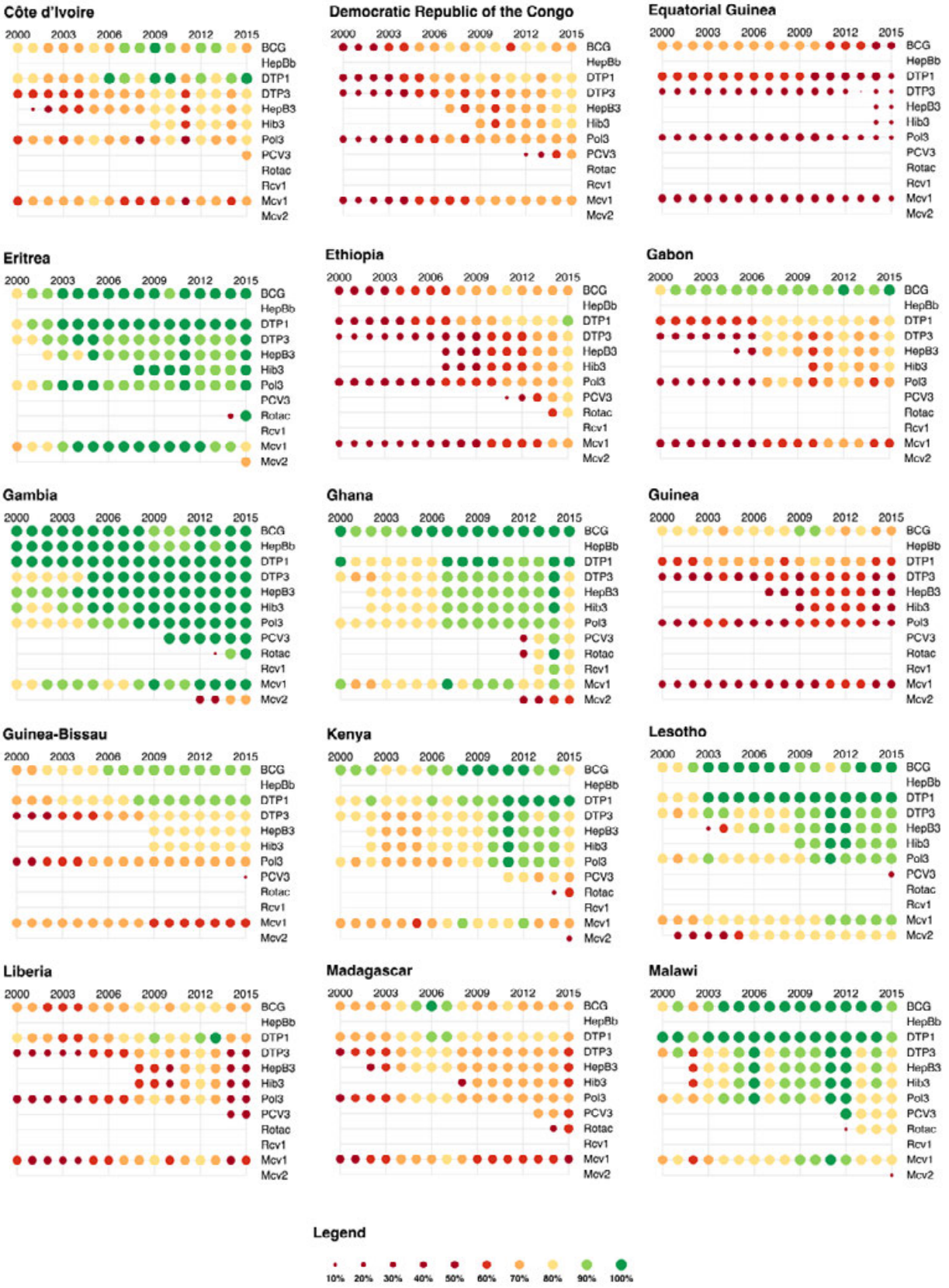
Figure 2.10: Global coverage estimates for BCG, DTP (1st and 3rd doses), measles (1st and 2nd doses), HepB (birth and 3rd doses), Hib3, PCV3 and rotavirus vaccine (last dose), 1980–2015



Source: WHO/UNICEF coverage estimates, 2015 revision. July 2016.

ANNEX 2.1: Immunization national coverage rates by country, 2000–2015

a: African Region


Côte d'Ivoire
Democratic Republic of the Congo
Equatorial Guinea
Eritrea
Ethiopia
Gabon
Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Lesotho
Liberia
Madagascar
Malawi
2000 2003 2006 2009 2012 2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%


Mali
Mauritania
Mauritius
Mozambique
Namibia
Niger
Nigeria
Rwanda
Sao Tome and Principe
Senegal
Seychelles
Sierra Leone
South Africa
South Sudan
Swaziland
2000
2003
2006
2009
2012
2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10%
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40%
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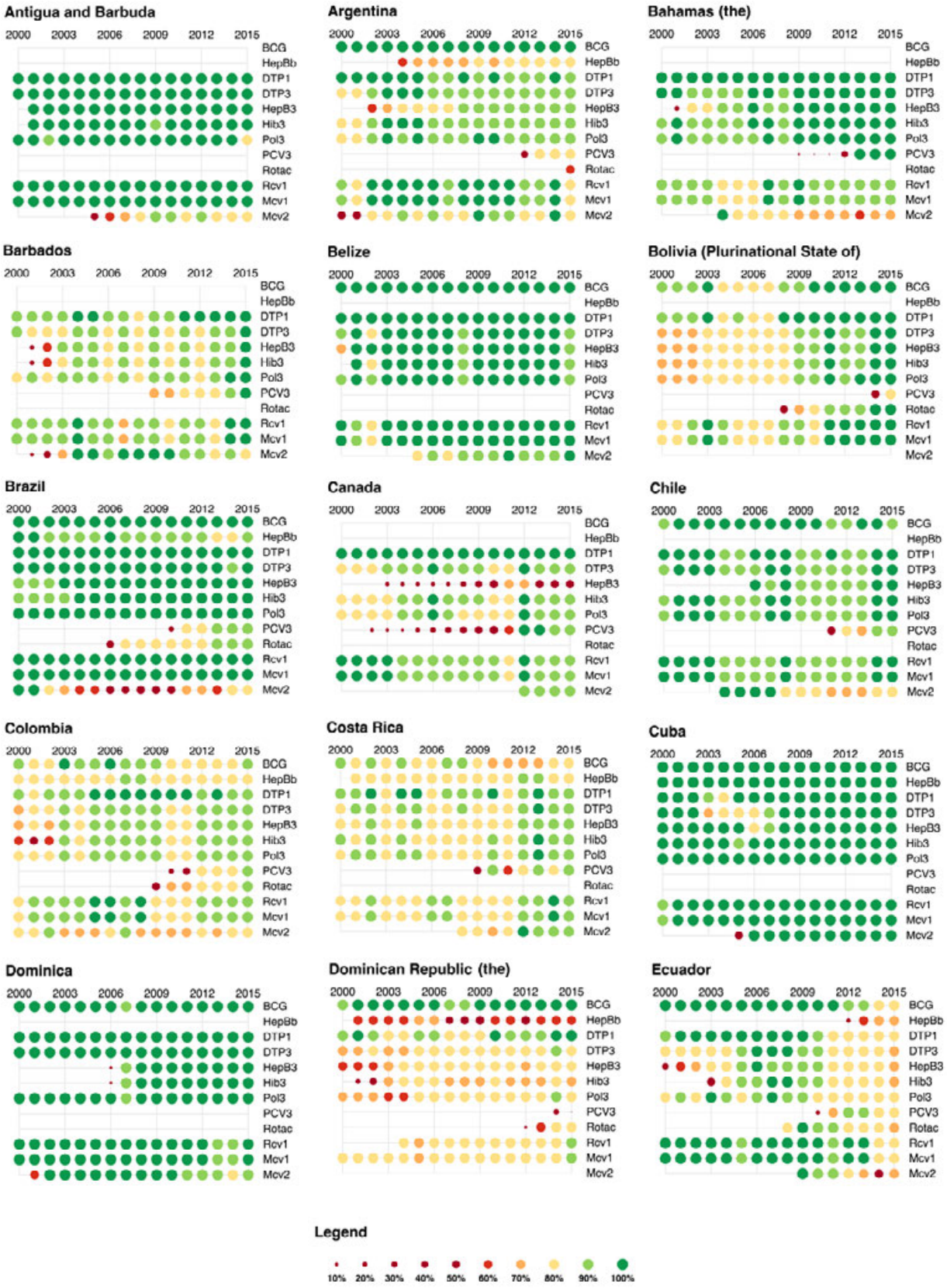
70%
80%
90%
100%

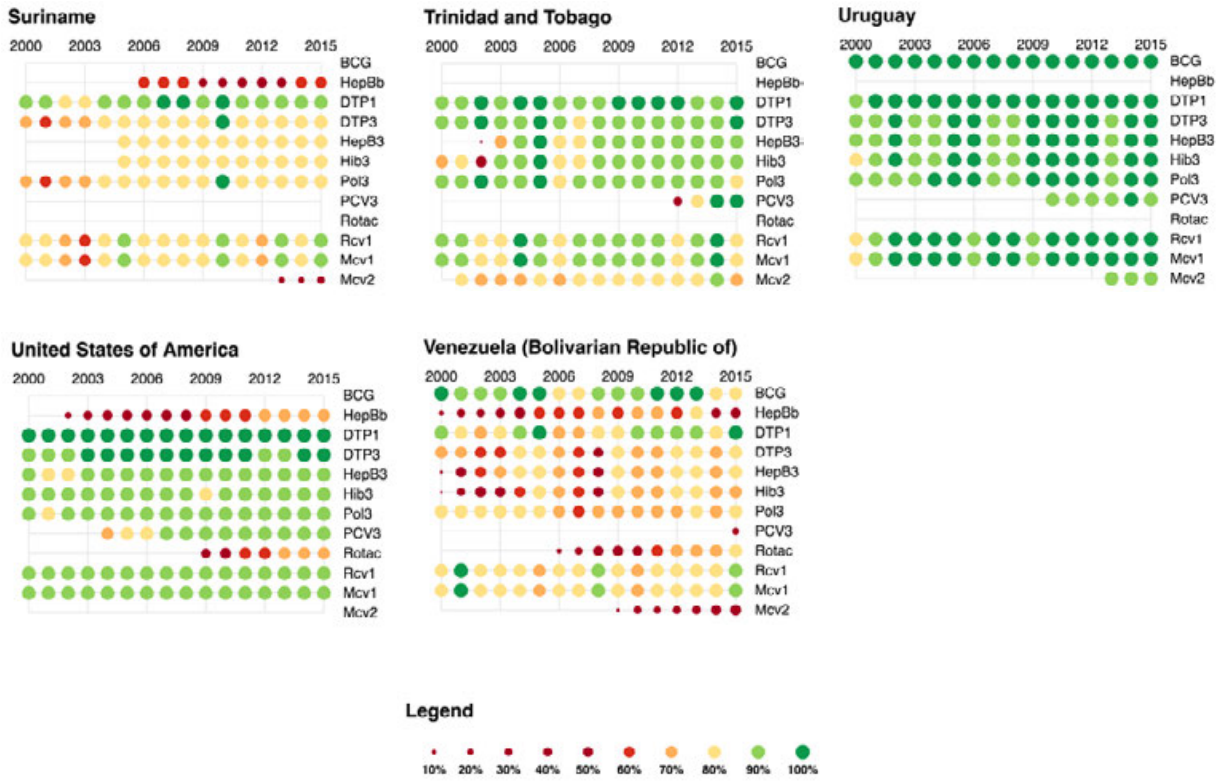

Togo
Uganda
United Republic of Tanzania
Zambia
Zimbabwe
2000 2003 2006 2009 2012 2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

© WHO

b: Region of the Americas




El Salvador
Grenada
Guatemala
Guyana
Haiti
Honduras
Jamaica
Mexico
Nicaragua
Panama
Paraguay
Peru
Saint Kitts and Nevis
Saint Lucia
Saint Vincent and The Grenadines
2000 2003 2006 2009 2012 2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%



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c: Eastern Mediterranean Region


Somalia
Sudan
Syrian Arab Republic
Tunisia
United Arab Emirates
Yemen
2000
2003
2006
2009
2012
2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
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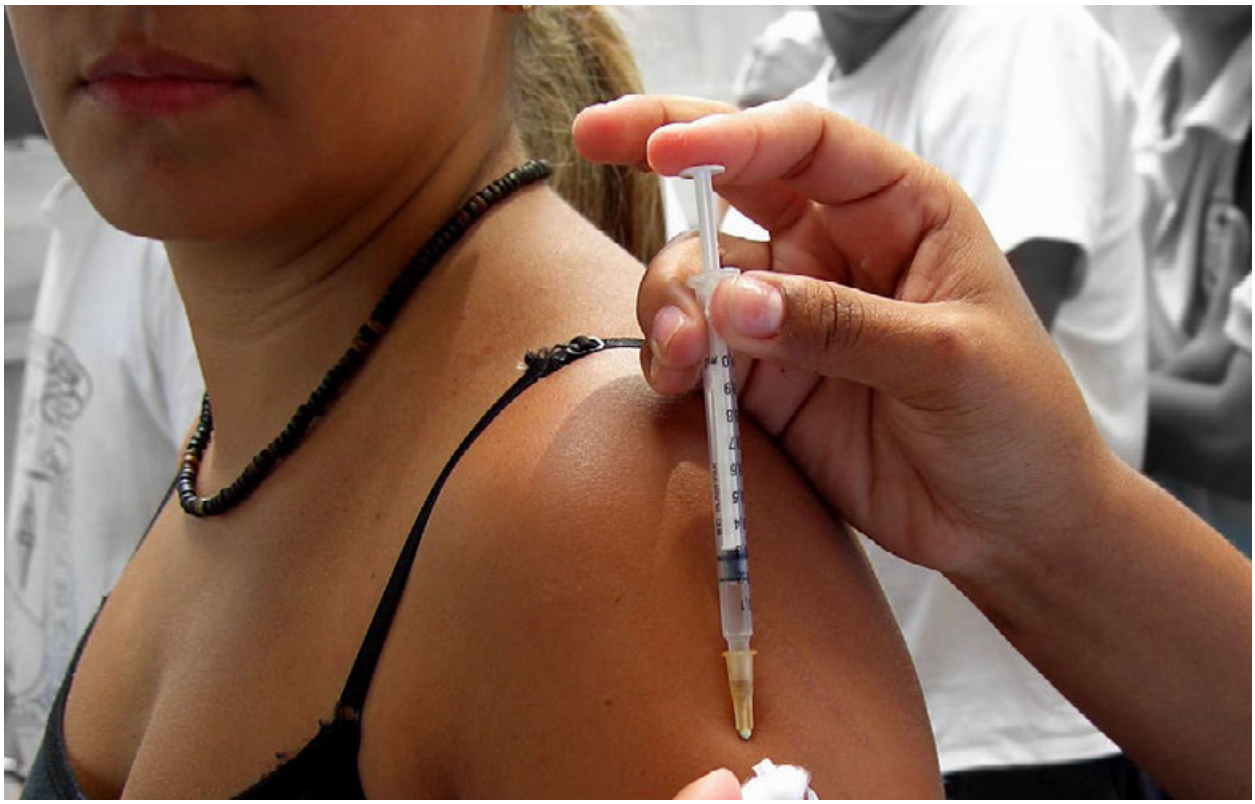
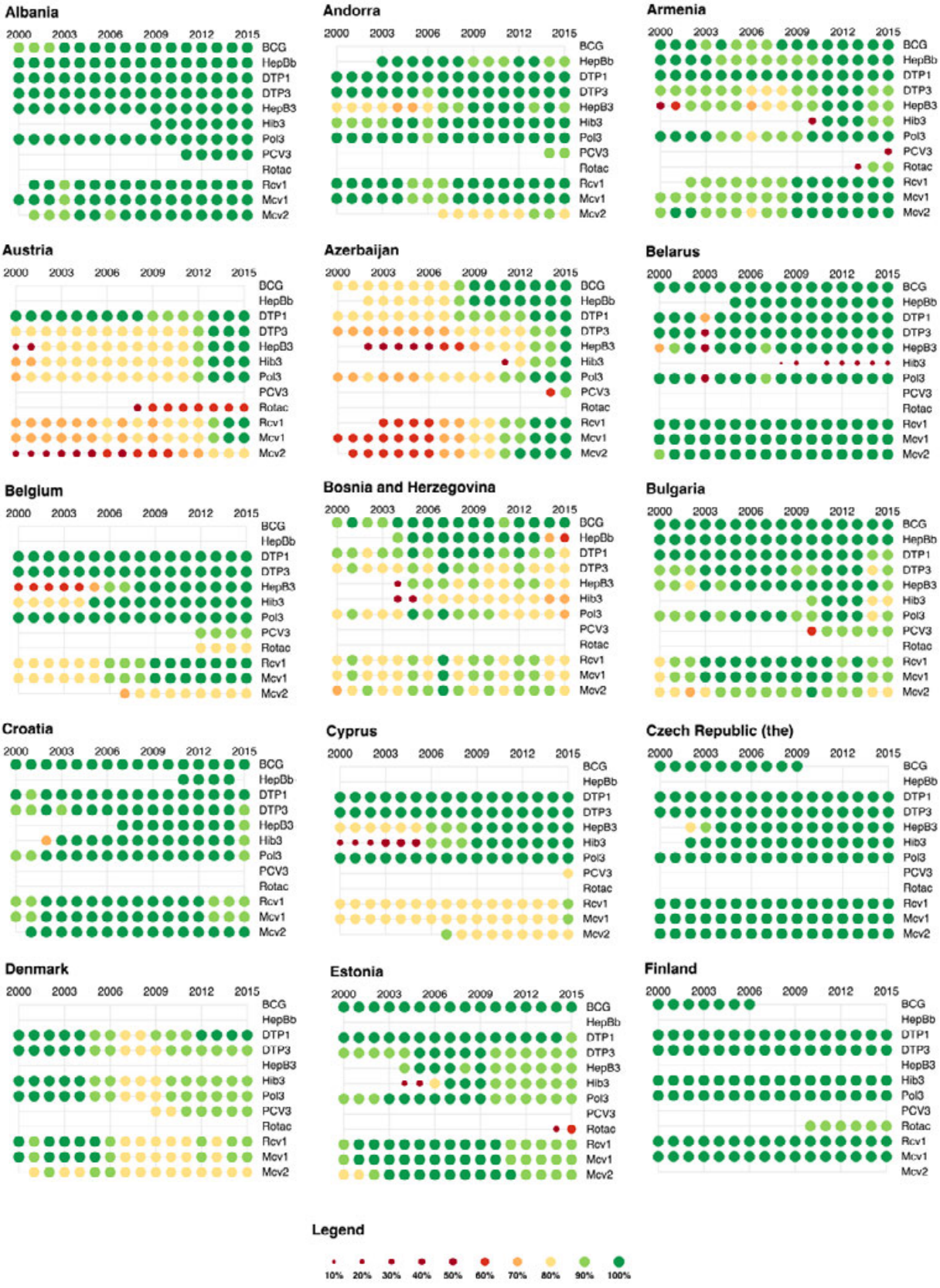
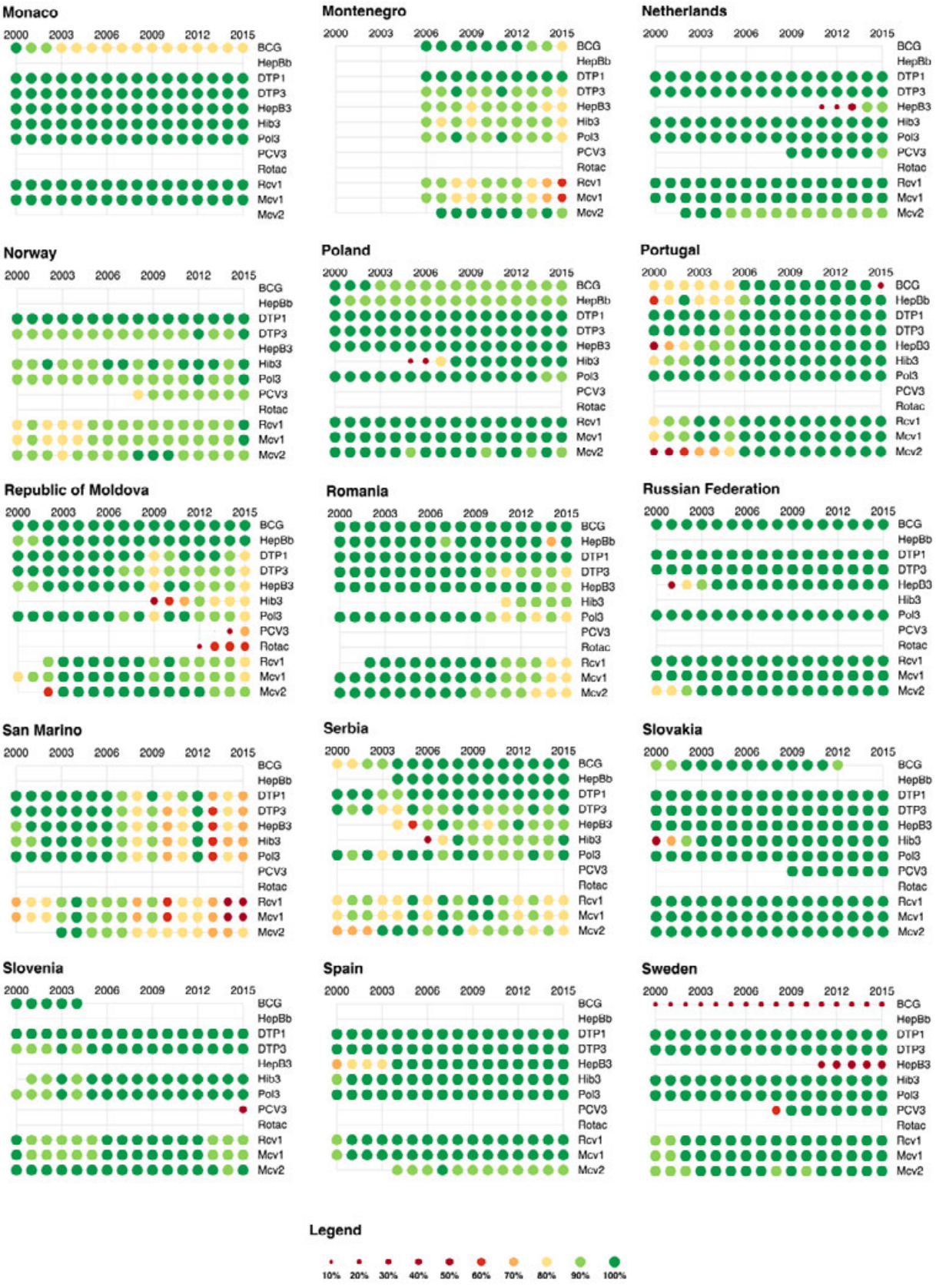


d: European Region

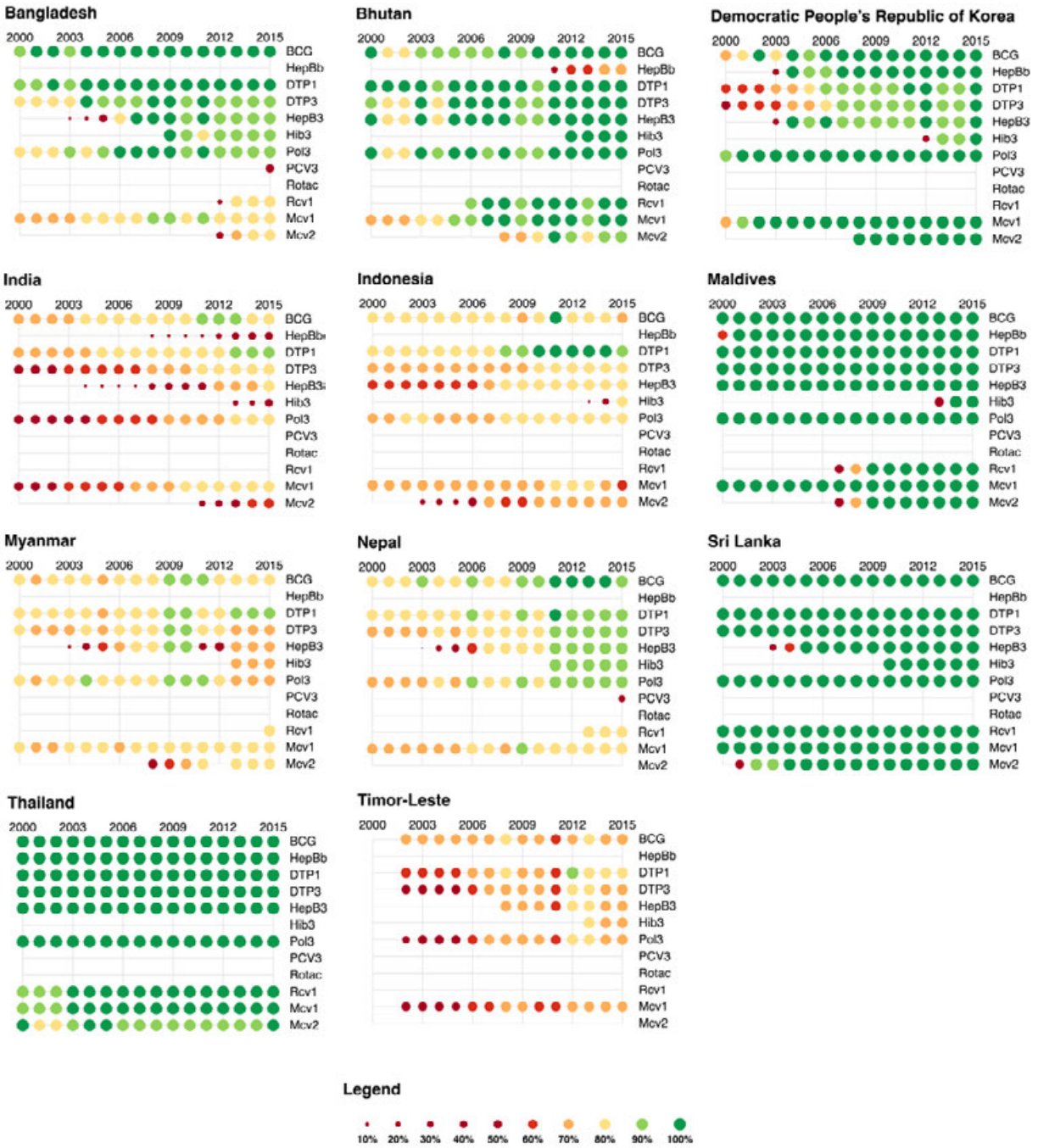



France
Georgia
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Luxembourg
Malta
2000 2003 2006 2009 2012 2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

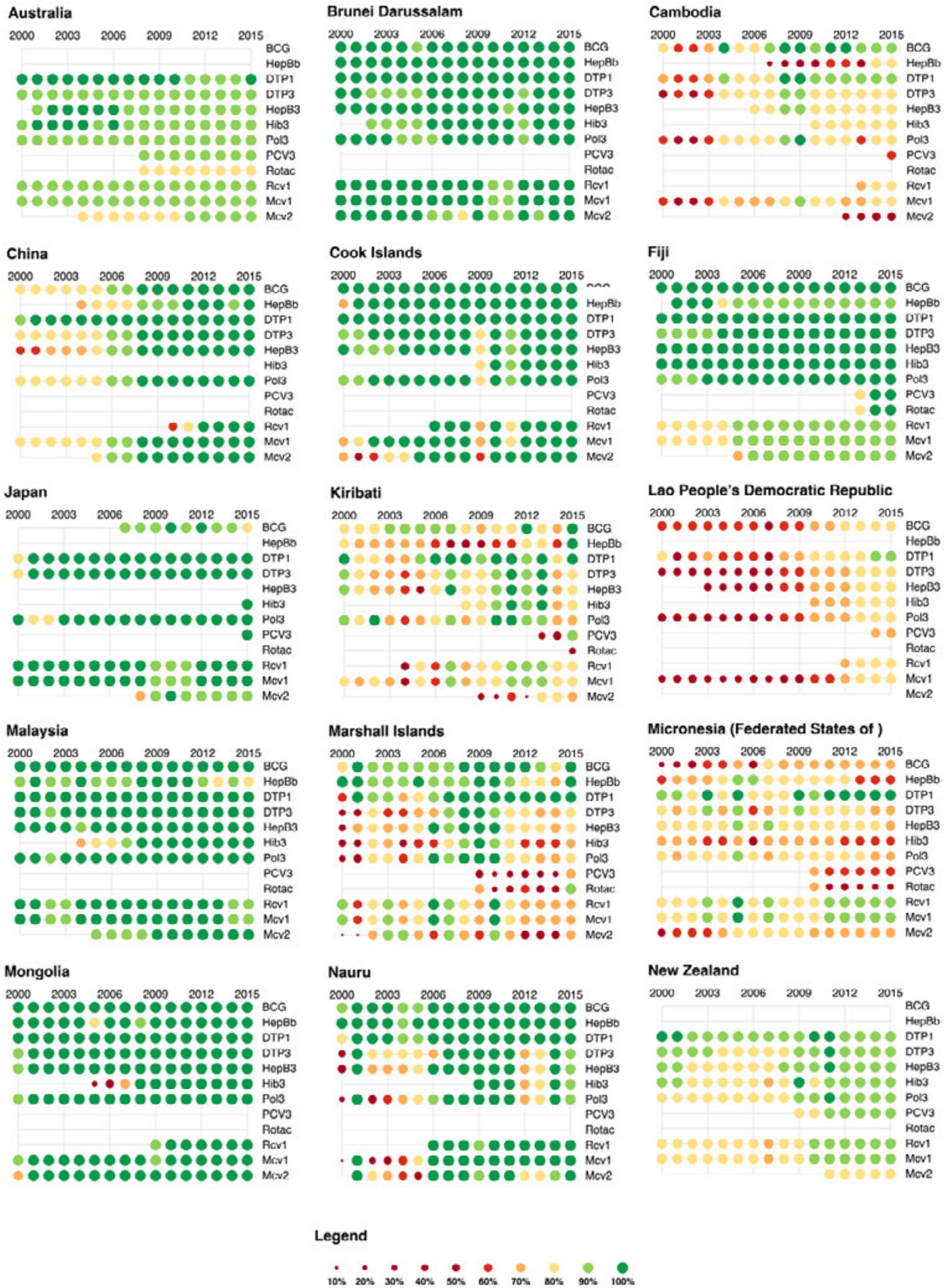

Monaco
Montenegro
Netherlands
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia
Slovakia
Slovenia
Spain
Sweden
2000 2003 2006 2009 2012 2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

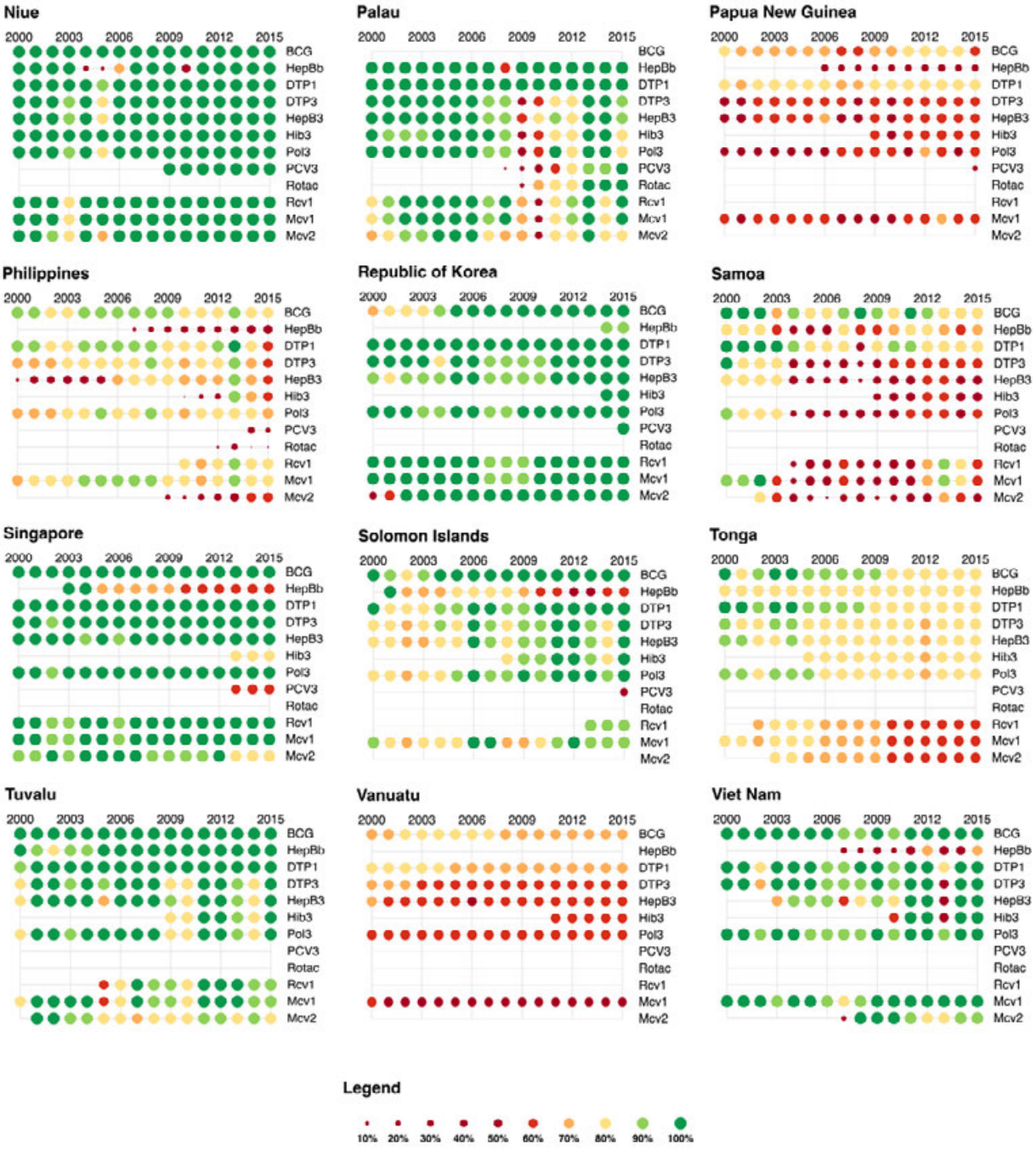

Switzerland
Tajikistan
The former Yugoslav Republic of Macedonia
Turkey
Turkmenistan
United Kingdom of Great Britain and Northern Ireland (the)
Ukraine
Uzbekistan
2000
2003
2006
2009
2012
2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

e: South-East Asia Region



f: Western Pacific Region




Niue
Palau
Papua New Guinea
Philippines
Republic of Korea
Samoa
Singapore
Solomon Islands
Tonga
Tuvalu
Vanuatu
Viet Nam
2000
2003
2006
2009
2012
2015
BCG
HepBb
DTP1
DTP3
HepB3
Hib3
Pol3
PCV3
Rotac
Rcv1
Mcv1
Mcv2
Legend
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s) (Indicator SO3.2)

Highlights

- Data from DHS or MICS surveys conducted between 2008 and 2014 on national diphtheria–tetanus–pertussis (DTP3) coverage rates by wealth quintiles were available for 64 Member States (68%) compared to 61 Member States in the previous year's report; only 49 (65%) of the 75 Countdown countries[29] have DTP3 coverage rates by wealth quintiles available.
- Coverage in most Member States was generally higher in the wealthiest quintile than in the poorest quintile, with 11 exceptions.
- Of the 64 countries with available data, 44 (69%) have met the target of < 20% difference in immunization coverage between the highest and lowest wealth quintiles (including 11 Member States for which DTP3 national coverage for the richest population is lower than for poorest).
- Among the 33 countries with the difference in immunization coverage between the highest and lowest wealth quintiles between 0 and 20% (and for which the poorest population is less covered than the richest population), 11 countries (16%) still had a quintile differential < 20% but ≥ 10% and only 16 (48%) Member States have DTP3 coverage ≥ 90%.
- Twenty countries (31%) had a quintile differential ≥ 20% and have thus failed to meet the target. Of those, no countries had DTP3 coverage ≥ 90%, meaning that all 20 countries have failed to meet both targets.

DEFINITION OF INDICATOR	• DTP3 immunization coverage among 1-year-olds distributed by wealth quintiles for the period 2008–2014 • Determination of wealth index as defined in DHS and MICS surveys • Data are to be measured at least twice (by special study or survey), with an early and late measure
TARGET	Increasing trend in equity in immunization coverage Proportion of Member States with < 20% difference in DTP3 coverage between the lowest and highest wealth quintile: 60% by 2015 75% by 2020
DATA SOURCES	WHO Health Equity Monitor database of the Global Health Observatory data repository,[30] which contains data on more than 30 reproductive maternal, neonatal and child health indicators disaggregated by child's sex, place of residence (rural versus urban), wealth quintile and educational level The consolidated data come from DHS and MICS surveys conducted in 94 Member States (90 DHS and 106 MICS, between 1993 and 2013) – 64 of these countries have data available for DTP3 coverage by wealth quintile from 2008–2014 (49 of which are Countdown countries). The Health Equity Assessment Toolkit (HEAT) helps visualize data from the WHO Health Equity Monitor database and allows for exploring and comparing inequality between countries[33]

[29] This refers to the 75 countries where more than 95% of all maternal and child deaths occur (including the 49 lowest-income countries) according to the Countdown collaboration (http://www.countdown2015mnch.org).
[30] The database can be found at: http://apps.who.int/gho/data/node.main.HE-1540?lang=en.
[31] The tool can be found at: https://whoequity.shinyapps.io/HEAT/.

Data availability and quality

Data for this indicator were derived from a re-analysis of publicly available[32] DHS and MICS micro-data. Standard indicator definitions as defined in DHS and MICS documentation for economic status and immunization coverage were used. Health inequality data, particularly the proxy methods used by DHS and MICS surveys, have several limitations and must be interpreted with caution *(1)*. Since estimates of household wealth and immunization coverage are only available through DHS and MICS surveys, which are conducted periodically, these data cannot be generated for each country on an annual basis. We chose to limit our analysis to surveys conducted between 2008 and 2014 (data from surveys conducted in 2015 are not yet published).

There may be minor discrepancies for a few countries between the data reported here and in previous DHS or MICS country reports, owing to small differences in the definition and calculation of some indicators. As new information becomes available every year, historical WHO-UNICEF WUENIC are updated, which can lead to differing estimates from one year to the next. More information about the indicator criteria is available in the WHO Indicator and Measurement Registry (www.who.int/gho/indicator_registry/en/).

To identify trends, at least two time points are required. Baseline data were defined as data from DHS or MICS surveys that took place in 2008 or later. The DHS and MICS surveys provide data on children aged 12 to 23 months, meaning the birth year of the cohort is the year before the surveys were conducted (i.e. a DHS survey conducted in 2008 corresponds to the 2007 birth cohort). Because the data relate to infant immunizations, DTP3 coverage data used for each country correspond to the birth year of the cohort and not the year the national surveys were conducted.[33]

If multiple years of survey data were available within the relevant time period, data from the most recent survey were chosen for inclusion in the analysis. For example, surveys were conducted in Nigeria in 2011 and in 2013, but only the data from the survey conducted in 2013 were included in this analysis. If national DTP3 coverage was available from survey data, it was used despite the limitations of representative sample surveys when compared to national studies. When the national DTP3 coverage rate was not available from survey data, WHO-UNICEF WUENIC data were used instead.

At the time of this report, 64 countries had data on DTP3 coverage rates by wealth quintiles between 2008 and 2014. Data availability has improved since last year, with three more countries providing data and three providing updated data, all in the African Region. A total of 127 Member States have performed a DHS or MICS survey in the past, but only 94 of them are included in the Health Equity Monitor database; this attrition is due to the availability of micro-data for re-analysis. Sixty-two of the 75 Countdown countries are in the Health Equity Monitor database, but only 49 (65%) of them have data on DTP3 coverage rates by wealth quintile from 2008 to 2014.

For those Member States that have not conducted a survey since 2008, a new survey will be needed to establish a baseline. The United Nations (UN) Secretary-General's Global Strategy for Women's and Children's Health recommends household surveys every three years for the 75 Countdown countries. Therefore it is expected that at least these countries will collect three sets of data during the decade, to monitor reduction in coverage inequities.

Results

Baseline data on DTP3 coverage rates for the highest and lowest wealth quintile from DHS and MICS surveys conducted from 2008 to 2014 in 64 Member States was used to calculate the quintile differential defined as the lowest wealth quintile's coverage rate subtracted from the highest wealth quintile's coverage rate. The quintile differentials for all countries with ≥ 10% quintile difference are displayed in Figure 2.11.

Of the 64 countries with data, 44[34] (69%) have met the target of < 20% difference in immunization coverage between the highest and lowest wealth quintiles. Among those 44 countries, 11 Member States[35] (25%) had higher coverage in the poorest quintile than in the wealthiest quintile.

Eleven countries (25%) had a quintile differential < 20% but ≥ 10%, and 22 countries (50%) had a quintile differential < 10% but ≥ 0%. Although the 11 countries with a quintile differential < 20% but ≥ 10% have met the goal, additional efforts to lower the quintile differential to below 10% are needed. These should include efforts to meet the DTP3 national coverage target of ≥ 90% as only two of those 11 countries – Nepal and Zimbabwe – have national coverage of ≥ 90%.

[32] Immunization: DTP3 Equity: wealth quintile, data by country (http://apps.who.int/gho/data/node.main.HE-1590?lang=en).
[33] DTP3 coverage: WHO-UNICEF review of national immunization coverage, 1980-2014 (http://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html#P).
[34] Albania, Armenia, Bangladesh, Belize, Bolivia (Plurinational State of), Bosnia and Herzegovina, Burkina Faso, Burundi, Cambodia, Chad, Colombia, Costa Rica, Egypt, Gabon, Gambia, Ghana, Guyana, Haiti, Honduras, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Malawi, Maldives, Mauritania, Mongolia, Nepal, Peru, Philippines, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Suriname, Swaziland, Tajikistan, The former Yugoslav Republic of Macedonia, Timor-Leste, Togo, Uganda, United Republic of Tanzania and Zimbabwe.
[35] Albania, Belize, Burundi, Gambia, Kazakhstan, Kyrgyzstan, Maldives, Sierra Leone, Suriname, Swaziland and Tajikistan.

The remaining 20 countries (31%) had a quintile differential ≥ 20% and none have reached the target for DTP3 coverage of ≥ 90%. Therefore they have not met either the DTP3 national coverage or the wealth quintile coverage gap reduction targets. For these nations, a strategy to increase the overall national coverage – but with a targeted focus on the lower wealth quintile populations – will be essential in making progress towards both goals. The results for each Member State are shown in Table 2.6, Table 2.7 and Table 2.8.

In general, Member States with high national coverage were likely to have smaller differences in coverage between wealth quintiles. Only two of the Member States with national DTP3 coverage rates of ≥ 90% had a quintile differential ≥ 10%, while the other 14 had quintile differentials < 10% but ≥ 0%.

It should be noted that this indicator cannot be properly assessed globally until all countries conduct DHS or MICS surveys. As it stands, the underlying target for all countries to have baseline data by 2015 has not been met. However, preliminary results indicate that countries with DTP3 coverage below 90% have a tendency to have greater wealth quintile differentials, and it is important for those countries with lower national coverage to conduct a national survey to assess equity in immunization coverage.

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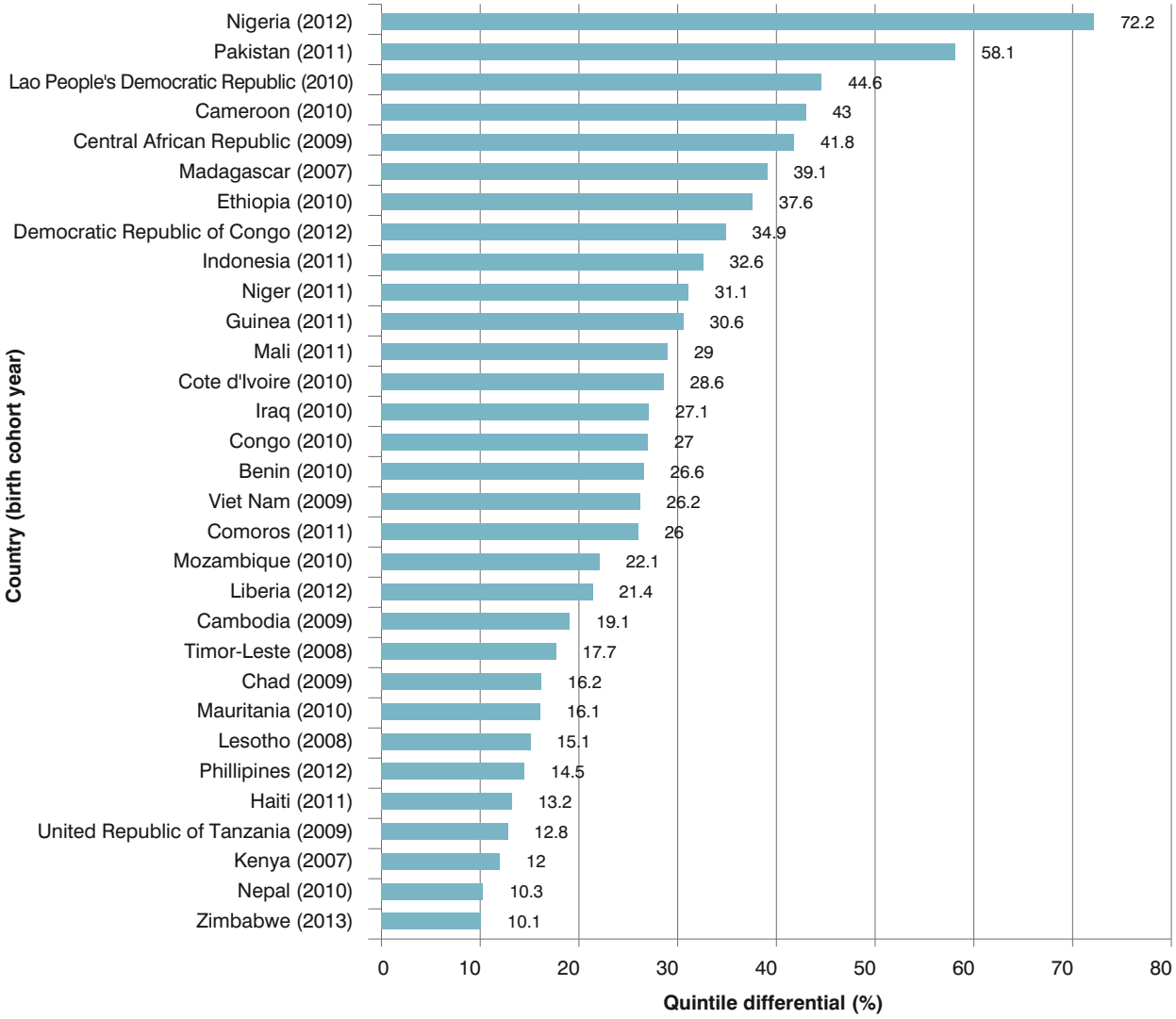
Figure 2.11: DTP3 quintile differential for 31 Member States having a quintile differential of ≥ 10%



Source: Data from DHS or MICS surveys conducted between 2008 and 2014.

Table 2.6: DTP3 national coverage, DTP3 coverage by wealth quintile, and quintile differential for 20 Member States having a quintile differential of ≥ 20%

Country (data year)	DTP3 coverage[a]	Quintile 1 (poorest)	Quintile 5 (richest)	Quintile differential
Nigeria (2012)	39	7.4	79.6	72.2
Pakistan (2011)	65	29.9	88.0	58.1
Lao People's Democratic Republic (2010)	56	36.8	81.4	44.6
Cameroon (2010)	69	44.6	87.6	43.0
Central African Republic (2009)	32	17.8	59.6	41.8
Madagascar (2007)	73	53.6	92.7	39.1
Ethiopia (2010)	37	26.0	63.6	37.6
Democratic Republic of the Congo (2012)	61	48.1	83.0	34.9
Indonesia (2011)	72	52.5	85.1	32.6

Country (data year)	DTP3 coverage[a]	Quintile 1 (poorest)	Quintile 5 (richest)	Quintile differential
Niger (2011)	69	53.3	84.4	31.1
Guinea (2011)	50	32.4	63.0	30.6
Mali (2011)	64	48.6	77.6	29.0
Côte d'Ivoire (2010)	64	52.1	80.7	28.6
Iraq (2010)	70	55.2	82.3	27.1
Congo (2010)	69	54.6	81.6	27.0
Benin (2010)	74	59.0	85.6	26.6
Viet Nam (2009)	74	59.3	85.5	26.2
Comoros (2011)	73	57.5	83.5	26.0
Mozambique (2010)	77	65.4	87.5	22.1
Liberia (2012)	72	58.0	79.4	21.4

[a] Coverage data from http://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html#P.

Source: Data from DHS or MICS surveys conducted between 2008 and 2014.

Table 2.7: DTP3 national coverage, DTP3 coverage by wealth quintile, and quintile differential for 11 Member States having a quintile differential of ≥ 10% and < 20%

Category	Country (data year)	DTP3 coverage[a]	Quintile 1 (poorest)	Quintile 5 (richest)	Quintile differential
DTP3 ≥ 90% n=2 (3%)	Nepal (2010)	92	88.1	98.4	10.3
	Zimbabwe (2013)	95[b]	84.9	95.0	10.1
DTP3 < 90% n=9 (14%)	Cambodia (2009)	85	73.5	92.6	19.1
	Timor-Leste (2008)	66	54.8	72.5	17.7
	Chad (2009)	24[b]	11.4	27.6	16.2
	Mauritania (2010)	64[b]	51.5	67.6	16.1
	Lesotho (2008)	84	73.2	88.3	15.1
	Philippines (2012)	86[b]	78.5	93.0	14.5
	Haiti (2011)	63	54.7	67.9	13.2
	United Republic of Tanzania (2009)	88	84.1	96.9	12.8
	Kenya (2007)	87	77.6	89.6	12.0

[a] Coverage data from http://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html#P.

Source: Data from DHS or MICS surveys conducted between 2008 and 2014.

Table 2.8: DTP3 national coverage, DTP3 coverage by wealth quintile, and quintile differential for 22 Member States having a quintile differential of < 10% but > 0%

Category	Country (data year)	DTP3 coverage[a]	Quintile 1 (poorest)	Quintile 5 (richest)	Quintile differential
DTP3 ≥ 90% n=15 (23%)	Burkina Faso (2009)	90	83.4	92.9	9.5
	Armenia (2009)	95	88.3	96.9	8.6
	Costa Rica (2010)	94	89.3	97.2	7.9
	Colombia (2009)	91	84.9	92.5	7.6
	Bangladesh (2010)	93	90.3	97.8	7.5
	Senegal (2013)	92[b]	85.6	91.6	6.0
	Mongolia (2009)	93	91.2	96.1	4.9
	Jordan (2011)	98	96.2	99.1	2.9
	Malawi (2009)	93	91.4	94.3	2.9
	Rwanda (2009)	97	96.1	98.7	2.6
	Bosnia and Herzegovina (2010)	92	91.4	93.8	2.4
	Egypt (2007)	98	97.1	98.9	1.8
	Honduras (2010)	96	96.4	98.1	1.7
	Ghana (2010)	93	93.0	94.4	1.4
	The former Yugoslav Republic of Macedonia (2010)	95	92.7	94.0	1.3
DTP3 < 90% n=7 (11%)	Guyana (2008)	85	76.5	86.2	9.7
	Gabon (2011)	73	62.2	71.8	9.6
	Togo (2012)	84[b]	84.0	90.9	6.9
	Peru (2011)	84	83.4	88.6	5.2
	Sao Tome and Principe (2007)	87	86.5	91.0	4.5
	Bolivia (Plurinational State of) (2007)	86	85.7	86.1	0.4
	Uganda (2010)	72	74.5	74.8	0.3

[a] Coverage data from http://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html#P.

Source: Data from DHS or MICS surveys conducted between 2008 and 2014.

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1. Handbook on health inequality monitoring: with a special focus on low- and middle-income countries. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85345/1/9789241548632_eng.pdf, accessed 15 August 2016).

Number of low-income and middle-income countries that have introduced one or more new and underutilized vaccines (Indicator G4.3)

Highlights

- There has been significant progress over the past five years in the introduction of new vaccines.
- The 2015 goal for introduction of new or underutilized vaccines in low- and middle-income countries is achieved and actually exceeding the target, with 99 low- and middle-income countries having introduced at least one new and underutilized vaccine to their national immunization programme and sustained vaccine use for at least 12 months.
- A total of 160 vaccine introductions took place in these 99 low- and middle-income countries during the first half of the Decade of Vaccines. These countries account for two thirds of the low- and middle-income Member States (73%).
- Among the 99 low- and middle-income countries that have introduced at least one new and underutilized vaccine to their national immunization programme and sustained vaccine use for at least 12 months during the period 2010–2015, 64 (88%) have benefited from Gavi Alliance support.

DEFINITION OF INDICATOR	A vaccine is added to the national immunization schedule and used for a sustained period of at least 12 months. New and underutilized vaccines are all vaccines that were not previously included in the national immunization schedule Introduction of a single dose of OPV as part of the polio eradication end-game strategy is not considered as an inclusion criterion for this indicator. Only countries that replace OPV with IPV or introduce IPV as part of a sequential schedule are included
TARGET	2015: At least 90 low- and middle-income Member States 2020: All low- and middle-income Member States
DATA SOURCES	WHO-UNICEF joint reporting forms (JRFs)
DATA AVAILABILITY AND QUALITY	The limitations of JRF and WUENIC coverage data were discussed in the GVAP Secretariat report 2013[36]

Results

In the first five years of the Decade of Vaccines – January 2010 to December 2014 – 99 low- and middle-income countries added at least one new and underutilized vaccine to their national immunization programme and sustained vaccine use for at least 12 months, i.e. until December 2015 (Table 2.9). These vaccines include: Hib-containing vaccine, PCV, rotavirus vaccine, human papillomavirus vaccine (HPV), rubella and Japanese encephalitis vaccines. These 99 countries represent more than 70% of the world's population that live in low- and middle-income countries.

[36] For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).

Table 2.9: Number of low- and middle-income Member States that introduced a new and underutilized vaccine Jan. 2010–Dec. 2014 and sustained its use for at least 12 months, by vaccine, Gavi support and World Bank income group

Country classification	Total no. of countries by category	Member States that have introduced at least 1 vaccine	Hib	PCV	Rotavirus	HPV	Rubella	JE
Countries that have ever benefited from Gavi support	73	64 (88%)	14	43	31	3	9	2
Non Gavi-eligible lower-middle income	11	9 (82%)	4	5	3	1	3	0
Non Gavi-eligible upper-middle income	51	26 (51%)	9	13	7	13	0	0
Total	**135**	**99 (73%)**	**27**	**61**	**41**	**17**	**12**	**2**

JE, Japanese encephalitis.

Fifty-two of these 99 low- and middle-income countries introduced one vaccine from 2010 to 2014, while 47 countries introduced more than one vaccine. A total of 160 vaccine introductions took place in these low- and middle-income countries during the first half of the Decade of Vaccines. Table 2.10 shows the breakdown by WHO region.

All but two countries[37] had introduced and sustainably used Hib-containing vaccine by the end of 2015 (Figure 2.12). An increase in new and underutilized vaccine introductions during recent years was seen with the additions of pneumococcal and rotavirus vaccines in lower-middle-income countries, of 45% and 30%, respectively (Table 2.9).

JRF data also show that between 2010 and 2014, 12 low- and middle-countries had introduced and sustained use of rubella vaccine, and 17 low- and middle-countries had introduced and sustained use of HPV vaccine. Only two of these 17 countries – Lesotho and Rwanda – are eligible for Gavi support. There remain 118 countries that have not introduced HPV into their national immunization schedule.

Among the 47 Member States which introduced and sustained more than one vaccine during the period, 14 are upper-middle-income countries, 19 are lower-middle-income countries and 14 are low-income countries.

Table 2.10: Number of Member States that have added one or more new and underutilized vaccines to their national immunization schedule, by year and WHO region (excluding IPV)

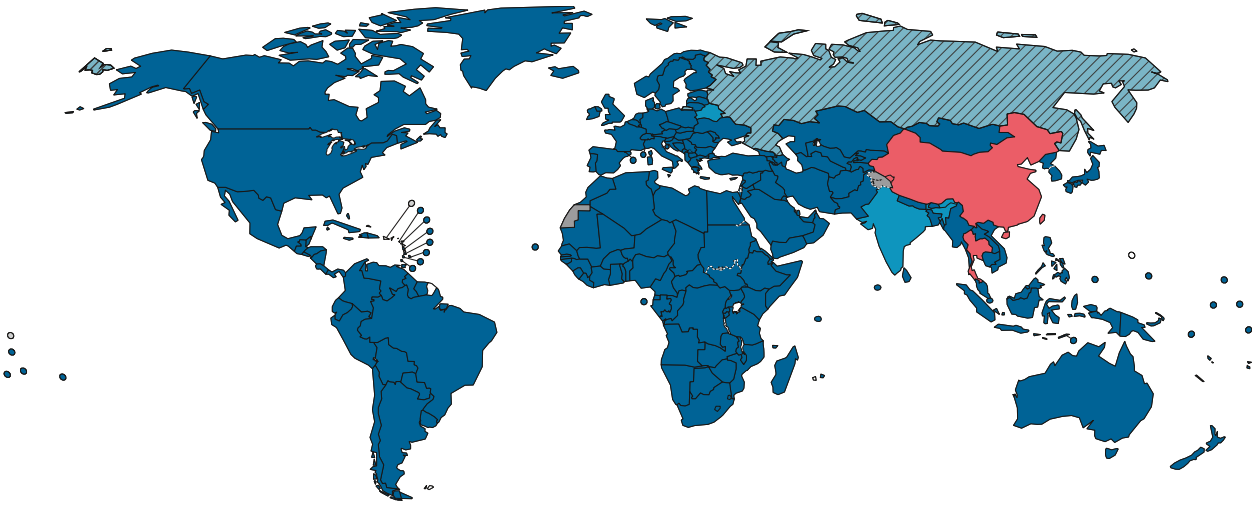
WHO region	No. of low- and middle- income countries[a]/ total Member States in region, 2014	Number of low- and middle-income countries having introduced at least one vaccine[a]				
		2010	2011	2012	2013	2014
African Region	45/47	2 (4%)	11 (24%)	9 (20%)	12 (27%)	23 (51%)
Region of the Americas	24/35[c]	8 (33%)	4 (17%)	6 (25%)	3 (13%)	4 (17%)
South-East Asia Region	15/21	1 (7%)	3 (20%)	3 (20%)	3 (20%)	6 (40%)
European Region	19/53	4 (21%)	2 (11%)	2 (11%)	4 (21%)	3 (16%)
Eastern Mediterranean Region	11/11	0 (0%)	3 (27%)	4 (36%)	2 (18%)	1 (9%)
Western Pacific Region[b]	21/27	5 (24%)	2 (10%)	3 (14%)	6 (29%)	1 (5%)
Total	**135/194**	**20 (15%)**	**25 (19%)**	**27 (20%)**	**30 (22%)**	**38 (28%)**

[a] The same country can introduce several new vaccines during different years, which will result in being counted multiple times (e.g. Cambodia introduced Hib vaccine in 2010 and rubella vaccine in 2013 and therefore is counted in two columns: in 2010 and 2013).
[b] The Cook Islands, Niue and Nauru were not classified by the World Bank, but were considered as upper-middle-income countries for this report.

[37] China has introduced pentavalent vaccine in its national EPI but not as a vaccine fully free of charge. Thailand does not plan to introduce Hib-containing vaccine into its national EPI programme, and Belarus and India only introduced it in some parts of the country.

Figure 2.12 to Figure 2.15 show the status of the use of Hib-containing, pneumococcal conjugate, rotavirus and human papillomavirus vaccines in national immunization programmes worldwide.

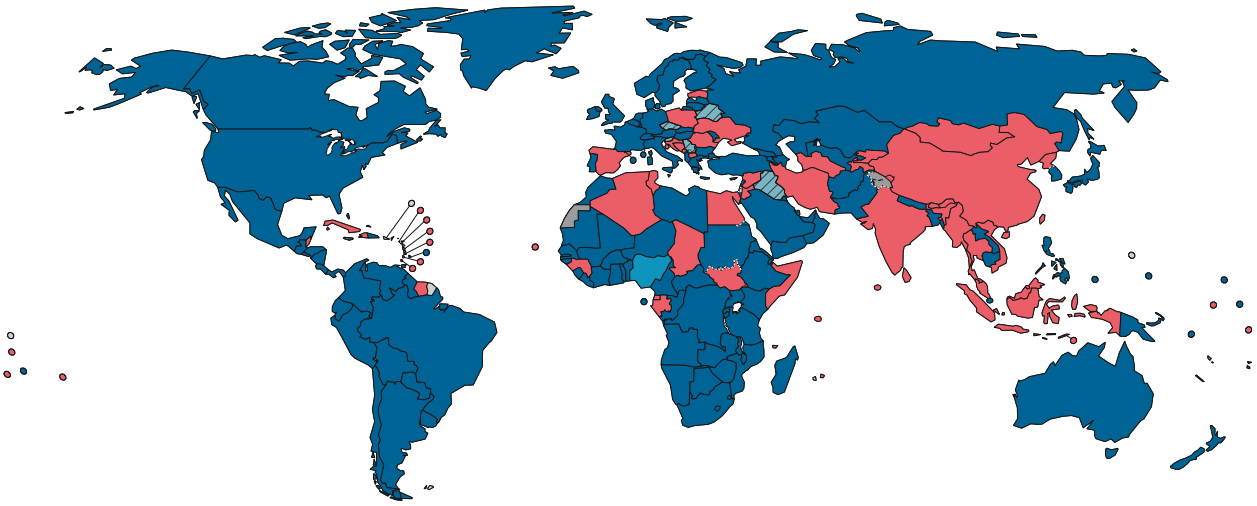
Figure 2.12: Member States with Hib-containing vaccine in their national immunization programme (as of 31 December 2015)



Introduced *(189 countries or 97%)*
Introduced in some parts of the country *(2 countries or 1%)*
Introduced for risk groups only *(1 country or 1%)*
Not introduced *(2 countries or 1%)*
Not available
Not applicable

Data source: WHO/IVB Database, as of 24 June 2016.

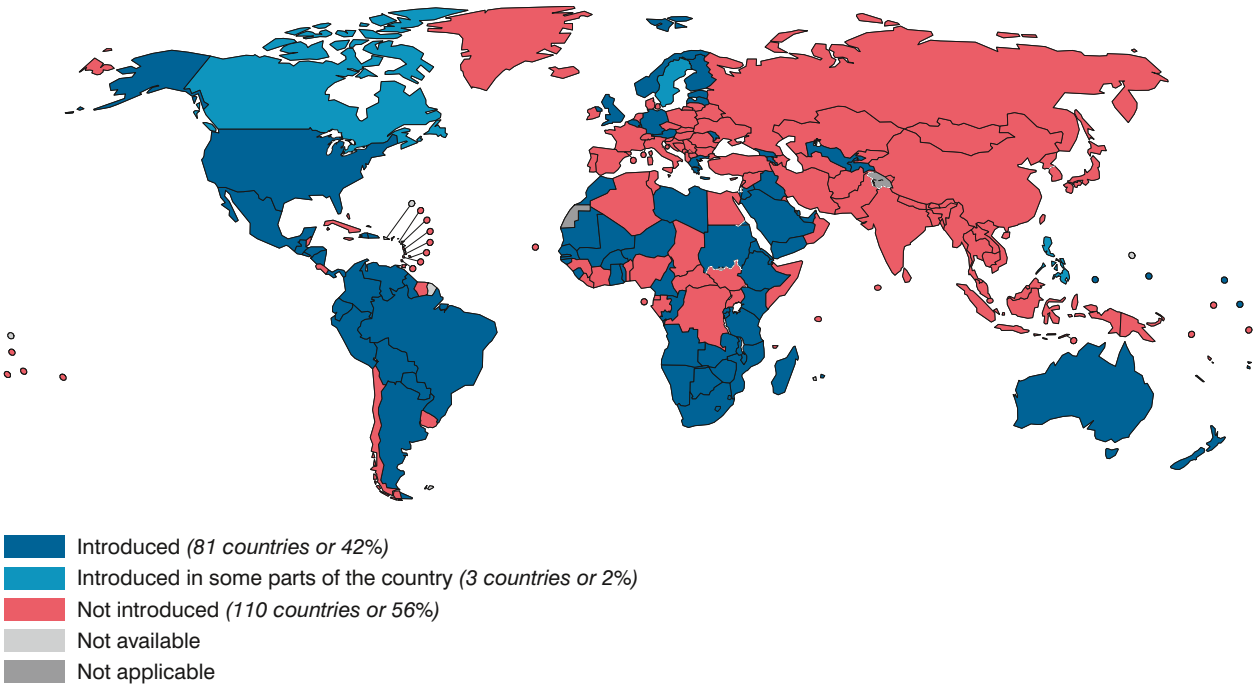
Figure 2.13: Member States with pneumococcal conjugate vaccine in their national immunization programme (as of 31 December 2015)



Introduced *(127 countries or 65%)*
Introduced in some parts of the country *(1 countries or 1%)*
Introduced for risk groups only *(6 country or 3%)*
Not introduced *(60 countries or 31%)*
Not available
Not applicable

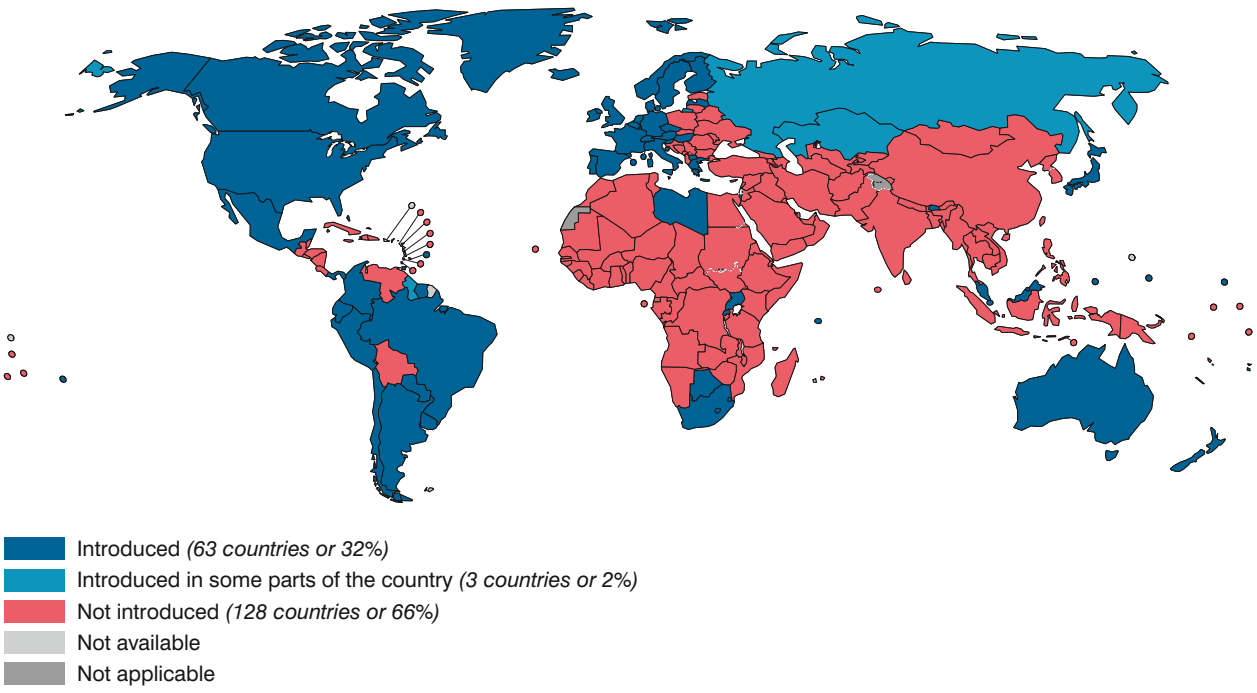
Data source: WHO/IVB Database, as of 24 June 2016.

Figure 2.14: Member States with rotavirus vaccine in their national immunization programme (as of 31 December 2015)

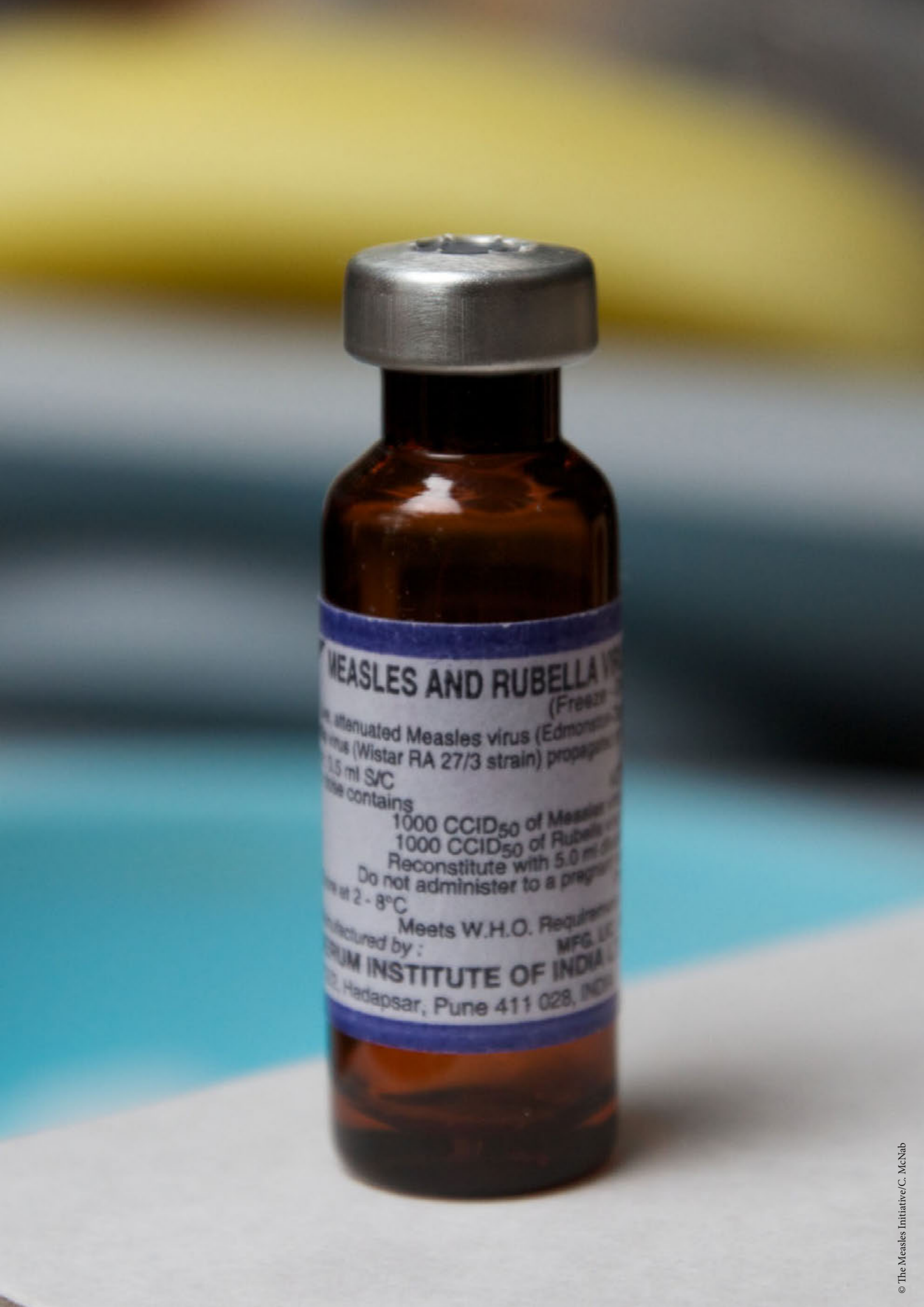


Data source: WHO/IVB Database, as of 24 June 2016.

Figure 2.15: Member States with HPV vaccine in the national immunization programme (as of 31 December 2015)



Data source: WHO/IVB Database, as of 24 June 2016.



3. MILLENNIUM DEVELOPMENT GOAL 4 AND INTEGRATION

Reduce under-five mortality rate (Indicator G5.1)

Highlights

- Substantial progress has been made towards achieving Millennium Development Goal (MDG) 4. The number of deaths of children aged under 5 years worldwide has halved, from 12.7 million in 1990 to 5.9 million in 2015.
- This translates into around 19 000 fewer children dying every day in 2015 than in 1990, but it still implies the deaths of about 16 000 children under the age of 5 every day in 2015.
- Since 1990, the global under-five mortality rate has dropped 53% – from 91 deaths per 1000 live births in 1990 to 43 in 2015. All UN regions, except the Pacific Islands subregion[38], have more than halved the under-five mortality rate. At country-level, about a third of countries *(62)* have reduced their under-five mortality by two thirds or more and achieved the MDG 4 target set in 2000. Among them are 24 low- or lower-middle income countries.

DEFINITION OF INDICATOR	Under-5 mortality rate per 1000 live births
TARGET	2015: Two thirds reduction compared to 1990 2020: Exceed 2015 target
DATA SOURCES	United National Interagency Group on Mortality Estimates *(1)*

Progress towards the achievement of the MDG 4 goal to reduce child mortality is monitored as part of the Countdown 2015 initiative. Progress is measured by the independent Expert Review Group (iERG), based on the recommendations of the Commission on Information and Accountability of the Global Strategy for Women's and Children's Health. The salient findings in the Countdown 2015 report and other reports are summarized below, with links to details.

- Overall, substantial global progress has been made in reducing child deaths since 1990. The number of deaths of children aged under 5 years worldwide has declined from 12.7 million in 1990 to 5.9 million in 2015 – 16 000 deaths every day compared with 35 000 in 1990 – and the global under-five mortality rate has dropped 53%, from 91 deaths per 1000 live births in 1990 to 43 in 2015.
- The world as a whole has been accelerating progress in reducing the under-five mortality rate – its annual rate of reduction increased from 1.8% in 1990–2000 to 3.9% in 2000–2015.
- Promisingly, sub-Saharan Africa, the region with the highest under-five mortality rate in the world, has also registered substantive progress. Its annual rate of reduction increased from 1.6% in the 1990s to 4.1% in 2000–2015.
- A total of 21 sub-Saharan African countries[39] have at least tripled their annual rates of reduction from the 1990s or reversed an increasing mortality trend in 2000–2015 compared with the 1990s.
- The remarkable decline in under-five mortality since 2000 has saved the lives of 48 million children aged

[38] This chapter is extracted from *Levels & trends in child mortality*. Report 2015, which uses the UN regional classification system.
[39] Angola, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Congo, Cote d`Ivoire, Gabon, Kenya, Lesotho, Mauritania, Namibia, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Swaziland, Zambia, Zimbabwe.

under 5 years – children who would not have survived to see their fifth birthday if the under-five mortality rate from 2000 onward remained at the same level as in 2000.

- Between 1990 and 2015, 62 of the 195 countries with available estimates met the MDG 4 target of a two thirds reduction in the under-five mortality rate between 1990 and 2015. Among them, 24 are low- and lower-middle-income countries.
- Despite these gains, the 53% decline in the under-five mortality rate globally is far from the two thirds reduction required to meet the MDG 4 target. Progress remains insufficient to reach MDG 4 globally and in many regions, particularly in Caucasus and Central Asia, Oceania, Southern Asia and sub-Saharan Africa.
- Accelerating progress in child survival urgently requires greater attention to ending preventable child deaths in southern Asia and sub-Saharan Africa. In sub-Saharan Africa 1 child in 12 dies before his or her fifth birthday – far higher than the average ratio of 1 in 147 in high-income countries. Southern Asia has the second-highest under-five mortality rate in the world – about 1 child in 19 dies before age 5.
- Globally, the neonatal mortality rate fell from 36 deaths per 1000 live births in 1990 to 19 in 2015, and the number of neonatal deaths declined from 5.1 million to 2.7 million. However, the decline in neonatal mortality from 1990 to 2015 has been slower than that of post-neonatal under-five mortality: 47% compared with 58% globally.
- The share of neonatal deaths is projected to increase from 45% of deaths of children aged under 5 years in 2015 to 52% in 2030. Moreover, 63 countries need to accelerate progress to reach the Sustainable Development Goal (SDG) target of a neonatal mortality rate of 12 deaths per 1000 live births by 2030 – more than the 47 countries for the under-five mortality target.
- Most child deaths are caused by diseases that are readily preventable or treatable with proven, cost-effective and high-quality interventions. Infectious diseases and neonatal complications are responsible for the vast majority of deaths of children aged under 5 years globally.
- The main killers of children aged under 5 years in 2015 include preterm birth complications (18%), pneumonia (16%), intrapartum-related complications (12%), diarrhoea (9%) and sepsis/ meningitis (9%). Importantly, almost half of all deaths of children aged under 5 years are attributable to under-nutrition, while more than 80% of neonatal deaths occur among new-born infants of low birth weight in the highest-burden settings.
- An acceleration of the pace of progress is urgently required to achieve the SDG target on child survival, particularly in high-mortality countries in sub-Saharan Africa. To achieve the SDG target of an under-five mortality rate of 25 or fewer deaths per 1000 live births by 2030, a total of 47 countries need to increase their pace of progress. Among these, 30 countries must at least double their current rate of reduction, and 11 of those 30 countries must at least triple their current rate of reduction.
- In order to continue to accelerate progress, it is critical to ensure that every pregnant woman and every newborn has access to and receives good quality care and life-saving interventions. The vast majority of maternal and newborn deaths can be prevented by relatively straightforward effective interventions. Quality of care in delivering these interventions along the continuum of care during pre-pregnancy, antenatal, intra-partum, childbirth and post-natal periods is paramount to ensure progress.
- Wide gaps in child mortality across subgroups or areas within countries have been documented in the low-mortality countries group of nations, warranting a call for an equity-focused approach to reducing child mortality. For example, Brazil is one of the countries that succeeded in meeting MDG 4 goal, but disparities still persist in the country. Indigenous children are twice as likely to die before reaching their first birthday as other Brazilian children. This example illustrates that even for countries with relatively low levels of mortality, greater efforts to reduce disparities at the subnational level and across different groups are required to achieve equity in child survival and lower mortality levels overall.
- Countries and the international community must take immediate action to further accelerate the pace of progress to fulfil the promise to children. Without intensified efforts to reduce child mortality, particularly in the highest-mortality areas and in contexts of persistent inequities, the SDG targets will be unattainable. Child survival must remain at the heart of the post-2015 SDG agenda.

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Integration of health care interventions and immunization activities (Indicator G5.2)

DEFINITION OF INDICATOR	The DoV Secretariat is proposing the following revised indicators: a) Composite Coverage Index (CCI)[40] *(1)*, a weighted average of coverage of a set of eight preventive and curative interventions for the 75 Countdown countries; and b) Comparative coverage by country of the CCI component interventions in 4 stages of the continuum of care (family planning, maternal and newborn care, immunization and case management of sick children), stratified by countries with CCI < 60, CCI 60–70, CCI > 70
TARGET	No target set
DATA SOURCES	**Countdown 2015 Report for CCI**[41]

Background

During their review of progress in 2013, the SAGE Decade of Vaccines working group requested the DoV Secretariat to develop an additional monitoring indicator specifically focusing on integration of immunization activities with other health interventions, with the objective of measuring countries efforts in reducing the number of missed opportunities for any preventive interventions aiming at reducing mother and child mortality. In its 2014 GVAP Secretariat report *(2)* the DoV Secretariat provided data on two indicators:

1. provision of vitamin A with routine or supplementary immunization; and
2. comparative rates of coverage with last dose of rotavirus vaccine, oral rehydration salts (ORS) use during diarrhoea and exclusive breastfeeding for six months.

The SAGE DoV working group was not fully satisfied with the second indicator and requested the DoV Secretariat to explore alternatives. Therefore, in 2015, the DoV Secretariat proposed to replace this indicator with:

- comparative coverage of the first antenatal visit (ANC1), protected at birth against neonatal tetanus (PAB), third does of DTP (DTP3) and first dose of measles-containing vaccine (MCV1).

In August 2015, the SAGE DoV working group expressed that this was a more meaningful measure of integration and proposed that it could be further improved by presenting countries stratified into three groups depending on their ANC1/DTP3/PAB/MCV1 status[42] (this stratification is presented in Annex 3.1). The SAGE DoV working group suggested consideration of other health interventions to highlight the importance of integrating the whole life-course and the issue of missed opportunities, but acknowledged that data availability limits the potential to reflect integration of health interventions.

Rationale for proposing revised indicators

For the 2016 analysis of the progress in 2015 for integration of immunization with other health services, the DoV Secretariat considered several options. Because the goal of an integration is the "management and delivery of health services so that clients receive a continuum of preventive and curative services" *(3)* the Secretariat aimed to select an indicator that was more comprehensive than previous reports; and since immunization service delivery "should continue to serve as a platform for providing other priority public health interventions…other priority programmes should also serve as a platform for delivering immunization" *(4)*, the DoV Secretariat sought to select an indicator that would be useful in identifying missed opportunities in both directions (i.e. immunization as a platform for other services and other services as a platform for immunization). In addition, an indicator was sought that uses available data, and could be tracked

[40] Based on the weighted average of coverage of a set of eight preventative and curative interventions; the CCI gives equal weight to four stages in the continuum of care: family planning, maternal and newborn care, immunization and case management of sick children. The weighted average for a group (e.g. a country or a wealth quintile) is calculated as

$$\frac{1}{4}\left(FPS+\frac{SBA+ANCS}{2}+\frac{2DPT3+MSL+BCG}{4}+\frac{ORT+CPNM}{2}\right)$$

FPS is family planning needs satisfied, SBA is skilled birth attendant, ANCS is antenatal care with skilled provider, DPT3 is three doses of diphtheria–pertussis–tetanus vaccine, MSL is measles vaccination, BCG is BCG (tuberculosis) vaccination, ORT is oral rehydration therapy for children with diarrhoea, and CPNM is care seeking for pneumonia. More information at: http://www.countdown2015mnch.org/documents/2015Equity/2015_CD_equity_profiles_all.pdf.

[41] Data available at www.countdown2015mnch.org.

[42] Minutes of the 12 August 2015 teleconference of the SAGE Decade of Vaccines working group discussing the GVAP Secretariat report (unpublished).

over time. Five candidate indicators were considered and exploratory analyses were performed to test the feasibility and usefulness of each.

The five possible indicators for integration considered for the 2016 report were, in the 75 Countdown countries[43]:

1. **Vitamin** A provision with routine or supplementary immunization activities
2. a) **Comparative coverage** for ANC1, PAB, DTP3 and MCV1, stratified by countries where
   - ANC1 significantly lower than DTP3/PAB/MCV1 coverage
   - ANC1 significantly higher than DTP3/PAB/MCV1 coverage
   - ANC1 and PAB well below DTP3 and MCV1 or

   b) Comparative coverage similar to a) that includes ANC4, PAB, DTP3 and MCV1, family planning, skilled birth attendant, postnatal care and exclusive breastfeeding.
3. Proportion of countries that have introduced **hepatitis B birth dose** (within 24 hours of birth)
4. Proportion of countries in which routine doses of vaccine are administered in **school**
5. **CCI, and comparative coverage of the CCI component interventions in four stages of the continuum of care** (family planning, maternal and newborn care, immunization and case management of sick children), with stratification of countries by:
   - CCI < 60
   - CCI 60–70
   - CCI > 70

Options 1, 3 and 4 (vitamin A, hepatitis B birth dose, school immunization) were determined to be too limited in scope. Option 2 (various versions of comparative coverage levels) was determined to be too complex for understandable presentation. The exploratory analyses for these options are included in Annex 3.1.

Proposed revised integration indicators

The DoV Secretariat proposes **option 5** (an analysis using CCI) for the following reasons, and presents the findings herein.

Proposed is a modification of the CCI, a weighted average of coverage of a set of eight preventative and curative interventions for the 75 Countdown countries. Rather than present only a single composite indicator, a modification is presented that includes a comparative coverage of the CCI component interventions in four stages of a continuum of care:

1. family planning needs satisfied
2. maternal and newborn care (skilled birth attendant, antenatal care with skilled provider)
3. immunization (DTP3, MCV1, BCG)
4. case management of sick children (ORS for children with diarrhoea, care seeking for pneumonia).

The Secretariat considered presenting coverage levels for the eight separate interventions, but opted for presenting coverage levels for the four stages to render the data more interpretable. Additionally, to better guide interpretation and design of activities to improve integration, the results are stratified by countries with CCI < 60 (weak health systems), CCI 60–70 (less weak systems), CCI > 70 (stronger systems) (Figure 3.1, Figure 3.2 and Figure 3.3).

Maternal and child health interventions as measured by CCI are well-correlated with child mortality in the first five years of life. At the child level, a unit increase in CCI was associated with an odds ratio of 0.86 for child mortality (95% confidence interval, CI, 0.82–0.90) and ecologically associated with a reduction in child mortality of 29 per 1000 (95% CI -43.2 to -14.7) *(5)*. While encompassing a range of interventions, a composite indicator like CCI provides a single measure for easier cross-country comparisons. Rather than depending on the single index alone, the values are presented for the four stages of the continuum of care to identify the relative standing of the immunization component. Rather than presenting all the components of the CCI, we opted to show the collapsed version of the 8 interventions into the 4 stages of care to render it more interpretable. By presenting the differences between immunization and other services, potential missed opportunities can be identified.

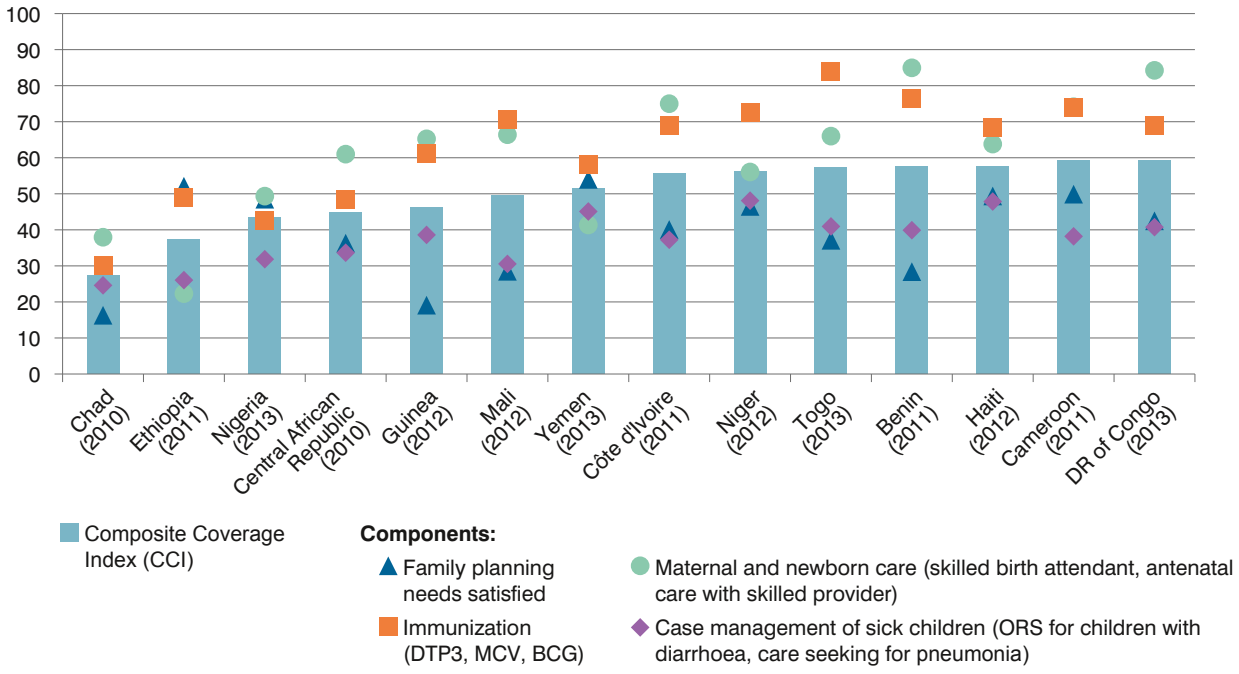
Data availability and quality

The CCI data is from the Countdown Equity Analyses by Country-2015.[44] WUENIC estimates for DTP3, MCV1 and BCG are used in the CCI. Although WUENIC estimates are available annually, for accurate comparability, the immunization estimates used are those included in the CCI (i.e.in the same year as the most recent CCI data). Updated CCI data are not available each year because most elements are from

[43] For a list of the 75 Countdown countries, see: http://www.countdown2015mnch.org/country-profiles.
[44] Data available at www.countdown2015mnch.org and http://www.countdown2015mnch.org/about-countdown/countdown-data.

DHS and MICS surveys. Analyses were limited to data from 2010 forward. CCI data were unavailable (due to lack of recent data or missing data) for 30 Countdown countries.

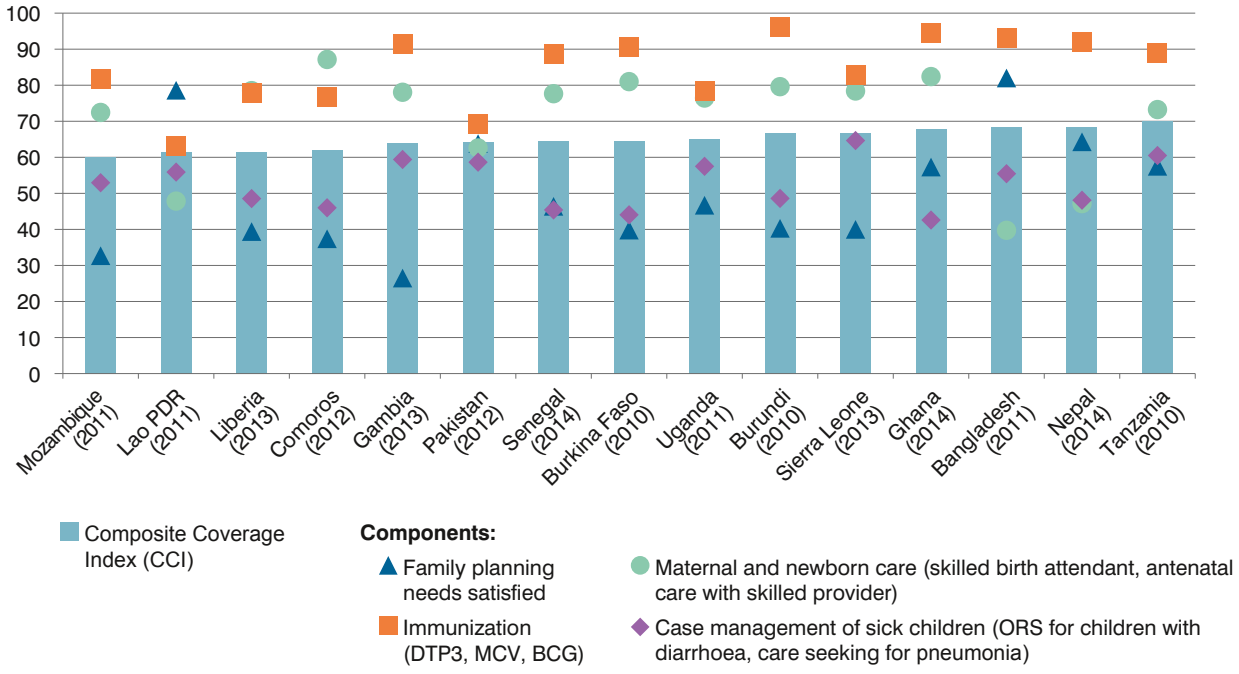
Figure 3.1: Composite Coverage Index (CCI) and coverage for four CCI components in Countdown countries[a] with a CCI < 60% (year indicated for each country)



[a] Countdown countries with available data since 2010.

Source: Countdown to 2015 report data *(6)*.

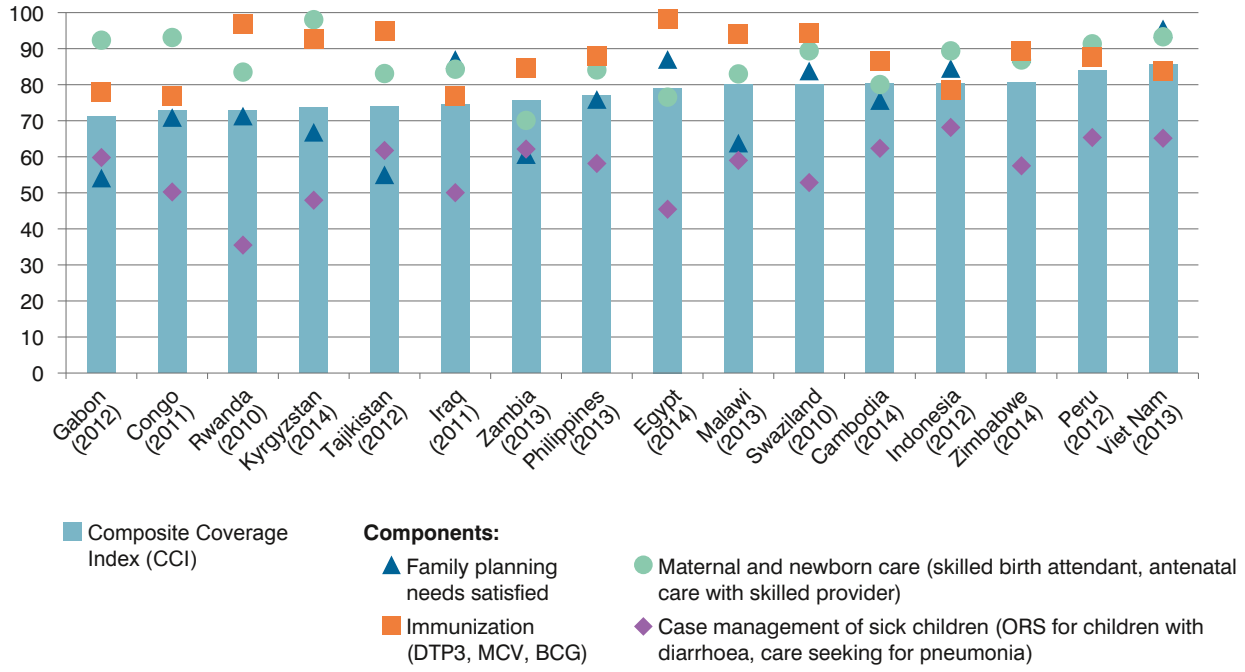
Figure 3.2: Composite Coverage Index (CCI) and coverage for four CCI components in Countdown countries[a] with a CCI 60–70% (year indicated for each country)



[a] Countdown countries with available data since 2010.

Source: Countdown to 2015 report data *(6)*.

Figure 3.3: Composite Coverage Index (CCI) and coverage for four CCI components in Countdown countries[a] with a CCI > 70% (year indicated for each country)



[a] Countdown countries with available data since 2010.

Source: Countdown to 2015 report data *(6)*.

Figures 3.1–3.3 show the CCI and the coverage of its four components by Countdown country, with stratification by countries with CCI < 60, CCI 60–70, CCI > 70. Across all three categories of CCI, there are several countries with wide variations in the coverage of the four components, suggesting that missed opportunities may exist. Improvements in coverage for some services with low coverage could improve by linking with other services with higher coverage (e.g. immunization). However, particularly in weak health systems, care should be taken to avoid overburdening functioning services without provision of additional human and logistical resources. Of note: in the vast majority of countries, the component with the lowest coverage was either "case management of sick children" or "family planning needs satisfied" (Table 3.1).

Table 3.1: Median coverage of the four Composite Coverage Index (CCI) components in Countdown countries with a CCI < 60%, 60–70%, and > 70%

Categories	Median across all countries	Median across countries with CCI < 60%	Median across countries with CCI 60–70%	Median across countries with CCI > 70%
Family planning needs satisfied	54%	41%	46%	76%
Maternal and newborn care	78%	65%	78%	86%
Immunization	82%	69%	89%	88%
Case management of sick children	49%	38%	53%	59%

Given the higher coverage for immunization and the low coverage for other interventions, particularly family planning and case management of sick children, opportunities should be sought during immunization visits to address low coverage interventions when feasible (e.g. referral for family planning services, counselling parents about when to seek care for sick children).

Immunization was the component with the highest coverage in the majority of countries. In only a few countries (e.g. Indonesia or Gabon), maternal and

newborn care (skilled birth attendant, antenatal care with skilled provider) was higher than immunization. This suggests that there may be missed opportunities for reminders about the importance of child immunization during antenatal care in those countries, although in many of these countries coverage differences between immunization and maternal and newborn care were small.

There are limitations to using the modification of CCI as an indicator for integration. Thirty Countdown countries did not have recent CCI data available (since 2010). Although WUENIC immunization estimates are available annually, updated CCI estimates are not available each year because they are derived from household (DHS and MICS) surveys. The DoV Secretariat opted to time match immunization data with other CCI component data for accurate comparability, so some countries' data are from a few years ago, although data prior to 2010 was excluded. However, radical changes in maternal child indicators are unlikely over short time spans, so such a comparison should not introduce error. Finally, it should be noted that maternal child health indicators are imperfectly measured. For example, accurately ascertaining "care seeking for pneumonia" is difficult when asking parents retrospectively about clinical presentation.

Countries may wish to perform equity analyses on CCI to better target interventions in their local context. WHO's Health Equity Assessment Toolkit (HEAT)[45] is a user-friendly tool that enables health inequality comparisons of numerous maternal child indicators (including CCI) within and across countries.

References

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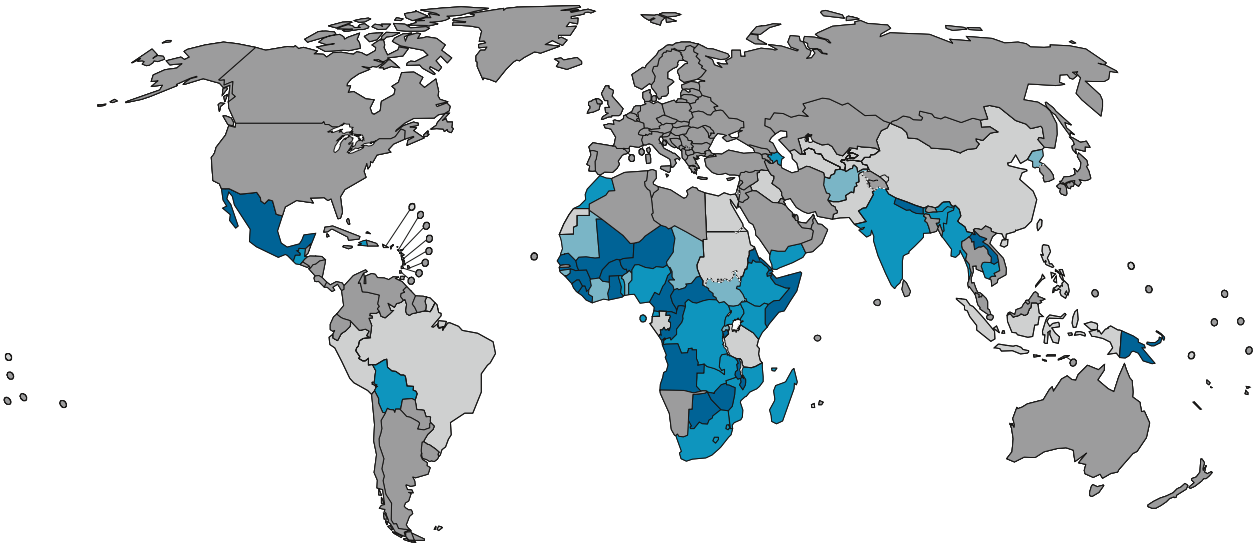
[45] The tool can be found at: https://whoequity.shinyapps.io/HEAT/.

ANNEX 3.1: Exploratory analyses for considered options for integration indicators considered by the DoV Secretariat

Option 1. Vitamin A provision with routine or supplementary immunization

Similar to 2014, in 2015, among the 75 Countdown countries, 23 (32%) of countries provided vitamin A with both routine and supplementary immunization activities (Figure A3-1), 24 countries (33%) provided vitamin A only with routine immunization services and nine countries (13%) provided vitamin A only with supplemental immunization activities. In 16 countries (22%) vitamin A was not distributed and in three countries vitamin A was not considered a public health problem. In 2014, the ratio of vitamin A coverage to DTP3 coverage was included in the report but there were questions about the denominators used. For the exploratory analyses this year, the coverage ratio was not calculated because the number of countries with vitamin A data (data are from UNICEF) and the specific countries with data changes from year to year, precluding comparisons over time. In addition coverage comparisons are problematic because vitamin A is typically given on a 6-month schedule starting at 6 months of age in most countries, whereas MCV1 is typically given at 9 months.

Figure A3-1: Countries providing vitamin A supplementation with routine and/or supplementary immunization activities, 2015



Vitamin A distributed with routine and supplementary immunization activities (*23 countries or 32%*)
Vitamin A distributed only with routine immunization services (*24 countries or 33%*)
Vitamin A distributed only with supplementary immunization activities (*9 countries or 13%*)
Not available/No vitamin A distribution (*16 countries or 22%*)
Not a Countdown country (*119 countries*) or Countdown country for which vitamin A deficiency is not a public health problem (*3 countries*)

Source: WHO/UNICEF database, as of 24 June 2016.

Option 2. Comparative coverage levels

In 2015 the SAGE DoV working group requested:

a. **Comparative coverage for ANC1, PAB, DTP3 and MCV1, stratified by countries where**

- ANC1 significantly lower than DTP3/PAB/MCV1 coverage
- ANC1 significantly higher than DTP3/PAB/MCV1 coverage
- ANC1 and PAB well below DTP3 and MCV1.

Exploratory analyses were performed using both 10% (percentage points and 20% differences); see Table A3-1.

Table A3-1: Percentage of women who attended at least ANC1 compared to coverage rates for DTP3 and MCV1 and percentage of live births protected through maternal immunization with at least 2 doses of TT (PAB) for all Countdown countries

Number		Number of Countdown countries	Comment
1	ANC1 10% lower than all DTP3/PAB/MCV1	8	(4/8 also fit into number 3)
2	ANC1 10% higher than all DTP3/PAB/MCV1	10	
3	ANC1 and PAB below both DTP3 and MCV1	15	(4/8 also fit into number 1)
4	None of these categories	46	
5	ANC1 20% lower than all DTP3/PAB/MCV1	3	
6	ANC1 20% higher than all DTP3/PAB/MCV1	1	
7	ANC1 and PAB below both DTP3 and MCV1	15	
8	None of these categories	56	

Source: DTP3, PAB, MCV1, 2014 WUENIC estimates. ANC1, UNICEF global databases 2015 based on DHS, MICS, and other nationally representative surveys.

These analyses pose interpretation challenges because: 1) the large number of countries that fit into no category, 2) the non mutually-exclusive categories when the more inclusive 10 percentage-point difference is used, 3) missing data for ANC1 and PAB (e.g. nine of the 75 countries have no PAB estimates because PAB estimates are made only for countries for which TT vaccination is in the national immunization schedule for pregnant women), and 4) the four indicators represent a limited look at health service delivery during the pregnancy-birth-infant continuum. Therefore, another option was explored, b) below.

b. **As a more comprehensive approach to a) above, an analysis was done (called "life course")** which compared coverage for ANC4, PAB, DTP3, MCV1, family planning, skilled birth attendant, postnatal care-mother, postnatal care-baby and exclusive breastfeeding. Initially an attempt was made to group the countries into three groups (uniformly high coverage, uniformly low coverage and wide variation in coverage) based on a 20% difference between highest and lowest coverage within a country. However, there was only one country with a difference less than 20%. The median difference in coverage between the highest and lowest interventions was 55% among the 75 countries. Next a 51% difference between highest and lowest was explored.

Group 1: 15 countries were sorted into 1) uniformly high coverage—these countries had 51% or less difference between the highest and lowest indicators and the highest indicator was equal to or greater than 90%.

Group 2: 18 countries were sorted into 2) uniformly low coverage—these countries had 51% or less difference between the highest and lowest indicators and the highest indicator was less than 90%.

Group 3: 42 countries were sorted into 3) wide variation in coverage—these countries had a greater than 51% difference between the highest and lowest indicator.

However, this categorization was difficult to interpret, especially given the variations that occur with nine component indicators and the large number of countries in group 3. Therefore, exploration was done grouping the countries into eight categories: uniformly high coverage, uniformly low coverage and variation in coverage (subdivided into which CCI intervention had the lowest coverage: FPS, ANC4, SBA, PNC-mother, PNC-baby and EBF). However many countries had missing data for a variety of indicators. Only 34 countries had values for every indicator. One example: nine of the 75 countries have no protected at birth against neonatal tetanus (PAB) estimates because PAB estimates are made only for countries for which TT vaccination is in the national immunization schedule for pregnant women. In addition, the large number of intervention without a standardized index rendered interpretation difficult.

Option 3. Proportion of 75 Countdown countries that have introduced hepatitis B birth dose (within 24 hours of birth)

Hepatitis B birth dose requires integration of birth dose administration with maternal and newborn care in health facilities or with home visits. Hepatitis B birth dose varies from other vaccinations in that delivery of vaccine is not schedulable, placing special demands on a health system to respond within 24 hours of childbirth. In a test analysis in 2014, 96 of 194 (49%) countries globally and 25 of 75 (33%) Countdown countries had introduced Hepatitis B birth dose.[46] The median coverage in 25 Countdown countries that have introduced was 78%.

Option 4. Routine immunization offered in school

Twenty-three of the 75 (30.7%) Countdown countries responded yes to having routine doses of vaccine given to children at school (Table A3-2). A total of 52 of the 75 (69.3%) Countdown countries responded no to having routine doses of vaccine given to children at school.

Table A3-2: Countdown countries providing routine immunization at school[a]

Are any routine doses of vaccine given to children at school?	Countries
Yes	Angola, Bolivia (Plurinational State of), Botswana, Brazil, Egypt, Eritrea, Indonesia, Iraq, Kyrgyzstan, Lesotho, Malawi, Mexico, Mozambique, Papua New Guinea, Peru, Philippines, Rwanda, Sierra Leone, Solomon Islands, South Africa, Swaziland, Uganda, Uzbekistan
No	Afghanistan, Azerbaijan, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, Central African Republic (2014), Chad, China, Comoros, Congo (2014), Cote d`Ivoire, Democratic People`s Republic of Korea, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guatemala (2012), Guinea, Guinea-Bissau, Haiti, India, Kenya (2014), Lao People`s Democratic Republic, Liberia, Madagascar, Mali, Mauritania, Morocco, Myanmar, Nepal (2014), Niger, Nigeria, Pakistan, Sao Tome and Principe, Senegal, Somalia, South Sudan, Sudan, Tajikistan, Togo, Turkmenistan, United Republic of Tanzania, Viet Nam, Yemen, Zambia, Zimbabwe

[a] Unless otherwise noted, data are taken from 2015.

Source: WHO. Immunization provided at school http://www.who.int/immunization/monitoring_surveillance/data/en/.

[46] Data source: WHO/IVB Database as at 30 June 2016 and ECDC published data at http://vaccineschedule.ecdc.europa.eu/Pages/Scheduler.aspx.

4. COUNTRY OWNERSHIP

Presence of an independent technical advisory group that meets the defined criteria (Indicator SO1.2)

Highlights

- A total of 77 Member States (including 49 developing countries and five low-income countries) reported access to a National Immunization Technical Advisory Group (NITAG) that met all six process indicators, representing a 108% increase over the 37 countries reported on in 2010;
- A total of 116 (60%) Member States reported the existence of a NITAG with an administrative or legislative basis (accounting for 88% of the global population);
- There has been no change in the number of countries meeting the six process indicators since 2014 (10 new countries met the six functionality criteria, while 10 countries dropped from the list).
- Formalization of approaches to allow small Member States to benefit from subregional or other Member States' advisory groups have lagged and need to be prioritized.
- At the 11–12 May international NITAG meeting, there was a strong call by countries to proceed with the establishment of a global NITAG network, which would accelerate progress on reaching the target.
- During this meeting emphasis was put on the value for countries of evaluating their NITAG using the evaluation tool developed by the WHO Collaborating Centre AMP-HPID.

DEFINITION OF INDICATOR	A functional NITAG has been defined as one that meets all of the six following process indicators agreed upon in 2010 by WHO and its partners involved with the strengthening of NITAGs: 1. legislative or administrative basis for the advisory group; 2. formal written terms of reference; 3. at least five different areas of expertise represented among core members; 4. at least one meeting per year; 5. circulation of the agenda and background documents at least one week prior to meetings; 6. mandatory disclosure of any conflict of interest These six indicators do not guarantee the functionality of the NITAG but have been agreed upon as a minimum set of indicators that will allow for monitoring of progress at the global level. A more comprehensive set of indicators has been published for use at national level *(1)*
TARGET	Functional NITAGS in all Member States by 2020
DATA SOURCES	Process indicators related to the establishment of NITAGs have been included in the WHO-UNICEF JRF since 2011 and in that year data were collected for 2010. In this summary of information from Member States regarding the existence of a NITAG, the specific criteria are derived from the 2015 JRF and compared with JRF data collected for previous years. For those Member States that did not submit or fully complete the JRF for 2015, information from the previous year's JRF was used The denominator used to calculate the proportion of NITAGs in existence is the number of Member States that completed the NITAG-related section of the JRF. The results are presented by WHO region, World Bank national income status categories and population size. Population figures are those from the United Nations Population Division *(2)*

Data limitations

As highlighted in the previous GVAP Secretariat report *(3)* these results are subject to data limitations including some lack of data completion, the absence of a systematic data validation process with national counterparts and some confusion with the countries inter-agency Coordinating Committee (ICC). This confusion was actually documented but has been minimized overtime. An increasing number of countries have corrected the information provided during previous years and corrections were retrospectively applied to the reported data for the previous years concerned. In order to assess the evolution of NITAG implementation and functionality since 2010, we conducted a thorough data cleaning based on consistency of responses on the overall time trend with final approval at country level.

When Member States report the existence of a NITAG with formal terms of reference or the existence of a NITAG with a formal administrative or legislative basis, data should be less susceptible to reporting bias than the mere reporting of the existence of a NITAG, and therefore the number of such groups should be closest to the actual number with respect to the existence of a NITAG. The number of Member States reporting the existence of a NITAG which complies with all six indicators is also less susceptible to reporting bias/error.

Results

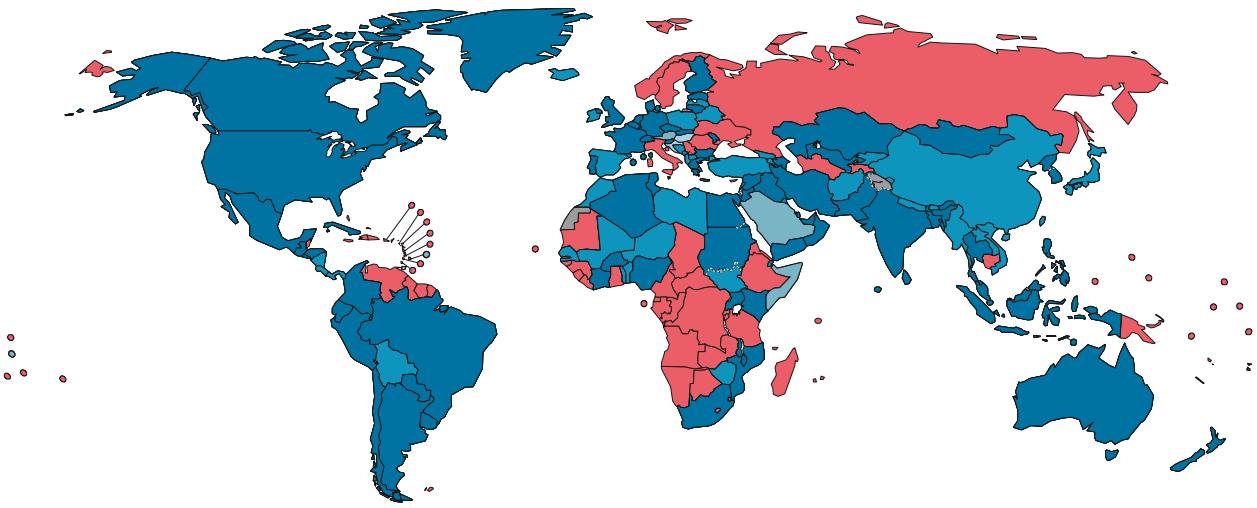
As of 26 June 2015, 183 (94%) Member States had completed the 2015 JRF,[47] reporting immunization-related data for 2014 and 181 (93%)[48] provided a response to at least one of the NITAG-related JRF questions. Among the Member States that did not submit their JRF or their NITAG-related data for 2015 all of them had reported NITAG data in the past two years (i.e. data for 2013 and 2014). Data for 2013[49] and 2014 were included in the 2015 data set for these Member States. Monaco reported considering the French NITAG being theirs and therefore data from France were included in the data set for Monaco.

Therefore, data for 194 Member States were available for the analysis as presented in Figure 4.1 and Table 4.1. Table 4.1 also presents the 2015 NITAG-related indicators status at the global and regional levels.

Figure 4.2 attempts to present the 2010–2015 trajectory in the establishment of NITAGs and highlights the need for acceleration of progress to reach the GVAP NITAG target. The comparison between 2010 and 2015 is only provided at global level as progress encountered in some regions prior to 2010 could lead to spurious interpretation of the trends when broken down by region.

[47] As at 24 June 2016, Member States that have yet to submit 2016 JRF data for 2015 include Albania, Finland, Greece, Libya, Monaco, Netherlands, Poland, Singapore, Turkey, Tuvalu and Ukraine.
[48] Member States that have not completed the NITAG portion of JRF include Luxembourg and Sudan.
[49] Luxembourg and Ukraine.

Figure 4.1: National Immunization Technical Advisory Groups in 2015



77 countries meeting the six NITAG criteria
116 countries having a NITAG with administrative or legislative basis
118 countries reporting the existence of A NITAG with terms of reference
124 countries reporting the existence of a NITAG
No NITAG/Not available
Not applicable

Source: WHO-UNICEF Joint Reporting Form Database.

Figure 4.2: Time trend 2010–2015 in the establishment of NITAGs meeting all six process indicators, and remaining progress needed to reach 2020 target

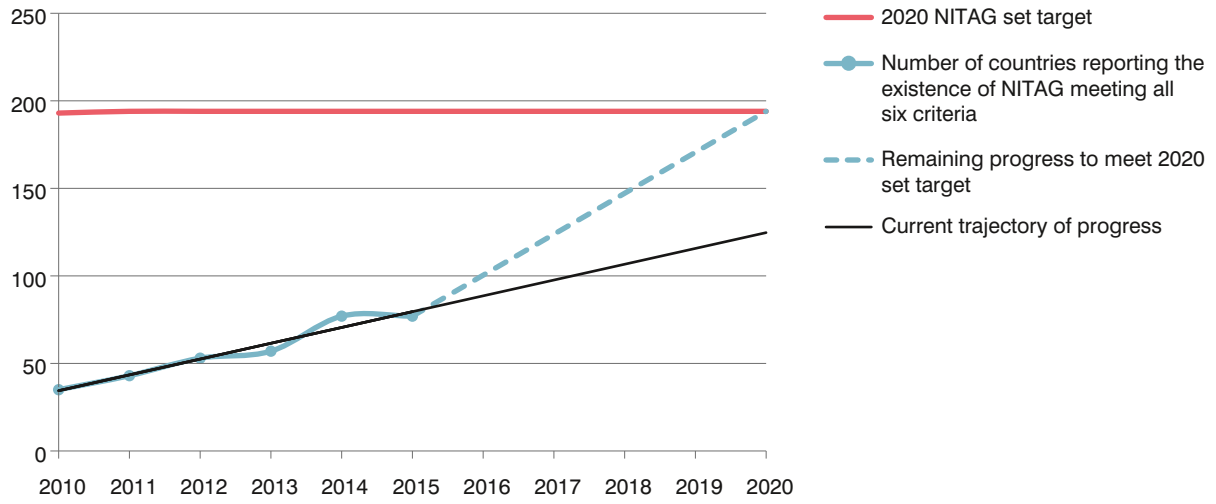


Table 4.1: NITAG characteristics at global level and by WHO region, 2015

INDICATOR		WHO region						
		Global	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region
	No. of Member States with NITAG data available (%)	194/194 (100)	47/47 (100)	35/35 (100)	21/21 (100)	53/53 (100)	11/11 (100)	27/27 (100)
Existence of a NITAG	No. of responding Member States reporting the existence of a NITAG (%)	124 (64)	16 (34)	21 (60)	21 (100)	42 (81)	11 (100)	13 (48)
	Percentage of population covered by a NITAG	89	55	94	100	66	100	99
NITAG meeting all six process indicators	No. of Member States reporting the existence of a NITAG meeting all six process indicators (%)	77 (62)	9 (56)	15 (71)	13 (62)	25 (60)	8 (73)	7 (54)
	Percentage of responding Member States with a NITAG meeting all six process indicators	40	19	43	62	47	73	26
	Percentage of the entire population covered with a NITAG meeting all six process indicators	59	45	91	80	42	96	12

Notable progress was achieved between 2010 and 2015, and 116 (60%) Member States overall reported the existence of a NITAG with a formal legislative or administrative basis. In 2015, there were 77 Member States[50] with a NITAG that met all six process indicators, including a total of 49 developing Member States. This is a 108% increase compared to 2010, when only 37 countries reported having a NITAG meeting all six process indicators. The global trend shows a stagnation of progress, however, in the number of countries meeting the six process indicators between 2014 and 2015. In 2015, 10 new countries[51] met the six process indicators, while 10 countries dropped from the list. The main cause of this drop is the fact that the NITAG did not meet in 2015 for nine of these countries.

In 2015, 16% of low-income countries, 38% of middle-income countries and 59% of high-income countries reported having a NITAG meeting all six process indicators. Overall, 59% of the global population live in a country with a NITAG that meets all six process indicators.

The South-East Asia Region (where all countries have now established a NITAG) had the highest proportion of Member States reporting the existence of a NITAG that met all six process indicators (73%) and the African Region the lowest (50%). Nevertheless, remarkable progress were made in the African Region between 2014 and 2015, multiplying by more than two the total population living in a country having a NITAG meeting the six process indicators (from 20% to 45%). The South-East Asia Region also had the greatest percentage (100%) of Member States that had a NITAG based on a formal legislative decree. Percentages in the other regions were 36% (African Region), 74% (European Region), 90% (Eastern Mediterranean Region), 44% (Western Pacific Region) and 54% (Region of the Americas) – these two latter regions being affected by a substantial number of small Member States.

[50] Algeria, Andorra, Argentina, Australia, Azerbaijan, Bahrain, Bangladesh, Belgium, Brazil, Bulgaria, Burkina Faso, Canada, Chile, Colombia, Côte d'Ivoire, Cuba, Czech Republic, Democratic People's Republic of Korea, Denmark, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, India, Indonesia, Iran (Islamic Republic of), Iraq, Israel, Jordan, Kazakhstan, Kenya, Lithuania, Luxembourg, Malawi, Malaysia, Maldives, Malta, Mexico, Monaco, Mongolia, Mozambique, Netherlands, New Zealand, Nigeria, Oman, Pakistan, Paraguay, Peru, Philippines, Portugal, Qatar, Republic of Korea, Republic of Moldova, Singapore, Slovakia, Slovenia, South Africa, Sri Lanka, Sudan, Switzerland, Syrian Arab Republic, Thailand, Timor-Leste, Tunisia, Uganda, United Arab Emirates, United Kingdom, United States of America, Uruguay, Uzbekistan, Yemen.

[51] These nine countries are Bulgaria, Burkina Faso, Egypt, Malawi, Mozambique, Nigeria, Timor-Leste, Uganda and United Arab Emirates. Data from Greece was not included in the last report but did report (late) that it met the six process indicators.

Narrative

The 2015 data shows a slight progress in the establishment of new NITAGs, however there is a relative stagnation on the strengthening of the NITAGs. While the data shown in Figure 4.2 should not be over-interpreted, the trend is clear: the target will not be met by 2020 through current activities; progress therefore should be accelerated.

In all regions there is now clear commitment to establishing NITAGs and all Regional Immunization Technical Advisory Groups have made strong statements with regard to the need to strengthen NITAGs. In addition, NITAG chairpersons have attended regional TAG meetings with immunization managers in all but one region to date and the fostering of exchanges between NITAGs have been received very positively by all and contribute to capacity strengthening. Country and intercountry NITAG workshops/meetings continue to be very successful and will further help accelerate progress.

Other positive developments include the establishment of a regional NITAG network in the South-East Asia Region, the attention given to strengthening NITAGs at the Ministerial Conference on Immunization in Africa held on 24–25 February 2016 in Addis Ababa, and the international NITAG meeting which took place on 11–12 May 2016 in Veyrier-du-lac and at which the establishment of a global NITAG network was decided.

Although the Middle Income Country Strategy proposed by the MIC Task Force and endorsed by SAGE in April 2015 featured the strengthening of evidence-based decision-making as one of the four main areas of action identified as the pillars of this strategy, it was not funded and implementation has sustained only limited developments.

The management board of the Gavi Alliance has approved a framework for its 2016–2020 strategy that includes the importance of improving country leadership, management and coordination, which includes NITAG strengthening. As a result the Gavi Alliance organized a consultation of stakeholders and major partners to engage them in this process in a manner that is sustainable and builds capacity at country level. Assisting countries to access Gavi funds allocated for health system strengthening to establish or strengthen NITAGs remains necessary, as few if any countries has yet used this opportunity. There has unfortunately not been much progress on this issue during the past year.

With respect to the special approach started to allow Member States with small populations to benefit from subregional advisory groups referred to in last year's report, definite advances have been made in the Americas (for the Caribbean islands) but the situation is not yet sorted on how to proceed for the small island nations in the Western Pacific Region.

Challenges to the establishment of NITAGs continue to include the need to ensure adequate expertise, independence from the government, transparency of the process, and quality review of the evidence on which recommendations are based. Efforts need to continue to ensure that NITAGs develop evidence-based recommendations according to standards. Several NITAGs remained only focused on the introduction of new vaccines and efforts should be made to expand their scope to reviewing the use and impact and optimizing strategies for already introduced/long standing vaccines.

The absence of systematic declaration of interests by core members remains problematic in some countries due to historical and cultural influences and is the main limiting factor for quite a few countries whose NITAG would otherwise meet all six specific indicators. Progress continues on meeting the indicator quality improvement in the processes of many NITAGs, although this remains hard to quantify at global level. Attention should also be given to the sustainability of the NITAGs. Indeed the fact that 10 of the NITAGs previously meeting the six process indicators failed to do so in 2015 with nine of them not having a single meeting in 2015 is worrisome.

Various NITAG-related tools including the finalization of a NITAG training manual and an evaluation protocol have been finalized by the WHO Collaborating Centre on "Evidence-informed immunization policy-making" at the Agence de Médecine Préventive, health policy and Institutional development unit (AMP-HPID). At the Veyrier-du-lac international NITAG meeting, the value of NITAG evaluations using the tool recently developed by AMP was stressed. This and other tools are accessible under the NITAG Resource Centre website *(4)*, which aims to be a centralized resource compiling information and providing a collaborative platform for NITAGs and is maintained by AMP-HPID.

Advocacy by involved stakeholders at national and global levels are necessary to ensure sufficient time, effort and money are invested. Currently insufficient funding threatens the implementation of technical support activities by the collaborating centre, WHO and partners and limits the implementation of evaluations. Funding for the functioning of the secretariat of the

global NITAG network is not yet secured. Countries still need to take an active role in establishing and maintaining NITAGs and to investigate innovative mechanisms to sustain funding for NITAGs. Without an accelerated and joint effort, the GVAP objective of all countries having a functional NITAG by 2020 will not be achieved.

Partners have agreed on the value of placing a specific session about NITAGs on the agenda of the April 2017 SAGE meeting, which would in particular allow stakeholders to reflect on the progress in establishing the NITAG global network and the implementation of evaluations.

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5. VACCINE HESITANCY

Individuals and communities understand the values of vaccines and demand immunization both as a right and a responsibility: vaccine hesitancy: percentage of countries that have assessed the top three reasons for vaccine hesitancy (indicator SO2.1) and assessments of the level of hesitancy in vaccination at a national or subnational level in the past five years (Indicator SO2.2)

Highlights

- The high response rate for both indicators highlights the general acceptance of the indicators.
- Of the 183 countries that submitted the form, 145 provided at least one reason for vaccine hesitancy (Indicator 1). Of these, 81 (56%) based their response on opinion, 55 (38%) based their response on evidence and 9 (6%) did not specify.
- Sixty-five (36%) of the 183 countries that submitted the form, reported having undertaken an assessment of vaccine hesitancy within the past five years, while 79 (43%) reported that no assessment had been undertaken and 39 (21%) did not respond to the question (Indicator 2).
- The 2015 WHO-UNICEF JRF data reveals that the most frequently listed determinants for vaccine hesitancy continue to be: a) risk–benefit issues of the vaccine, in particular concerns around vaccine safety; b) lack of knowledge and awareness of vaccination and its importance; c) religion, culture, gender and socioeconomic issues, in particular religious reasons.
- Convenience issues, such as mode of delivery and the design of the vaccination programme, may be a driving factor for hesitancy towards vaccination and need to be addressed by immunization programmes.

DEFINITION OF INDICATOR	**Indicator 1: Reasons for vaccine hesitancy** • Question 1: what are the top three reasons for not accepting vaccines according to the national schedule? • Question 2: is this response based on or supported by some type of assessment, or is it an opinion based on your knowledge and expertise? **Indicator 2: Percentage of countries that have assessed the level of hesitancy towards vaccination at the national or subnational level in the previous five years.** • Question 1: has there been some assessment (or measurement) of the level of confidence in vaccination at national or subnational level in the past (< 5 years)? • Question 2: if yes, please specify the type and year and provide assessment title(s) and reference(s) to any publication or report
TARGET	Assess the top three reasons for vaccine hesitancy in the country in the past year to monitor determinants of vaccine hesitancy over time. Monitor the trend in the percentage of Member States that have assessed the level of hesitancy towards vaccination at national or subnational level in the previous five years
DATA SOURCES	All 194 countries within the six WHO regions included both indicators in their 2016 JRF to collect country data for 2015 (referred to as 2015 JRF data)

Background

As part of the Decade of Vaccines GVAP, the SAGE working group on immunization vaccine hesitancy was asked to develop indicators that could be used to monitor vaccine hesitancy and measure how well individuals and communities understand the value of vaccines and demand immunization as both a right and a responsibility. Two proposed indicators were first included in the 2012 JRF, which underwent revision and pilot testing in the European Region in 2013. The current version of the indicators was introduced globally into the JRFs in 2014. Therefore, these analyses reflect the second provision of data on the two updated indicators.

Results

INDICATOR SO2.1: REASONS FOR VACCINE HESITANCY (INDICATOR 1)

Of the 194 WHO Member States, 183 countries submitted the JRF form by 24 June 2016. Of these 183 countries, 145 provided at least one reason for vaccine hesitancy (Table 5.1).

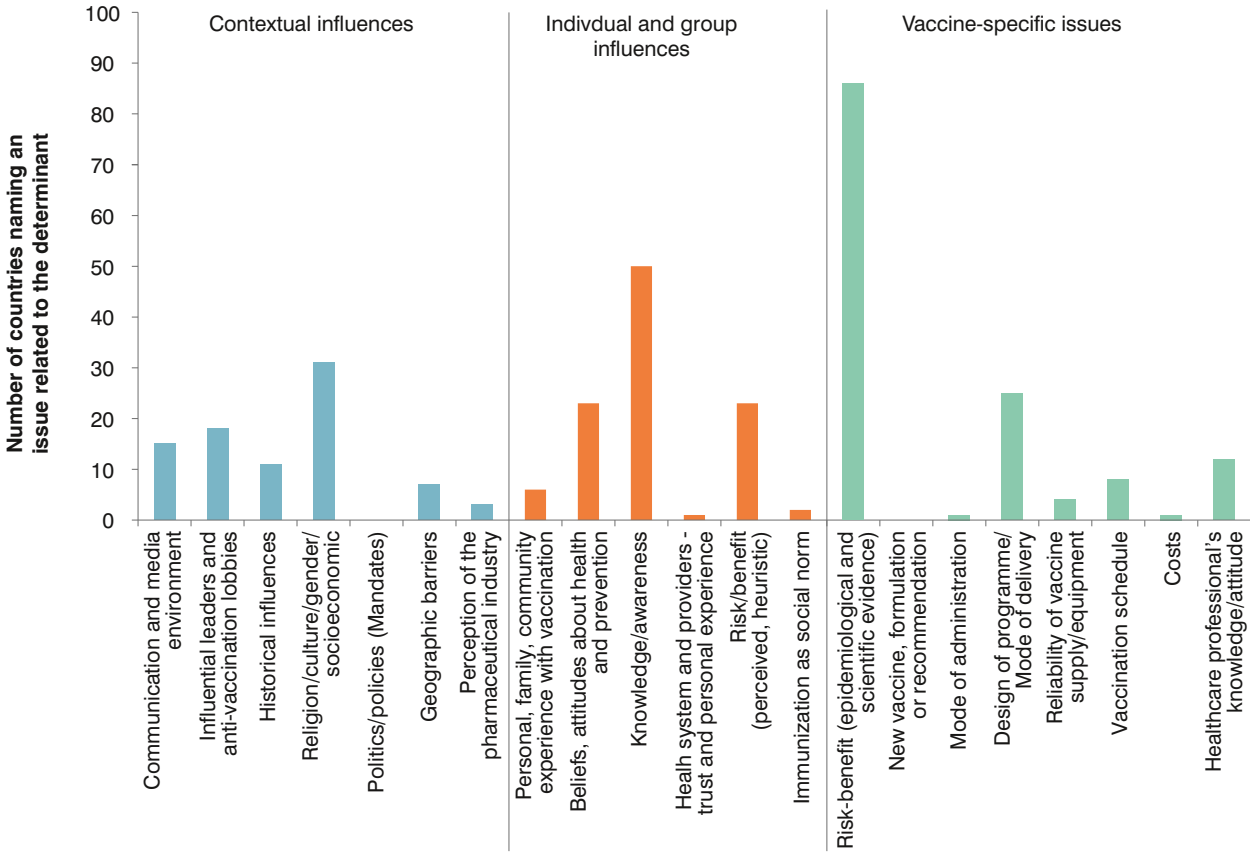
Table 5.1: Number and percentage of countries that provided the top three reasons for vaccine hesitancy (Indicator 1) in 2015, by WHO region

	All regions n (%)	African Region n (%)	Region of the Americas n (%)	Eastern Mediter-ranean Region n (%)	European Region n (%)	South-East Asian Region n (%)	Western Pacific Region n (%)
Reasons given	145 (79)	33 (70)	30 (86)	15 (75)	38 (84)	11 (100)	18 (72)
Question not completed	38 (21)	14 (30)	5 (14)	5 (25)	7 (16)	0 (0)	7 (28)
Total	183	47	35	20	45	11	25

These data show a steady increase in response to Indicator 1: 79% (145/183) in 2015, compared to the two previous years. During the JRF piloting of the indicators in 2013, 36% (16/45) of the countries in the European Region provided information. In 2014, 73% (131/180) of countries globally named at least one reason for vaccine hesitancy.

As a means of interpretation, the data collected for the top three reasons were grouped according to the matrix of determinants *(1)* of vaccine hesitancy which is assembled into three categories: contextual influences, individual and group influences as well as vaccine/vaccination-specific influences (Figure 5.1).

Figure 5.1: Main themes indicated as top three reasons for vaccine hesitancy for all WHO regions from the 2015 JRF data (Indicator 1)



The most common reasons reported for vaccine hesitancy globally related to the determinants of epidemiological or scientific risk–benefit of vaccines (n=86), knowledge/awareness issues (n=50) and religion, culture, gender and socioeconomic factors (n=31). The fourth most frequent global determinant of vaccine hesitancy related to the design of the vaccination programme and the mode of delivery (n=25).

The countries were further asked whether these reasons were evidence-based or opinion-based relying on the expertise of the immunization manager providing the data for the JRF form. Of the 145 countries that provided a reason, 81 (56%) based their response on opinion, 55 (38%) based their response on evidence and nine (6%) did not specify. No difference was seen in regard to the ranking of the top two determinants between those who based their response on opinion and those who indicated their response was based on evidence (scientific risk–benefit of vaccines, n=52 and n=34; knowledge/awareness issues n=26 and n=24, respectively). Though those who based their response on opinion mentioned religion, culture, gender and socioeconomic factors as the third most frequent determinant (n=19), whereas within those basing their response on evidence, the factors related to the design of the vaccination programme and the mode of delivery (n=13) were ranked third.

When comparing the results across regions, similarities were observed. All regions mentioned either the risk–benefit of vaccination or knowledge/awareness issues

as the main reasons overall for vaccine hesitancy. Nevertheless, stratification by region highlighted that the predominating determinants vary across different geographic locations (Table 5.2). Although globally the most frequently listed reasons pertained to risk–benefit, only 4/6 regions have this issue among their main three reasons. Knowledge/awareness issues were prevailing in 5/6 regions. In total, three regions – the Americas, African and Western Pacific Regions – listed issues that pertained to the religion/culture/gender/socioeconomic determinant of vaccine hesitancy among the top three.

Table 5.2: The top three determinants of vaccine hesitancy in the 2015 JRF data, by WHO region

WHO region	Top three determinants of vaccine hesitancy	Frequency (n)
African Region	Knowledge/awareness	n=13
	Design of programme/Mode of delivery	n=11
	Religion/culture/gender/socioeconomic	n=8
Region of the Americas	Risk–benefit (epidemiological and scientific evidence)	n=16
	Religion/culture/gender/socioeconomic	n=10
	Influential leaders and anti-vaccination lobbies	n=10
South-East Asia Region	Knowledge/awareness	n=6
	Risk–benefit (epidemiological and scientific evidence)	n=6
	Beliefs, attitudes about health and prevention; Risk–benefit (perceived, heuristic); Design of programme/Mode of delivery	n=3/each
European region	Risk–benefit (epidemiological and scientific evidence)	n=39
	Knowledge/awareness	n=12
	Risk–benefit (perceived, heuristic)	n=11
Eastern Mediterranean Region	Knowledge/awareness	n=7
	Beliefs, attitudes about health and prevention	n=4
	Risk–benefit (perceived, heuristic)	n=4
Western Pacific Region	Risk–benefit (epidemiological and scientific evidence)	n=13
	Knowledge/awareness	n=6
	Religion/culture/gender/socioeconomic	n=4

Twelve (7%) of the 183 countries that submitted the JRF form reported no knowledge of vaccine hesitancy in their population.

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INDICATOR SO2.2: ASSESSMENT OF VACCINE HESITANCY (INDICATOR 2)

Of the 183 Member States that submitted the JRF, 144 (79%) responded to the second indicator. In total, 65 (36%) of the 183 countries reported that an assessment of vaccine confidence had been completed in their country within the previous five years; 79 (43%) reported that no assessment had taken place; and 39 (21%) countries did not provide an answer to this question (Table 5.3). Sixty-four countries provided assessment title(s) and reference(s) to publications or reports on vaccine confidence.

Table 5.3: Number and percentage of assessments conducted at a national or subnational level

	All regions n (%)	African Region n (%)	Region of the Americas n (%)	South-East Asia Region n (%)	European Region n (%)	Eastern Mediter-ranean Region n (%)	Western Pacific Region n (%)
Assessment	65 (36)	19 (40)	9 (26)	5 (45)	20 (45)	6 (30)	6 (24)
No assessment	79 (43)	14 (30)	23 (66)	5 (45)	18 (40)	7 (35)	12 (48)
Question not completed	39 (21)	14 (29)	3 (8)	1 (10)	7 (15)	7 (35)	7 (28)
Total	**183**	**47**	**35**	**11**	**45**	**20**	**25**

More countries reported some form of vaccine hesitancy assessment (36%; 65/183) in the 2015 JRF data than the previous year. In 2014, 29% (52/180) of all countries reported having conducted an assessment to assess the level of confidence in vaccination.

Discussion

The further increase in response rate compared to the 2014 JRF data continues to confirm the general consent and understanding of the two proposed indicators on vaccine hesitancy across all regions.

The majority of reported reasons for vaccine hesitancy were directly related to vaccine and vaccination-specific issues. Scientific evidence of risk–benefit and history of safety issues can prompt individuals to hesitate in obtaining immunization for themselves or their dependents, even when safety issues have been clarified and addressed. Examples of specific responses provided in the JRF include the "fear and worry of adverse events following immunization" and "anxiety regarding vaccine safety". Knowledge and awareness issues were the second most frequently cited reason for vaccine hesitancy. Specifically mentioned was "parents to be unaware of importance of vaccinations", "lack of awareness on the need for immunization" or "knowledge gaps related to immunization". The third most frequent determinant of vaccine hesitancy globally mainly related to religious issues such as "Religious beliefs" or "Religious reasons", though the type of faith was often not specified. These data coincide with the main three reasons provided in the 2014 JRF data.

Vaccine hesitancy has been defined as a delay in acceptance or refusal of vaccines despite available vaccination services. It is a complex, context-specific and rapidly changing global phenomenon that varies across time, place and by vaccine. It is influenced by factors such as complacency, convenience and confidence *(1)*. Indicator 2 questions whether an assessment of the level of confidence has taken place. Narrowing the scope of the assessment to vaccine confidence may not encompass a broader assessment of vaccine hesitancy, which is influenced by further factors such as complacency and convenience. It is suggested, therefore, to revise the wording of the second indicator to ensure that assessments of vaccine hesitancy are fully captured.

In the 2015 JRF data, immunization managers specifically pointed out convenience issues as a driving influence for hesitancy towards vaccination. This is especially important as despite the implementation of reliable vaccination programmes, the health centre may be too far away, waiting times at the facilities may be too long or the opening hours may be inconvenient. Some of the specific answers pertained to "crowded health care facilities", the "lack of evening clinics" and the "inconvenience of clinic times particularly for working parents". This can result in lower participation in vaccination programmes and lower vaccination coverage, which ultimately leads to negative consequences for the entire community. Immunization programmes should therefore be tailored to meet the needs of vaccine recipients and caregivers.

One issue, not among the main three reasons for vaccine hesitancy globally, though mentioned a number of times (n=6) by immunization managers, was "the fear of injections or needles", "caregivers who find the immunisation experience emotionally distressing" or "vaccine shots perceived as painful". In 2015 SAGE reviewed the issue of pain mitigation during immunization. SAGE concluded that the related pain is manageable and recommended that age-specific measures should be implemented by national

immunization programmes. Specific information can be found in the related WHO position paper *(2)*.

To support countries in addressing vaccine hesitancy, WHO identified centres of expertise to assist countries in assessing concerns and developing targeted strategies related to vaccine hesitancy. Further information on vaccine hesitancy can be found on the WHO website.[52]

Overall, the high response rate demonstrates general acceptance of the indicators. The data gathered from these indicators highlight issues and differences in factors contributing to vaccine hesitancy across regions and show that vaccine hesitancy affects the majority of the countries globally. Both indicators continue to be of great value to monitor progress in addressing vaccine hesitancy across regions and are particularly important in order to obtain a global assessment of the causes of vaccine hesitancy. Further, the two indicators contribute to raising awareness about hesitancy and may encourage countries to assess hesitancy and develop targeted strategies to reduce it.

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6. SURVEILLANCE

Strategic Objective 4: strong immunization sytems are an integral part of a well-functioning health system. Indicator SO4.4: number of countries with case-based surveillance for vaccine-preventable diseases: invasive bacterial vaccine-preventable and rotavirus disease surveillance

Highlights

- Case-based sentinel hospital surveillance for meningitis, pneumonia/sepsis, and diarrhoea with clinical data linked to laboratory results is being received at WHO from globally representative, high-performing surveillance sites in all six WHO regions.
- The Global IB-VPD and Rotavirus Disease Surveillance Networks have built up national, regional and global laboratory capacity for identifying and monitoring circulating strains of Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and rotavirus.
- The surveillance networks are being leveraged to test for additional vaccine-preventable diseases and diseases with vaccines in development, such as typhoid and other enteric pathogens such as norovirus, *Shigella* and enterotoxigenic *Escherichia coli*.
- Surveillance data are being shared through the new revised global electronic bulletin, regional bulletins and peer-reviewed publications.
- Surveillance data have been used to inform decision-making, support evidence-based vaccine introduction and monitor the impact of pneumococcal conjugate, rotavirus and Hib vaccines.

DEFINITION OF INDICATOR	The number of countries that report conducting case-based surveillance, including laboratory confirmation, for rotavirus and invasive bacterial vaccine-preventable diseases (IB-VPDs), at one or more hospital-based sentinel sites, the data from which are included in WHO databases
TARGET	75% of low- and middle-income countries for sentinel site surveillance by 2020
DATA SOURCES	Data reported annually through the WHO-UNICEF JRF; and data reported by sentinel sites participating in a WHO-coordinated surveillance network

Overview of the WHO-coordinated Global IB-VPD and Rotavirus Disease Surveillance Networks, 2008–2015

In 2008, WHO brought together existing regional surveillance to establish standardized global sentinel hospital surveillance networks for rotavirus disease and IB-VPD. These active, syndromic sentinel site surveillance networks report case-based clinical and laboratory data for children aged under 5 years hospitalized with acute gastroenteritis (to monitor rotavirus) and IB-VPD (currently cases of meningitis, pneumonia or sepsis to monitor *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*). When the networks were initiated, the main objectives were as follows:

- During the pre-vaccine introduction period:
  a. provide data for describing disease epidemiology, including disease burden estimates;
  b. establish a platform to measure impact of vaccine introduction;
  c. identify circulating serotypes of genotypes of the principal vaccine-preventable pathogens.

- In the post-vaccine introduction period:
  a. assess disease trends;
  b. monitor changes in circulating strains;
  c. use the platform to monitor programme impact and document vaccine effectiveness.

WHO provides managerial oversight, technical assistance to countries and financial support to countries for surveillance activities, with a focus on Gavi-eligible countries. WHO has established networks of sentinel hospital and national laboratories supported by regional and global reference laboratories and conducts an annual external quality assessment (EQA) programme that targets participating laboratories; conducts sentinel site assessments; provides technical advice and laboratory supplies to sites; and shares data semi-annually via a global surveillance and information bulletin that was revised in 2015 (available at http://eepurl.com/bZTDAz). An online data management tool is in development and is currently being piloted. This tool will facilitate the case-based data collection, entry and analysis at the sentinel site and also the consolidation of data at WHO headquarters.

In 2013, WHO, under the oversight of the internal Technical Advisory Group (iTAG) and with technical partner guidance, conducted a strategic review of the surveillance networks. As of 2015, all but two of 40 recommendations from the 2013 Strategic Review and 35 recommendations from the 2014 Global Surveillance Meeting have been implemented. Of the remaining two recommendations, work is under way to conduct studies of surveillance costs to help strengthen in-country support of the network and improve sustainability. The other recommendation to share specimens with the regional reference laboratories among all the target hospitals was deemed not to be feasible by April 2015 because of limitations of capacity and the human and financial resources required; however, some hospitals and regions participate in quality-control activities.

In 2015, the Global Rotavirus Surveillance Network comprised 114 sentinel surveillance sites in 53 countries (Figure 6.1) and the Global IB-VPD Surveillance Network comprised 114 sentinel sites in 52 countries (Figure 6.2). In addition, in response to comments from the SAGE DoV working group and to better reflect the current status of surveillance globally, this year the GVAP Secretariat is reporting countries that conduct surveillance for IB-VPD and rotavirus but do not report surveillance data to WHO as part of the Global Rotavirus and IB-VPD Surveillance Networks. These countries may have either conducted surveillance according to WHO recommended methodology but not reported data to WHO, or they may have conducted surveillance using a method that is not recommended as the Network method, such as aggregated data instead of case-based, laboratory-based instead of syndromic surveillance, or limited to one pathogen, such as *S. pneumoniae*.

For sites not participating in the WHO coordinated network, WHO does not currently have the resources or capacity to assess the quality of their surveillance. However, some of these countries and surveillance sites participate in WHO-organized training activities and data sharing dissemination and meetings. In 2015, there were at least 44 countries that conducted rotavirus surveillance but were not part of the WHO-coordinated Global Rotavirus Surveillance Network Figure 6.2) and 63 countries that conducted IB-VPD surveillance but were not part of the WHO-coordinated Global IB-VPD Surveillance Network (Figure 6.1).

Comparison of SO4.4 indicator and target with strategic review recommendations

In 2014, SAGE accepted a change in the indicator and target for SO4.4, which was amended to read as follows:

- Number of countries meeting established surveillance standards with case-based surveillance for vaccine-preventable diseases and with viral and bacterial laboratory confirmation of suspect or probable cases.
- Seventy-five per cent of low- and middle-income countries have sentinel hospital surveillance that meets surveillance standards for rotavirus diarrhoea or other national priority vaccine-preventable diseases.

WHO monitors the performance of sites globally each quarter when data are reported, and regional offices are given an in-depth report of sentinel site performance. Based on discussions with the sentinel sites, the performance indicators were revised and simplified in 2015 from 15 to 4, for each network. In addition, all sentinel hospital laboratories or laboratories that process surveillance specimens should participate in EQA.

The surveillance standards for the IB-VPD sentinel surveillance sites are as follows:

1. Consistent reporting throughout year
   a. Green: 12 months and confirmed zero reporting if no cases
   b. Yellow: 10–11 months and confirmed zero reporting if no cases
2. Minimum number of cases reported annually
   a. Green: ≥ 100 suspected meningitis; ≥ 500 meningitis + pneumonia/sepsis
   b. Yellow: ≥ 80–99 meningitis; ≥ 400–499 meningitis + pneumonia/sepsis
3. Suspect cases with specimen collected
   a. Green: ≥ 90%
   b. Yellow: ≥ 80%
4. Laboratory-confirmed cases with serotype/group
   a. Green: ≥ 80%
   b. Yellow: ≥ 60%

Most IB-VPD sites performed well and maintained or improved their performance in 2015 compared with previous years (Figure 6.3). However, the percentage of sites that consistently reported surveillance data decreased. A percentage of specimens with a serotype have not been presented for 2015 because laboratory testing data from 2015 are not yet complete.

The surveillance standards for the rotavirus disease sentinel surveillance sites are as follows:

1. Consistent reporting throughout year
   a. Green: 12 months and confirmed zero reporting if no cases
   b. Yellow: 10–11 months and confirmed zero reporting if no cases
2. Minimum number of cases reported annually
   a. Green: ≥ 100 suspected meningitis
   b. Yellow: ≥ 80–99 meningitis
3. Suspect cases with specimen collected
   a. Green: ≥ 90%
   b. Yellow: ≥ 80%
4. Specimens tested for rotavirus by enzyme immunoassays (EIAs)
   a. Green: ≥ 90%
   b. Yellow: ≥ 80%

In general, the rotavirus sites performed better than the IB-VPD sites (Figure 6.4). Similar to the IB-VPD sites, the rotavirus sites maintained or improved their performance in 2015 compared with previous years, except for consistent reporting. There were high-performing sites in all regions for both networks.

The future of IB-VPD and rotavirus surveillance

The Global IB-VPD and Rotavirus Disease Surveillance Networks have met their objectives and have matured into strong, long-standing surveillance systems. Globally representative, long-term surveillance for IB-VPD and diarrhoeal diseases in a selected number of high-performing sites is essential for continued monitoring of pneumococcal, Hib, meningococcal, and rotavirus diseases after vaccine introduction. Sustainable, high-quality surveillance that produces data that are used nationally and globally is the goal of the networks. Although there are high-performing sites in all regions, performance in some sites needs to be strengthened, especially for consistent reporting, laboratory confirmation of organisms and monitoring of strains. This underscores the need for consistent support and funding of surveillance at country level and for continued coordination and monitoring at regional and global levels.

The surveillance networks will need to work toward country ownership and finding sources of funding in addition to the Gavi Alliance, especially for Gavi-

graduating and middle-income countries. Within Gavi-eligible countries, funding for routine surveillance activities should as much as possible be transitioned to health systems strengthening funding, which is more sustainable than other sources of Gavi funds. The networks should consider collaborations and cost sharing with other VPD surveillance systems and projects, such as the Measles and Rubella Initiative and the Global Health Security Initiative. It will be important to consider how polio surveillance activities will affect these networks. As funding for polio activities decrease as the disease is eliminated, these networks will not be able to leverage polio-funded staff and support. In addition, polio containment affects collection and storage of diarrhoeal specimens as part of rotavirus surveillance.

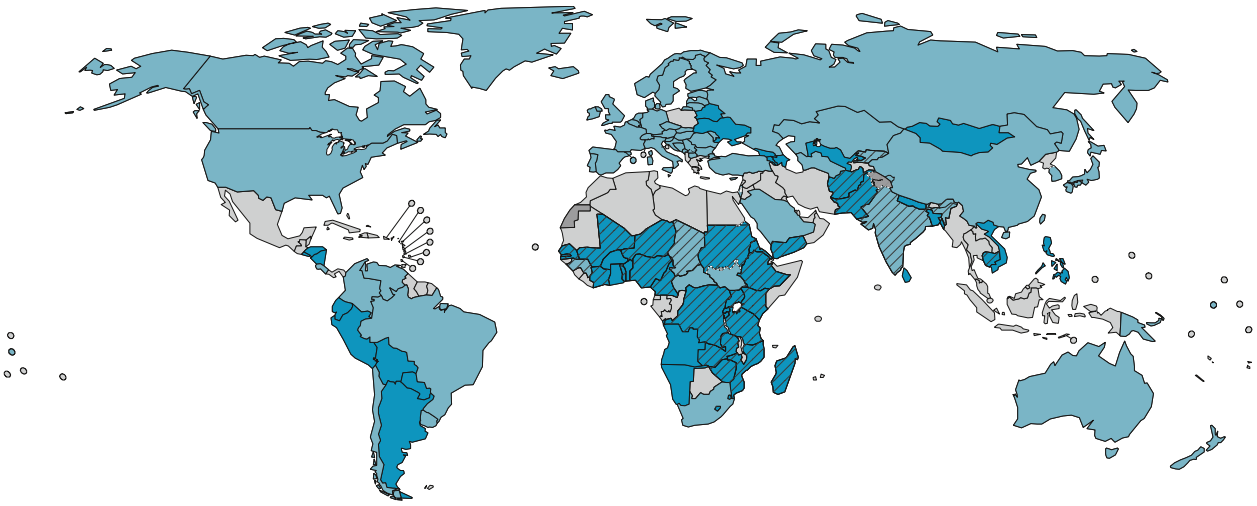
As the surveillance networks have matured, the objectives of surveillance have evolved. In addition to the original objectives, there is now a focus on burden and vaccine impact of pneumococcus and rotavirus in regions with gaps in data, namely Asia. Surveillance needs to monitor long-term changes after vaccine introduction, such as for pneumococcal serotype replacement, and to address new policy questions, such as for alternate and reduced PCV schedules. Antimicrobial resistance has also become a global concern that can be addressed through these networks.

In November 2013, SAGE noted the opportunities for integration by building upon the enhanced capacity developed by these networks to conduct surveillance for other diseases using a similar case definition (e.g. Japanese encephalitis is included in meningitis surveillance in regions such as the Western Pacific and South-East Asia) and laboratory procedures (e.g. identification of other bacterial pathogens in laboratories conducting IB-VPD surveillance). Pilot testing of integrated typhoid surveillance at four IB-VPD surveillance sites (two each in Africa and Asia) is under way; sites have been selected and surveillance in all four sites will start before the end of 2016. A survey of norovirus testing capacity was conducted at all regional laboratories and many national laboratories affiliated with the Global Rotavirus Surveillance Network. In some regions, such as PAHO, influenza is commonly monitored in the same sentinel sites that conduct pneumonia surveillance, and other respiratory pathogens such as respiratory syncytial virus (RSV) and pertussis could potentially be monitored as well.

One study leveraged a novel diagnostic test, the TaqMan Array Card (TAC), to test specimens gathered as part of the surveillance network for more than 25 enteric pathogens in addition to rotavirus. With support from the Bill & Melinda Gates Foundation (BMGF) and partners at the University of Virginia and the U.S. Centers for Disease Control and Prevention, TAC laboratory testing capacity was built at five regional references laboratories globally. More than 1200 specimens were tested from 11 countries in Africa, Asia and the Americas. The first phase of the project was completed in 2015 and showed that this novel diagnostic testing platform could be used successfully in many laboratories globally to identify the causes of diarrhoea in children, including those which have vaccines in development, such as norovirus, *E. coli* and *Shigella*.

The role of WHO in VPD surveillance is to generate and monitor surveillance trends globally; to lead, coordinate, and advocate for surveillance activities with countries and partners, including EQA/QC; to set global norms and standards for surveillance; to support countries with technical assistance and in evidence-based policy decisions; and to support research that uses surveillance data, builds on surveillance platforms, and informs surveillance, vaccine impact and policy. Being part of the networks can provide benefits to countries: technical support on epidemiology, laboratory, and data management; EQA/QC; linkages with partners; opportunities for network activities and studies (e.g. norovirus, typhoid, TAC), and in some cases funding. WHO will continue to support and work with countries to strengthen their surveillance and help them analyse their data so that they can be used and are available at country, regional and global levels.

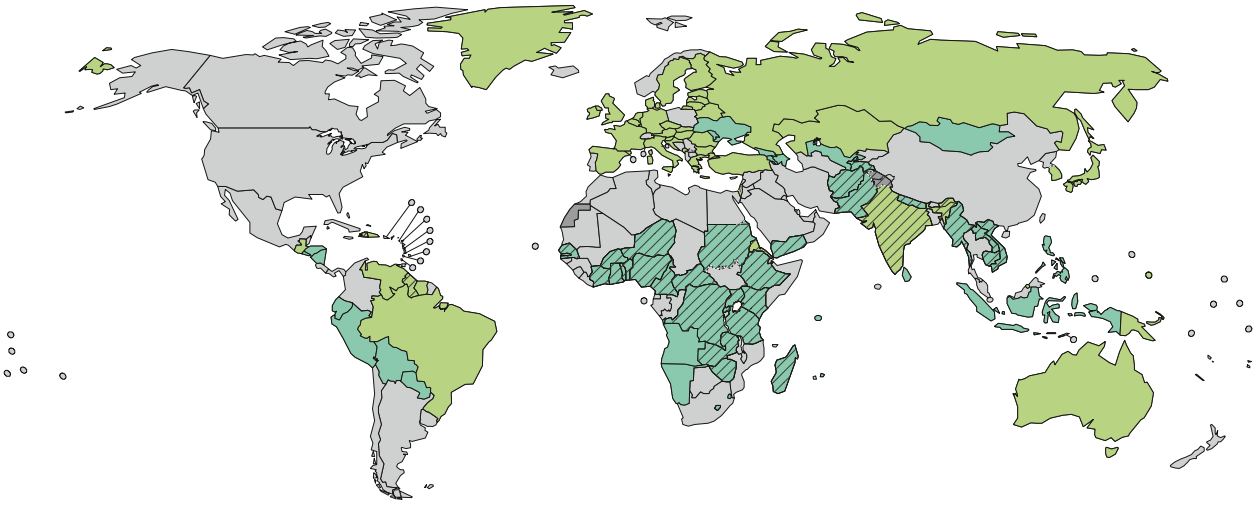
Figure 6.1: Countries that conducted IB-VPD surveillance in 2015



Non Gavi-eligible countries in the WHO IB-VPD Surveillance Network
Gavi-eligible countries in the WHO IB-VPD Surveillance Network
Non Gavi-eligible countries having a functioning surveillance system but not reporting to the WHO IB-VPD Surveillance Network
Gavi-eligible countries having a functioning surveillance system but not reporting to the WHO IB-VPD Surveillance Network
Not available
Not applicable

Data source: WHO/IVB Database.

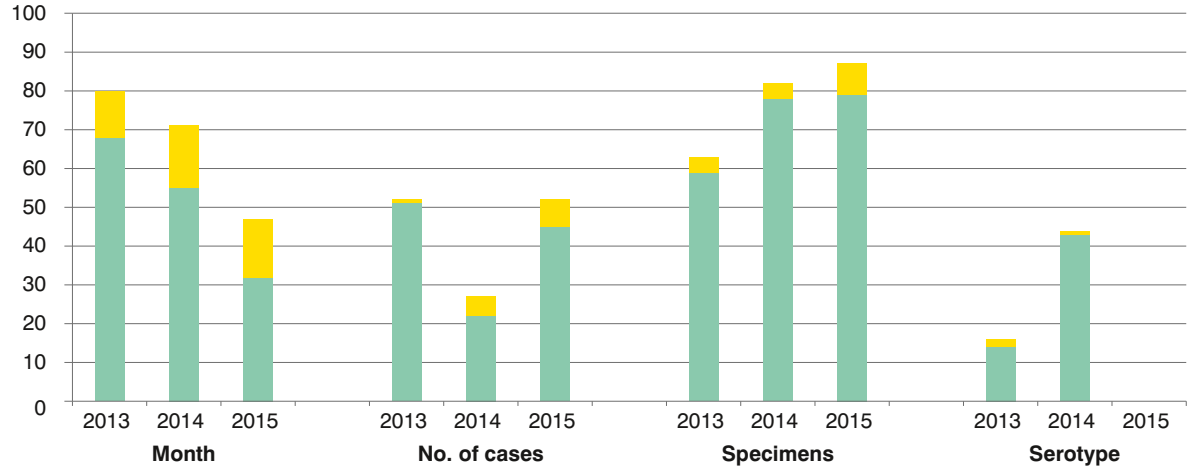
Figure 6.2: Countries that conducted rotavirus surveillance in 2015



Non Gavi-Eligible countries in the WHO Rotavirus Surveillance Network
Gavi eligible countries in the WHO Rotavirus Surveillance Network
Non Gavi-eligible countries having a functioning surveillance system but not reporting to the WHO Rotavirus Surveillance Network
Gavi-eligible countries having a functioning surveillance system but not reporting to the WHO Rotavirus Surveillance Network
Not available
Not applicable

Data source: WHO/IVB Database.

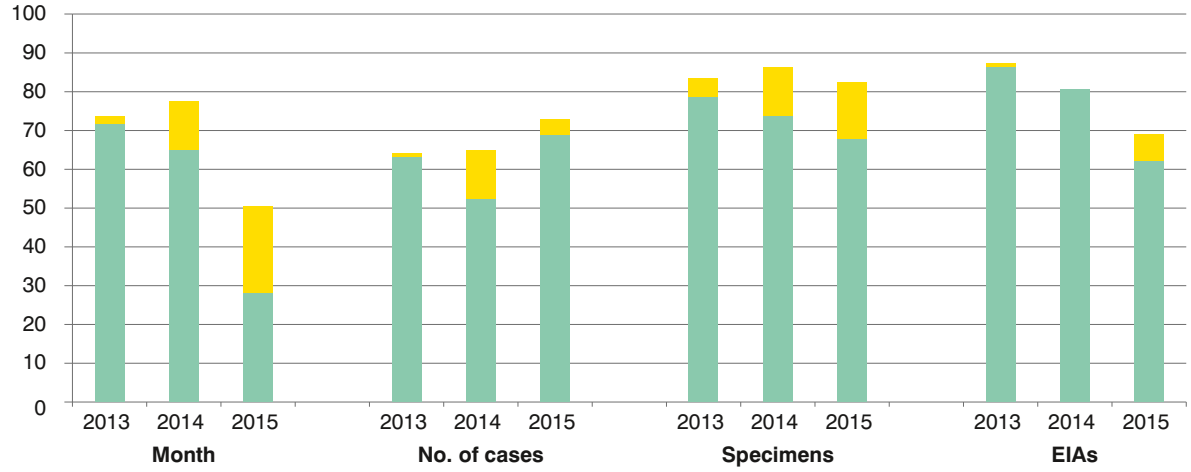
Figure 6.3: Global IB-VPD Surveillance Network sentinel site performance indicators



Legend:

1. Consistent reporting throughout year
   a. Green: 12 months and confirmed zero reporting if no cases
   b. Yellow: 10–11 months and confirmed zero reporting if no cases
2. Minimum number of cases reported annually
   a. Green: ≥ 100 suspected meningitis; ≥ 500 meningitis + pneumonia/sepsis
   b. Yellow: ≥ 80–99 meningitis; ≥ 400–499 meningitis + pneumonia/sepsis
3. Suspect cases with specimen collected
   a. Green: ≥ 90%
   b. Yellow: ≥ 80%
4. Laboratory-confirmed cases with serotype/group
   a. Green: ≥ 80%
   b. Yellow: ≥ 60%

Figure 6.4: Global Rotavirus Surveillance Network sentinel site performance indicators



Legend:

1. Consistent reporting throughout year
   a. Green: 12 months and confirmed zero reporting if no cases
   b. Yellow: 10–11 months and confirmed zero reporting if no cases
2. Minimum number of cases reported annually
   a. Green: ≥ 100 suspected meningitis; ≥ 500 meningitis + pneumonia/sepsis
   b. Yellow: ≥ 80–99 meningitis; ≥ 400–499 meningitis + pneumonia/sepsis
3. Suspect cases with specimen collected
   a. Green: ≥ 90%
   b. Yellow: ≥ 80%
4. Laboratory-confirmed cases with serotype/group
   a. Green: ≥ 80%
   b. Yellow: ≥ 60%

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7. VACCINES STOCKOUTS AND USE OF VACCINES IN A CONTROLLED-TEMPERATURE CHAIN

Stockouts: availability of vaccines for routine immunization at national level (Indicator SO5.2)

Highlights

- In 2015, 65 countries reported a total of 113 national level stock-out events for at least one vaccine and for at least one month.
- The year 2015 marks a set-back towards the GVAP target of a two thirds reduction in countries reporting national level stockouts by 2020 and breaks the overall downward trend in countries reporting stockouts seen since 2010.
- In 2015, 51% of national stock-outs events concerned DTP-containing vaccine. Lack of BCG vaccine accounted for another 34% of all stock-out events.
- Countries of all income groups were affected although 55% of stock-out events were reported by lower- and upper-middle-income countries – this group of countries accounts for 74% of the world's birth cohort.
- In 2015, 58 countries reported district level stockouts, 49 (86%) of which indicated that the subnational stockout was linked to the national level stockout.
- Of the 49 countries with district level stockouts, 47 (81%) countries experienced interruption of vaccination services because of the stockout.
- An analysis of four additional supply chain indicators is provided beyond those of the GVAP. The main findings indicate: (a) 26% of countries reported having e-stock management system at district level (vs a paper-based system); (b) less than 30% of subnational cold chain in countries is equipped with continuous temperature monitoring devices; (c) 50% of countries reported having an immunization supply chain improvement plan; (d) 65% of countries reported having a dedicated immunization supply chain manager.

Indicator SO5.2: Availability of vaccines for routine immunization at national level (stockouts)	
DEFINITION OF INDICATOR	Number of countries reporting a national level stockout of a least 1 vaccine for at least 1 month[53]
TARGET	Two thirds reduction in countries reporting national level stockouts by 2020 (from 2010 level)
DATA SOURCES	WHO-UNICEF joint reporting form (JRF)

[53] A stock-out event is defined as an event in which stockout of a vaccine occurred for at least one month at the national level. This indicator is a proxy measure of a stressed immunization supply chain system – a shortage of vaccines at national level is not a desirable situation and indicates that the recommended three-month safety stocks have been depleted and vaccine availability for lower levels of the system could be compromised. If a stockout in one country was reported for two vaccines, these would be considered as two stock-out events for that country. Note that events are defined by antigen. In the case of one national stockout of pentavalent vaccine, we would consider that several antigens had been affected by the stockout of that one vaccine. As such, the number of events is adjusted by antigen. To improve cross-country comparisons, the analysis focused on select vaccines common to all national immunization schedules. These include: BCG, DTP, measles-containing vaccines (e.g. DTP-HepB-Hib or MMR) and polio (e.g. OPV and/or IPV).

National level stockouts

In 2015 a total of 65 countries (or 34% of WHO Member States) reported a national level stockout for at least one vaccine and for at least one month. Compared to 2014, this represents a worsening of the situation where 50 countries (or 26%) had reported national level stockouts (Table 7.1).

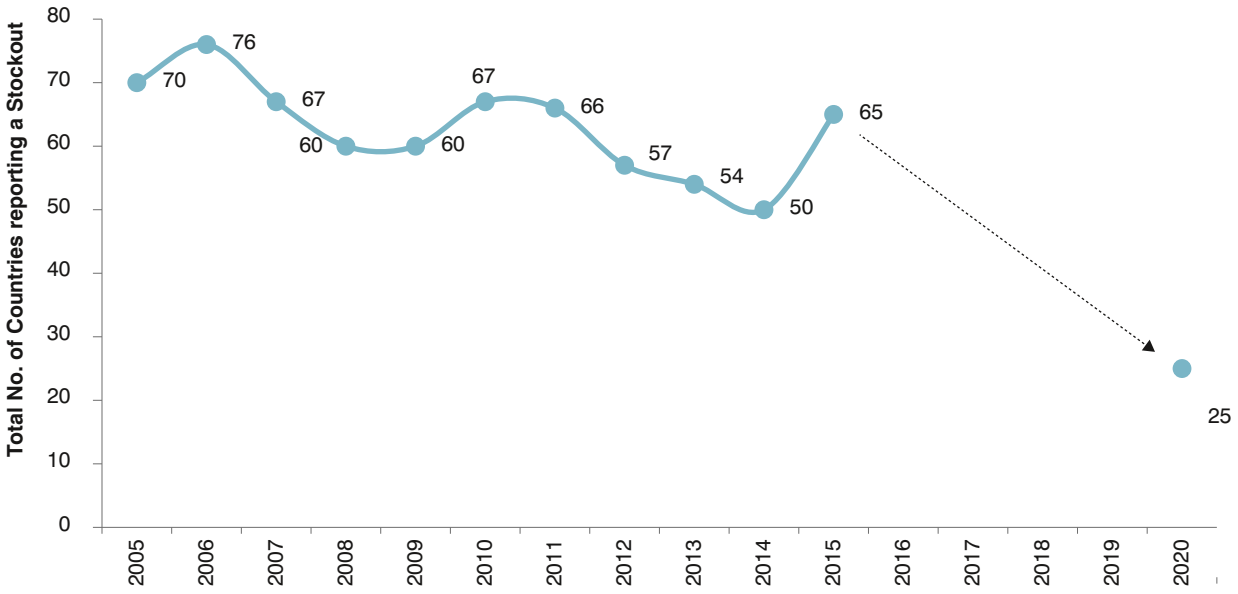
Table 7.1: Summary statistics for countries reporting at least one national level stock-out event[a]

	2015	Trend	2014	2013	2012	2011	2010
Total number of countries reporting stockouts	65	↑	50	54	57	66	67
% countries reporting stockouts	34%	↑	26%	28%	29%	34%	35%
Total number of stock-out events	113	↑	110	112	120	148	153
% of stock-out events[b, c]							
BCG vaccine	34%	↑	25%	33%	34%	28%	33%
DTP containing vaccines	51%	↑	40%	35%	42%	45%	47%
Measles-containing vaccines	5%	↓	14%	14%	9%	14%	7%
OPV/IPV vaccines	10%	↓	21%	18%	15%	13%	13%
Average number of stock-out events[c]	1.74	↓	2.20	2.07	2.11	2.24	2.28
Average duration of a stock-out event (days)[c]	43.8	↓	45.2	29.5	31.7	32.9	42.5

[a] For BCG, DTP, measles- and polio-containing vaccines.
[b] Some countries reported multiple stockouts in a given year, which is why this number is higher than the number of countries reporting stockouts.
[c] For countries reporting stockouts.

The year 2015 marks a set back towards the GVAP target of a two thirds reduction in countries reporting national level stockouts by 2020 and breaks the overall downward trend in countries reporting stockouts seen since 2010 (Figure 7.1).

Figure 7.1: Trend towards the GVAP goal for vaccine stockouts



For countries reporting national level stockouts, multiple events often occurred within the year if one or more vaccines had been affected (Figure 7.2 and Figure 7.3).

Figure 7.2: Number of countries grouped by the frequency of stock-out events, 2015

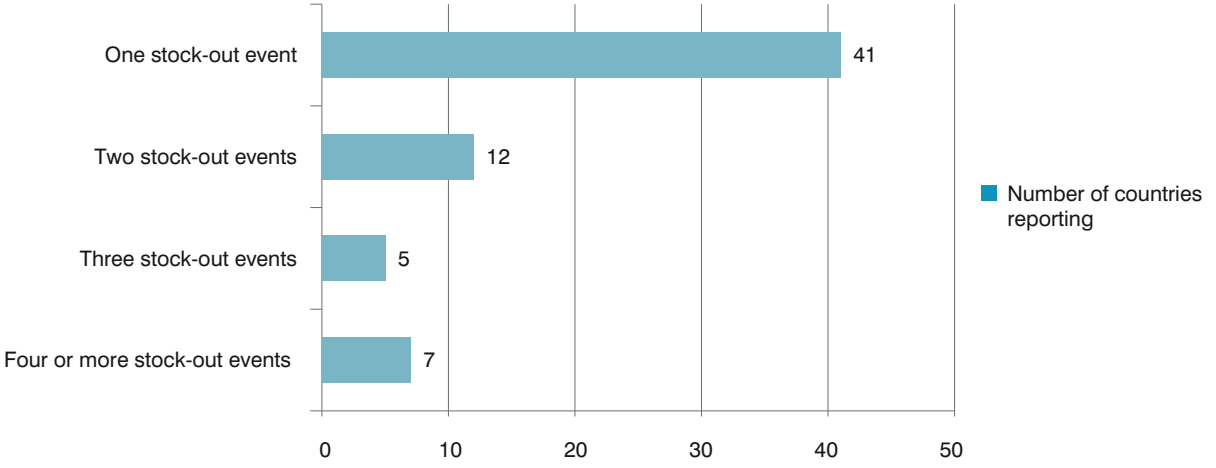
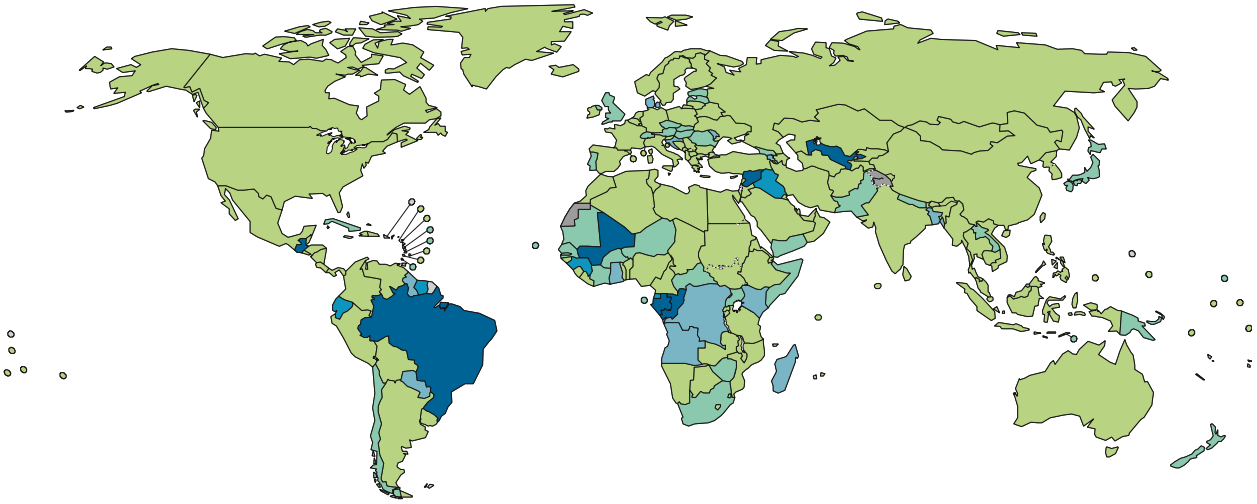


Figure 7.3: Map of countries with national level stock-out event, 2015



No stock-out event reported *(129 Member States)*
One stock-out events reported *(41 Member States)*
Two stock-out events reported *(12 Member States)*
Three stock-out events reported *(5 Member States)*
Four or more stock-out events reported *(7 Member States)*
Not applicable

In 2015, there were 113 stock-out events in 65 countries (an average of 1.74 stock-out events per reporting country – a slight improvement from the 2014 average of 2.20). The duration of a stock-out event was estimated at 44 days and similar to the average duration calculated in 2014 of 45. That said, the majority of countries (41 or 63%) reported only one stockout in 2015.

A deeper analysis by vaccine indicates that 51% of the stockouts concerned DTP-containing vaccines and 34% for BCG (Figure 7.4). For both, the proportion of stockouts increased from 2014. On the other hand, the proportion of stockouts relating to measles- and polio-containing vaccines dropped between 2014 and 2015. Stockouts of measles-containing vaccines went from representing 14% of all stock-out events in 2014

to 5% in 2015. Similarly, stockouts of polio-containing vaccines went from representing 21% of all stock-out events in 2014 to 10% in 2015 – the majority of the stockouts concerning OPV (eight countries) rather than IPV (three countries).

Table 7.2: Percentage of countries experiencing a national stock-out event, by WHO region, income classification and population[a]

	2015	Trend	2014	2013	2012	2011	2010
Grouping by WHO region							
Region of the Americas	17%	↓	32%	17%	16%	18%	19%
African Region, West	15%	↑	8%	19%	11%	9%	12%
African Region, Central	11%	↑	6%	11%	7%	8%	10%
African Region, East and South	8%	↓	18%	17%	21%	21%	16%
Eastern Mediterranean Region	9%	↑	6%	6%	5%	12%	7%
European Region	26%	↑	14%	7%	18%	17%	18%
South-East Asia Region	5%	↑	4%	7%	5%	2%	4%
Western Pacific Region	9%	↓	12%	17%	18%	14%	12%
Grouping by income classification[b]							
Low income	20%	↓	26%	28%	25%	24%	22%
Lower-middle income	28%	↑	26%	41%	35%	29%	37%
Upper-middle income	28%	↓	36%	24%	28%	29%	28%
High income	25%	↑	12%	7%	12%	18%	12%
Grouping by population size[c]							
< 100 000	43%	↑	38%	43%	49%	39%	37%
> 100 000 < 500 000	25%	↑	24%	22%	19%	23%	27%
> 500 000	32%	↓	38%	35%	32%	38%	36%

[a] Percentage of countries that experience at least one stock-out event for at least one vaccine during a period of at least one month.
[b] According to the World Bank classification of countries.
[c] As expressed by the number of births in the country.

A further review of stockouts by typology of countries uncovers the following three findings:

1. The incidence of national level stockouts was greatest in the European Region (20 countries affected or 26%) and in the African Region (West and Central Africa) (25 countries affected or 26%) (Table 7.2 & Figure 7.5). The vaccines most affected by stockouts in the European Region were DTP-containing vaccines and BCG. West & Central African countries experienced stockouts of all vaccines.

Figure 7.4: Proportion of national level stock-out events by vaccine, 2010 vs 2015

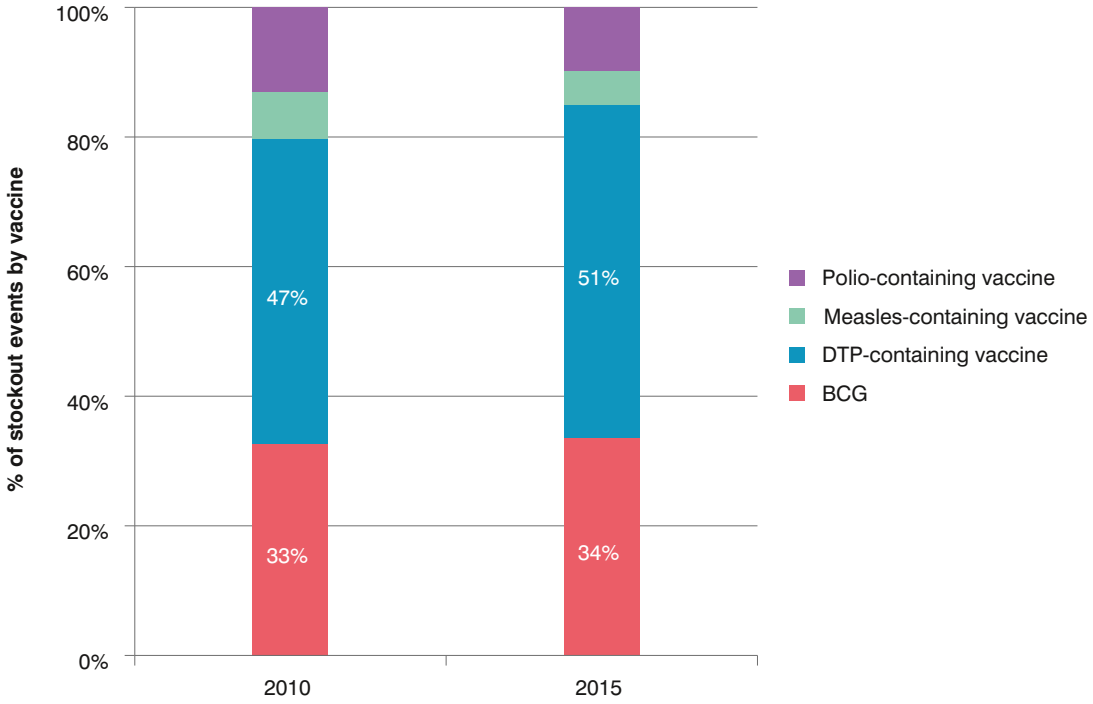
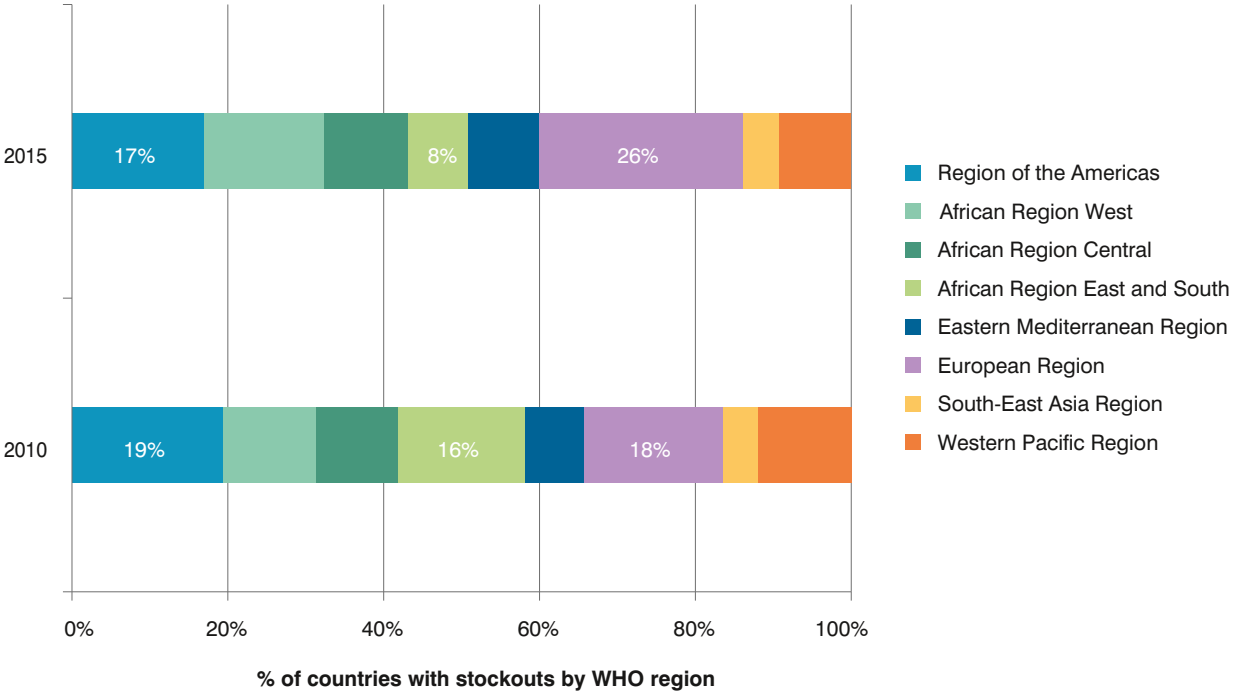
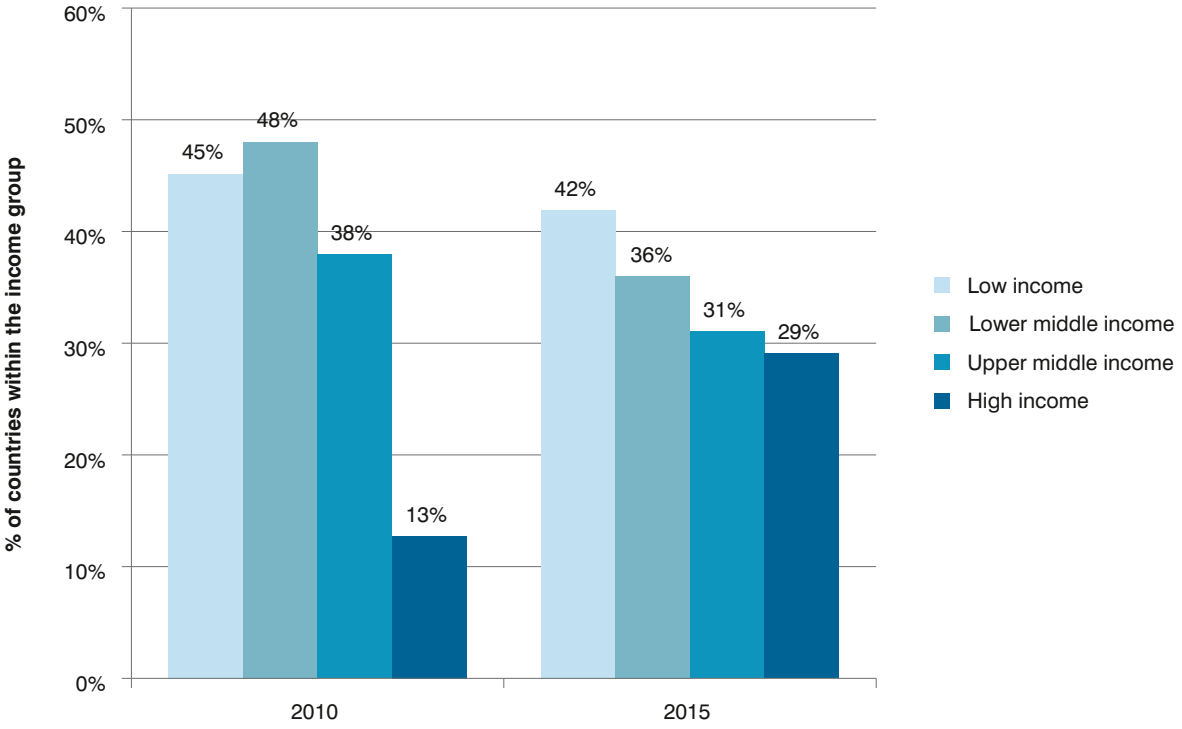


Figure 7.5: Proportion of countries with national level stock-out events by WHO region, 2010 vs 2015



2. Although national level stockouts were reported by countries of all income groups, the majority were reported by middle-income countries – 55% of stock-out events occurred in lower- and upper-middle-income countries (Figure 7.6). This group of countries accounts for 74% of the world's birth cohort. DTP-containing vaccine accounted for the majority of stockouts in upper-middle-income countries whereas BCG was the main vaccine where stockouts were experienced in all other income groups.

Figure 7.6: Percentage of countries with national stock-out events by income group, 2010 vs 2015



Another representation of the findings by income group is to analyse the proportion of countries within each income group that reported stockouts. This analysis uncovers that in 2015, 42% of all low-income countries reported a stock-out event. Of all lower-middle-income countries, 36% indicated experiencing a national level stockout in 2015. Interestingly, there is an increasing trend of stockouts among all countries classified as high income compared to 2010. Within the other three income groups the proportion of countries experiencing a stockout has declined in 2015 against the year 2010.

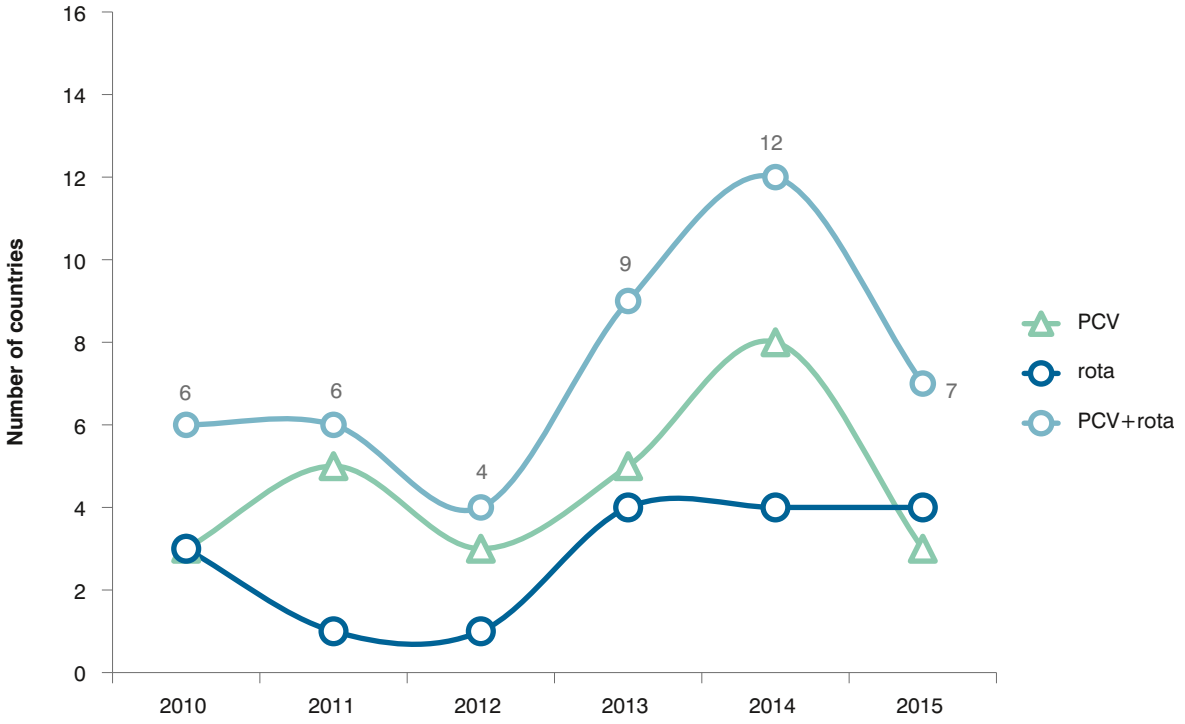
3. Close to 57% of countries reporting national level stockouts have medium to large birth cohorts. If national level stockouts do lead to subnational stockouts and interruption in vaccination service, the impact will be greater knowing that countries with medium to large birth cohorts are most prone to vaccine stockouts.

New vaccines (pneumococcal & rotavirus)

The previous analysis did not include the stockouts for some of the new vaccines given that the methodology relies on selecting a defined set of common vaccines permitting cross-country comparisons. That said, given the interest in new vaccines, this subanalysis focuses on reporting the 2015 situation as it related to pneumococcal conjugate and rotavirus vaccines

In 2015, a total of 129 countries had PCV and 84 had rotavirus vaccine in their national immunization schedule. Of these, three countries reported national level stockouts of PCV and four countries reported stockouts of rotavirus. This was an improvement over 2014 when 12 countries reported national level stockouts – eight for PCV and four for rotavirus vaccine (Figure 7.7).

Figure 7.7: Trend in the number of countries with national level stockout of PCV and rotavirus vaccine



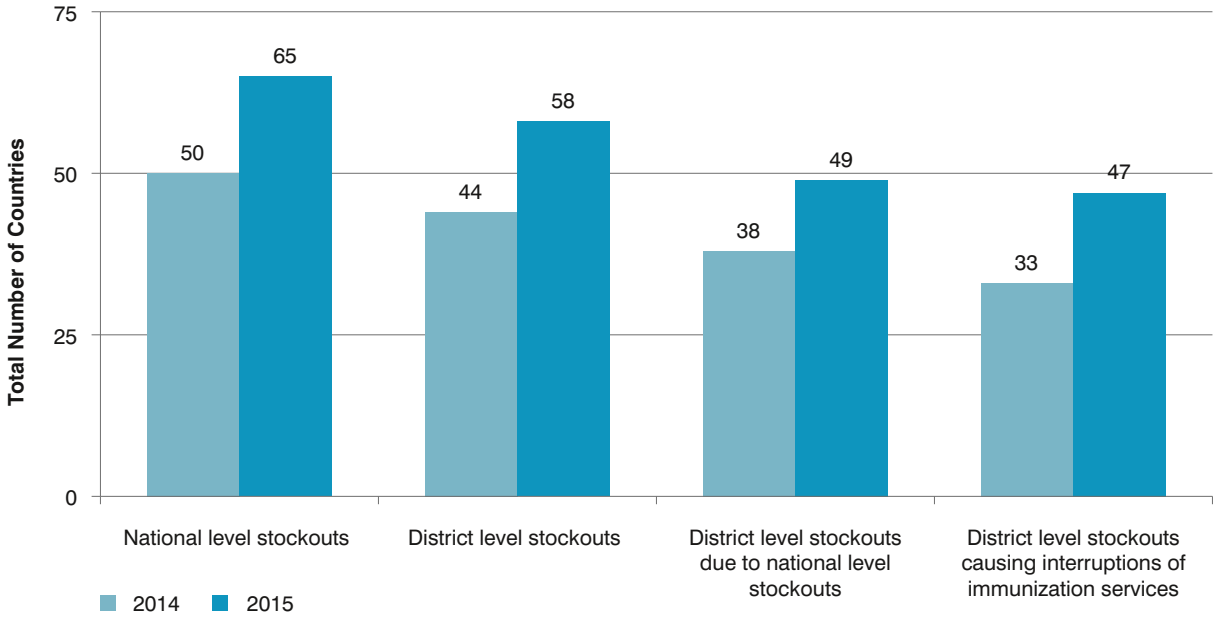
The average duration of a stock-out event in 2015 was 1.3 months for PCV and 1.0 month for rotavirus vaccine. This is a net improvement from 2014 where the average duration was respectively 3.3 and 5.0 months on average. The types of countries impacted are primarily middle-income countries in the Region of the Americas and in the European Region.

While these findings can only be considered illustrative (these vaccines are not introduced in all countries) it does show that new vaccines are also impacted by stockouts at national level even if, relatively speaking, many fewer countries are impacted – 2% of countries that have PCV in their schedule and 5% of countries with rotavirus vaccine in their national schedule.

Subnational level stockouts

Out of the 65 countries that reported national level stockouts, a total of 58 reported subnational stockouts at district level (Figure 7.8). Of these 58 countries, 86% of them (49 countries) indicated that the district and national level stockouts were linked – that the national stockout was the cause of the district stockout. For the remaining 14% of countries that reported district level stockouts, these were caused by other factors unrelated to the national level stockout – for instance, a breakdown of the distribution system or poor stock management at lower levels of the supply chain.

Figure 7.8: Subnational impact of national level vaccine stockouts, 2014 and 2015



More concerning about the results, however, are the following two facts.

- In 47 countries the district level stockout led to an interruption of vaccination services. This implies that there is an 81% chance that a district level stockout will cause an interruption of immunization services. How this impacted immunization performance and coverage remains unclear.
- The situation between 2014 and 2015 has worsened with more countries reporting district level stockouts and interruptions of vaccination services due to a district level stockout of vaccines – 47 countries in 2015 compared to 33 in 2014.

While the sublevel stockout indicators provide valuable insights, the magnitude of the problem is difficult to gauge without an understanding of how many districts were affected.

Other immunization supply chain indicators[54]

Whereas the stockout indicators analysed above are the primary GVAP performance measures for an immunization supply chain, four additional indicators (see Table 7.3) were included in the WHO-UNICEF joint reporting form as of 2014, which merit being analysed. These indicators further elucidated the performance of immunization supply chains according to the three objectives of availability, quality and efficiency[55] and are defined as follows.

1. Y/N to whether the country has an electronic stock management system at district level and below.[56] It is assumed that if a country has electronic stock management systems, higher levels of the supply chain can have better visibility on vaccine stocks at lower levels allowing managers to better plan distribution and avoid having too much vaccine to one location (leading to overstocking) or not enough in another location (leading to stockouts). This indicator touches on both the supply chain objectives of availability (avoiding stockouts) and efficiency (avoiding wasting vaccines from expiry due to overstocking).
2. The percentage of cold-chain equipment at subnational levels of the supply chain in a country that is equipped with continuous temperature monitors[57]. Keeping vaccines in the correct temperature range is vital to ensure that their potency is preserved up until the point of vaccination. The assumption behind this indicator is that having the cold chain equipped with devices for continuous temperature monitoring allows managers to mitigate the risk that there will be temperature breaks in the cold chain, which can compromise vaccine potency. This indicator attempts to capture performance on the second objective of an immunization supply chain.
3. Y/N to whether the country has an immunization supply-chain improvement plan[58] and whether there is a dedicated supply chain manager at national

[54] A report with a more comprehensive analysis of this topic was prepared by WHO and is available upon request.
[55] The three main objectives of an immunization supply chain are to secure: (1) uninterrupted availability of vaccine up to service delivery points so that no opportunities to vaccinate are missed because of unavailability of vaccine; (2) high quality cold-chain storage so that vaccine potency is safeguarded from end-to-end; and (3) supply-chain efficiency up to the last mile including management efficiencies, so as to reduce the overall costs to distribute a dose of vaccine.
[56] Respondents answered yes when 100% of district vaccine storage points use an electronic and computerized stock management system for managing vaccines. A no response indicated district vaccine storage points are using a paper-based system and paper ledgers for managing vaccine stocks.
[57] That is, an electronic device that continuously monitors temperature.
[58] Respondents answered yes when the national immunization programme has a multi-year supply chain improvement plan; a no response indicated it did not.

level[59] to oversee the immunization supply chain and the implementation of the plan.

While these new indicators are not among the GVAP indicators tracked for Goal 5, key findings from these new data points are provided in this report as complementary analyses.

The key findings are as follows.

- Only 26% of countries reported having an e-stock management system at district level, implying that the remaining countries continue to operate with a paper-based system[60]. This proportion of e-stock systems is highest in the African Region (West Africa) (59%) and in the Eastern Mediterranean Region (38%). It is lowest in the European and Western Pacific Regions – 11% and 15%, respectively (Figure 7.9).
- Less than 30% of subnational cold chain in countries is equipped with continuous temperature monitoring devices. This implies that potentially damaging temperature excursions can remain largely undetected and vaccine potency is not fully safeguarded. The proportion of countries where such devices are lacking is the highest in the African Region (West Africa) (82%) and in the South-East Asia Region (55%). It is lowest in the European and Western Pacific Regions – 15% and 26%, respectively.
- Fifty per cent of countries report having an immunization supply-chain improvement plan and 65% of countries report having a dedicated immunization supply chain manager. Regions where most countries have both are the African (West and Central Africa) and South-East Asia Regions (Figure 7.10).

Table 7.3: Other immunization supply chain indicators, 2014 and 2015

	2015	Trend	2014
Percentage of countries with an electronic stock management system at district level and below	26%	↑	21%
Percentage of subnational cold chain equipped with continuous temperature monitoring devices	28%	↔	28%
Percentage of countries with an immunization supply chain improvement plan	52%	↑	51%
Percentage of countries with dedicated immunization supply chain manager	65%	↑	61%

The analysis by income group highlights that low-income countries perform better on these indicators. With each increase in income group the performance on these indicators tends to drop (Figure 7.11). For the electronic stock management system, the immunization supply chain manager and improvement plan, this is likely due to the fact that richer countries tend to have more integrated supply chain systems. As such, they will have a health supply chain manager and plan rather than one that is specific for the immunization programme. Similarly, richer countries tend to have the supply chains managed by the private sector whereas these are managed by the national governments in low-income settings. More analysis is required to confirm these hypotheses.

[59] Respondents answered yes when the national immunization programme has a dedicated staff member that focuses on supply chain management of vaccines. An immunization supply chain manager is defined as an employee of the ministry of health working in the national immunization department who: (a) Is 100% dedicated to the management of the entire immunization supply chain from the arrival of vaccines at the national level to the service point; (b) has been formally trained in vaccine and supply chain management; and (c) has the authority and resources to manage the supply chain. A no response indicated the national immunization programme does not have a dedicated vaccine supply chain manager(s) but may have a cold chain or vaccine storage manager at the national level.

[60] As per the definition provided in the JRF for this indicator.

Figure 7.9: Use of electronic stock management and continuous temperature monitoring by WHO region, 2014 and 2015

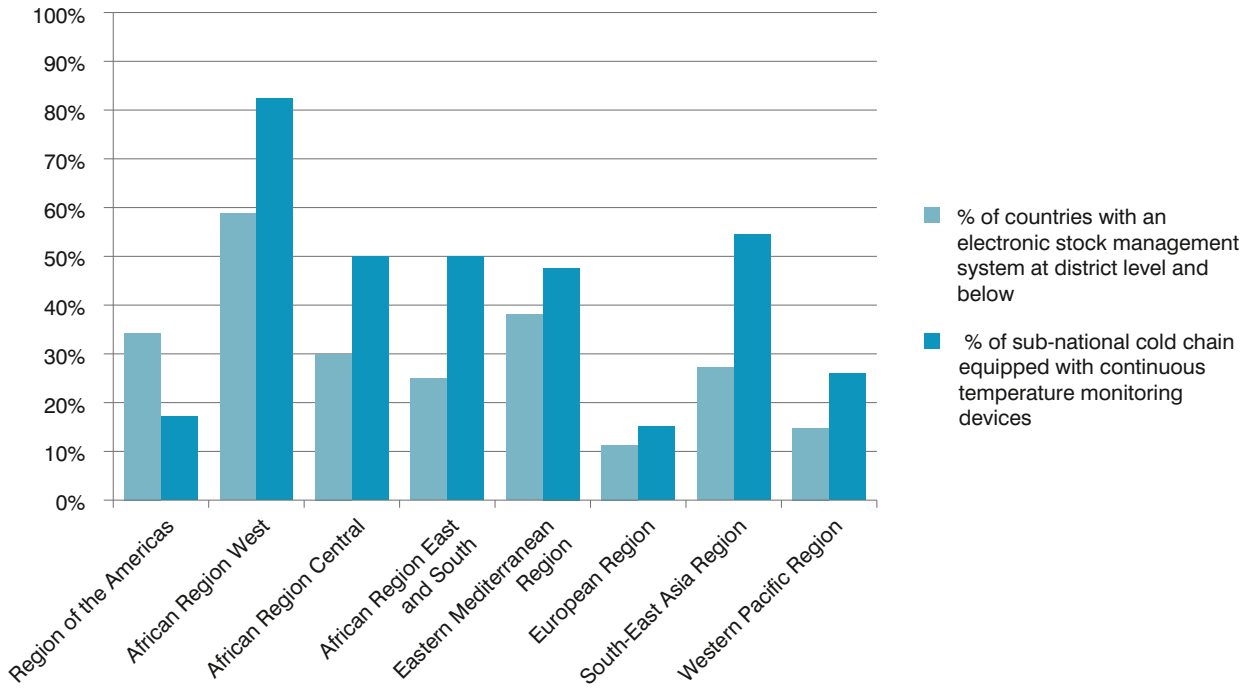


Figure 7.10: Use of improvement plans and supply chain managers by WHO region, 2014 and 2015

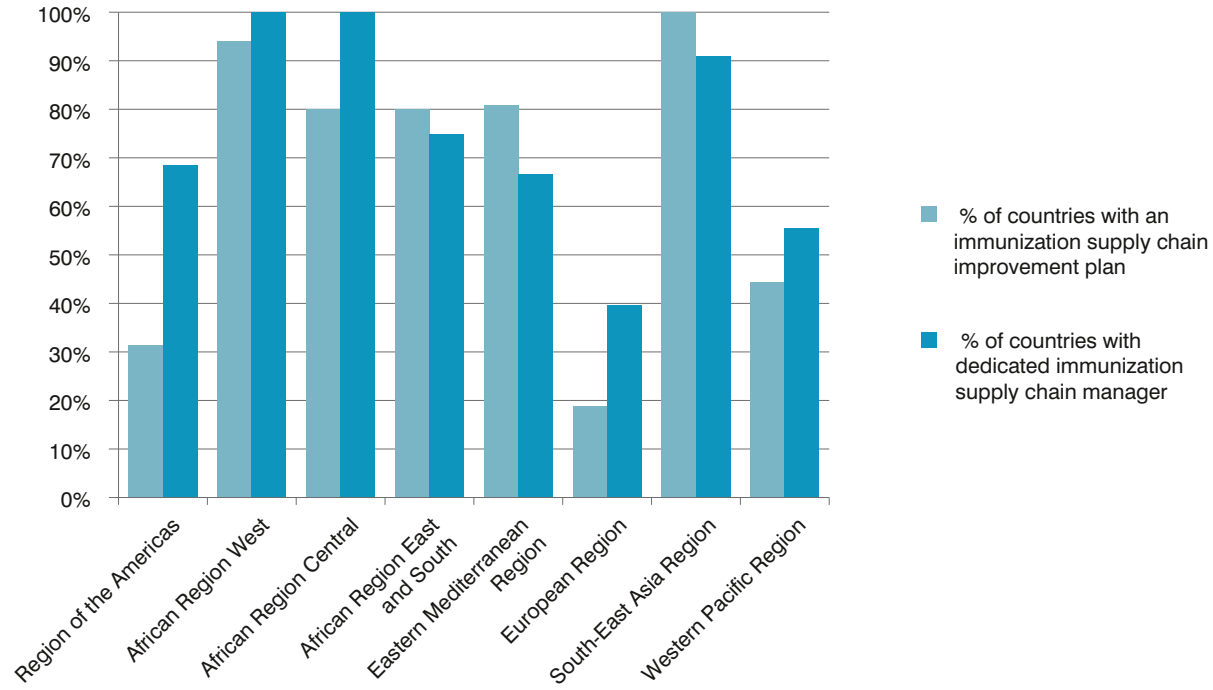
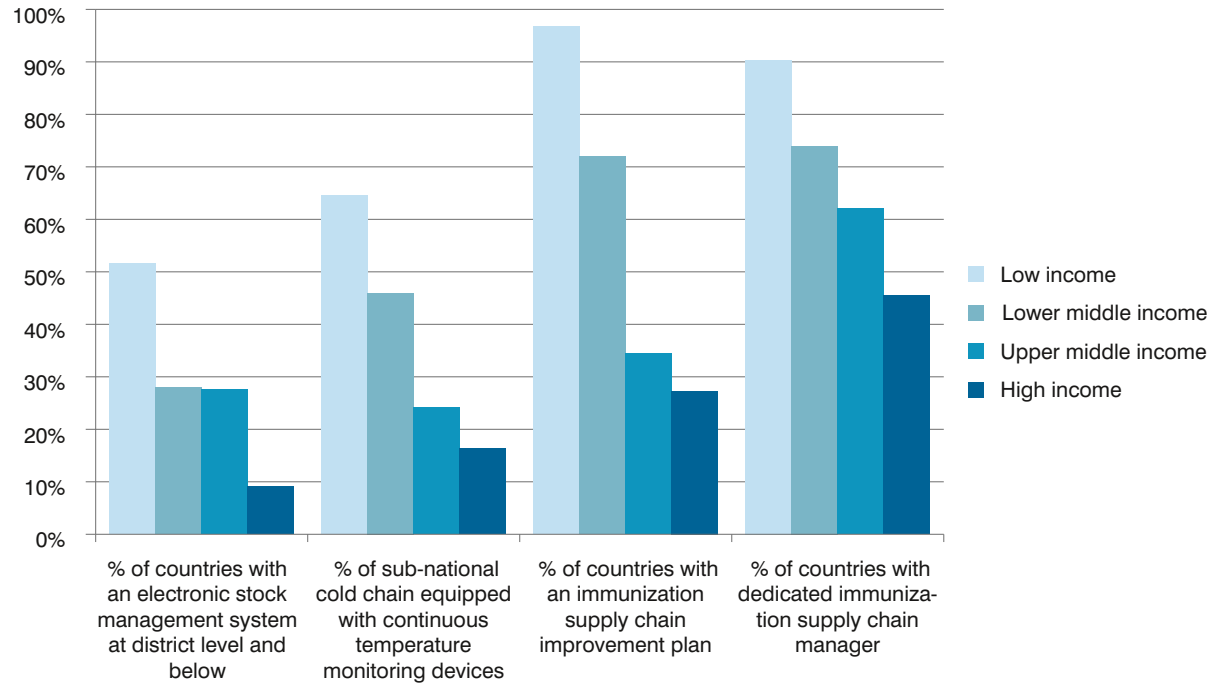


Figure 7.11: The additional supply chain indicators by income level grouping, 2015



Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8 °C range (Indicator SO6.4)

Highlights

- The June 2016 WHO prequalification of Gardasil, the quadrivalent HPV manufactured by Merck, brings the total number of vaccines approved for use in a controlled temperature chain (CTC) to three.
- A pilot study to use HPV vaccine in a CTC is being planned and expected to illustrate the advantages of CTC implementation far better than was possible with MenAfriVac due to the broader geographic and programmatic scope associated with HPV vaccination.
- Approximately 4 million people have been successfully vaccinated to date through the CTC approach in a total of six countries, proving the strategy is programmatically feasible, economically viable, and increasingly in demand by middle- and low-income countries which stand to benefit most from this strategy.
- The ongoing experience of evaluating oral cholera vaccines for CTC prequalification has revealed that there is significant variability in the protocols required to demonstrate vaccine thermostability and that some products possess particular complexities rendering the process more challenging.
- Following an in-depth evaluation of drivers and barriers for manufacturers considering CTC-compatibility for candidate vaccines, it has been confirmed that increased advocacy for CTC is required among partner institutions, as is the promotion of CTC consideration at the earliest stages of the product development continuum.

DEFINITION OF INDICATOR	This indicator measures the number of vaccines used in low- and middle-income countries that are licensed for use in a controlled temperature chain (CTC) for a limited period of time at ambient temperatures of up to 40 oC CTC is defined as: • allowing vaccines to be kept and administered at ambient temperatures, up to 40 oC, specified on their product label and with the appropriate temperature monitoring tools; • a single excursion for a limited period of time (length of time will vary by antigen and setting, although a minimum of three days is preferred by WHO) immediately preceding administration; • up until this excursion, the vaccine should continue to be kept in the traditional 2–8 oC cold chain
TARGET	None specified
DATA SOURCES	To monitor outcomes (label change): Revised vaccine product inserts allowing for use of the vaccine at ambient temperatures up to 40 oC, accessed from the WHO Vaccine Prequalification Database, manufacturers' websites and hard copies of product inserts To monitor progress: Public announcements made by vaccine companies of ongoing studies to assess feasibility of using their vaccines in a CTC, including journal articles, media reports and conference presentations Private correspondence and information disclosed to WHO under non-disclosure agreements such as email correspondence and meeting minutes

Definition of the indicator

This indicator measures the number of vaccines used in low- and middle- income countries that are licensed for use in a CTC for a limited period of time, at ambient temperatures of up to 40$^{oC.}$

WHO continues to define CTC as shown above under the "definition of indicator". In addition, it should be noted that through the development of the 2015 WHO *Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions (1),* the new term ECTC was coined to distinguish regulatory requirements from programmatic requirements, the latter only applying to CTC.

Comments on quality of data

Reliable data continues to be obtained through the following means:

a. coordination between the team responsible for managing the EPI, which drives the CTC programmatic agenda, and the team responsible for the WHO prequalification of vaccines;
b. direct dialogue maintained with respective vaccine manufacturers who are undertaking thermostability studies with a view to an eventual label variation submitted to the national regulatory authority (NRA) and WHO prequalification in support of a CTC approach;
c. oversight and technical support of country-level operational research linked to CTC implementation;
d. collaboration with partner institutions increasingly engaged in the CTC agenda, such as PATH, Médecins Sans Frontières (MSF), Gavi Alliance and UNICEF;
e. strategic guidance and technical outputs emerging from the newly established CTC working group, which operates as a subgroup to the Immunization Practices Advisory Committee (IPAC).

Narrative report

Results

On 1 June 2016, Gardasil, the quadrivalent HPV manufactured by Merck, was licensed and prequalified for use in CTC conditions for three days at temperatures up to 42 °C. Gardasil, represents the third vaccine product to be fully approved for use in a CTC, following in the successful tracks of MenAfriVac (meningitis A vaccine), which was approved by WHO in December 2012 and Prevnar13 (13-valent pneumococcal conjugate vaccine), which obtained WHO approval in May 2015.

The initial integration of CTC into HPV vaccination efforts will occur through a pilot study, the protocol for which is currently under development. The objectives of this study will be to demonstrate that this vaccine can be effectively and safely administered outside of the cold chain and that doing so can bring notable programmatic benefits, including reduced costs and logistical burdens. A component of the study will also focus on measuring wastage associated with CTC use and the ease of temperature monitoring associated with this strategy.

Data continues to be collected through CTC implementation linked to MenAfriVac use. Campaigns in both South Sudan and the Democratic Republic of Congo during the first half of 2016 allowed for new opportunities to apply the CTC strategy and confirmed the growing interest and recognized benefits of this approach. Benefits include potential cost savings and facilitated access to hard-to-reach areas where immunization services are the most challenged. As of July 2016, over four million people have been vaccinated against meningitis A through the CTC approach, across a total of six different countries (Benin, Cote d'Ivoire, the Democratic Republic of the Congo, Mauritania, Togo and South Sudan).

While downstream efforts for CTC have enjoyed increased momentum, upstream progress has proven slower than expected. Notably, the two oral cholera vaccine products under review for WHO prequalification continue to be the subject of extended discussions and it has become evident that the data provided by manufacturers thus far do not allow a decision with respect to use of the vaccine under CTC. This scenario is reflective of the increased evidence indicating that many vaccine products possess complex stability profiles that are not as easy to prove compatible to CTC as was MenAfriVac.

A recent assessment commissioned by WHO to clarify vaccine manufacturer's perceptions of CTC revealed that while manufacturers are generally interested and motivated to contribute to the CTC agenda, only 12 of the 21 manufacturers who participated in this assessment indicated having a proper understanding of CTC. The main reasons that make some manufacturers hesitate to invest in CTC are the timelines and potential costs involved in CTC relabeling as well as the limited information available about country uptake. A shared vision and strategy between the immunization community and manufacturers as well as documentation of country implementation will be instrumental in increasing interest in CTC among a broader set of stakeholders, including the vaccine industry. This is to be among the central objectives of the CTC working group established in June 2016 as a subgroup of the IPAC. This working group, consisting of subject experts, is to meet by teleconference every two months. Those discussions will be open to industry members. In addition, the group is available for closed consultations with specific manufacturers, on request.

Analysis

The licensure and WHO prequalification of Gardasil represents a significant milestone for the CTC agenda because it is the first occasion to pilot and scale up a vaccine other than MenAfriVac for use in a CTC, due to its status as a vaccine administered through campaigns or special strategies. The HPV vaccine offers a valuable opportunity to generate far more significant and replicable data on the advantages of CTC implementation because, contrary to the MenAfriVac labelled for CTC which is only licensed for meningitis A vaccine introduction and not routine use, Gardasil is a vaccine designed for routine use and eligible to be used in a far broader geographic context. Consequently, UNICEF procurement of HPV vaccine is financed by the Gavi Alliance on a much larger scale and the opportunities for integration of CTC are both more frequent and varied in scope.

The protocol for the HPV/CTC pilot study currently being planned is expected to serve as a foundation to subsequently develop implementation guidelines for HPV vaccines used in a CTC. Much as was the case for similar CTC field guidelines developed for the meningitis A vaccine, the content of the CTC guidelines for the HPV vaccine will benefit from IPAC input and endorsement by way of the dedicated IPAC working group for CTC. These latter guidelines will not be product or brand specific however, and will instead aim to provide generic guidance on use of HPV vaccines in a CTC. This is in great part because additional HPV products from other manufacturers are expected to be licensed and prequalified for CTC use in the near future.

The use of MenAfriVac via a CTC continues to scale up and more countries show interest, especially as many now face a need for catch-up campaigns. However, once introductions are complete and most countries in the "meningitis belt"[61] move to routine use, there will be minimal opportunity for CTC implementation with this vaccine, unless the routine version of MenAfriVac is relabelled for CTC. Serum Institute of India, MenAfriVac's manufacturer, has yet to commit to this given the priority expressed by WHO that CTC-compatible vaccines be mainly for campaigns or special strategies. The latter restriction still holds given that the benefits in a routine context are far more limited since most of the other vaccines that would need to be given in conjunction still require the cold chain, reducing any flexibility offered by CTC and making then the risk of confusion with non-CTC vaccines too significant.

It is believed that with the increased experience and understanding of CTC implementation afforded by the HPV vaccine, general demand for CTC-compatible vaccines at country-level will increase, helping boost momentum for upstream developments in stability testing and licensure. This could have a particularly positive impact on CTC relabeling of other vaccines such as hepatitis B for birth dose or TT, both of which are understood to be relatively heat stable but for which CTC licensure efforts are stalled due to lack of clear demand.

Boosting downstream experience and understanding of potential CTC benefits is expected to translate into increased demand. This, along with improved engagement and commitments upstream, will require that continued advocacy, stakeholder alignment and strategic guidance be among the key concerns of the IPAC working group for CTC.

References

1. Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions. Geneva: World Health Organization; 2015.

[61] The extended meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east (26 countries), has the highest rates of the disease.

8. SUSTAINABLE FINANCING AND SUPPLY FOR IMMUNIZATION

Note for the reader:

The sections on the GVAP indicators of "vaccine prices" and "immunization financing" have been gathered in this new section "sustainable financing and supply for immunization". This is to provide a detailed compiled response to the WHA resolution on sustained access to affordable vaccines (WHA68.6, 2015[62]).

Highlights

- For several years, WHO and partners have been implementing activities in multiple areas to facilitate the access of its Member States to sustainable and affordable vaccines, this includes activities in the following areas:
  - increasing political commitment and national funding for immunization;
  - improving country regulatory environment for vaccine introduction;
  - improving and sustaining country vaccine procurement systems;
  - improving vaccine supply security (i.e. vaccine research and development, technology transfer, WHO prequalification process);
  - promoting transparency and dialogue on demand, supply and regulatory matters;
  - access to supply during humanitarian emergencies.
- Highlights for the "immunization financing" indicator
  - Over the period 2010–2015, a total of 67 countries reported increased government expenditure on immunization from the baseline, while 37 countries reported decreasing expenditure.
  - While low-income countries and those transitioning out of Gavi Alliance support ("Gavi-transitioning countries"[63]) registered modest growth in spending over the past six years, global growth has been primarily driven by high-income countries.
  - Huge disparities remain in terms of absolute expenditure between countries in different income levels, signifying continued challenges in achieving the GVAP goals, in particular for low-income countries and middle-income countries transitioning out of Gavi support.
  - Although there have been some improvements in the quality of reported data, efforts to improve data reporting processes should be strengthened at country level.
- Highlights for "vaccine prices" indicator
  - Fifty countries shared vaccine price information with V3P in 2016, a 25% increase compared to last year (40 countries in 2015).
  - The V3P database now provides vaccine price information covering about 70% of the world, both in terms of number of countries and birth cohort.
  - Pooled procurement mechanisms manage to secure lower prices than self-procuring countries, except for self-procuring countries purchasing very large volumes.
  - WHO and partners remain very active in this area and will look at maintaining price transparency, strengthening the use of pricing data at country level, while key actors will increase their scope of work in the area of market shaping.

[62] http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf#page=27
[63] This refers to countries transitioning out of Gavi Alliance support. See for more information: http://www.gavi.org/support/apply/graduating-countries/.

Background

Inadequate financing and difficult access to supply are currently seen as a bottleneck for countries achieving and sustaining national, regional and global immunization goals. Several countries are reporting challenges accessing vaccines in the quantity they need (both traditional and "new" vaccines) as well as accessing sufficient financial resources to meet the increasing costs of immunization programmes (including due to high vaccine prices).

Several frameworks, strategies and resolutions highlight WHO's work in the area of sustainable financing and supply for national immunization programmes, including the WHO Global Framework for Action in Essential Drugs and Medicines *(2000)*, the Global Vaccine Action Plan (WHA65.17, 2012), sustained access to affordable vaccines (WHA68.6, 2015), the SAGE-endorsed Middle Income Country Strategy for immunization *(2015)* and the recent African Ministerial Declaration in February 2016. All these frameworks and resolutions highlight gaps and needs for WHO action across a few inter-linked work streams. These are: i) increasing political commitment and national funding for immunization; ii) improving the country regulatory environment for vaccine introduction; iii) improving and sustaining country vaccine procurement systems; iv) improving vaccine supply security; and v) promoting transparency and dialogue on demand, supply and regulatory matters.

For the first time, this GVAP chapter provides a single report on progress across all these work streams. The chapter provides an overview of main accomplishments, challenges and future directions across all areas. For immunization financing, vaccine pricing and prequalification of devices and regulatory-strengthening activities, more detailed information is also provided in Annexes 8.1–8.4.

This chapter also serves as a report on the actions taken by WHO and other partner agencies in response to resolution WHA68.6. This report will allow SAGE to assess progress against this resolution and include the assessment in their annual progress report to the WHO governing bodies.

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RESULTS

Increasing political commitment and national funding for immunization

Highlights

- In the period 2010–2015, a total of 67 countries reported increased government expenditure on immunization from the baseline, while 37 countries reported decreasing expenditure
- While low-income and Gavi-transitioning countries registered modest growth in spending, global growth has been primarily driven by high-income countries over the past six years.
- Huge disparities remain in terms of absolute expenditure between countries in different income levels, signifying continued challenges in achieving the GVAP goals, in particular for low-income countries and Gavi countries in transition.
- Although there have been some improvements in the quality of reported data, efforts to improve data reporting processes should be strengthened at country level.

Inadequate national financing – in some cases reflecting insufficient political will – as well as inefficient use of available resources will limit both new vaccine introduction and scaling-up immunization coverage. Over the past years, WHO has been working on collecting immunization financing information from countries with the purpose of monitoring its evolution globally and supporting countries to dedicate a larger proportion of national resources to immunization.

While data collection and data quality have been challenging, there have been improvements in the quantity and quality of immunization financing data reported by countries in recent years. This has followed several efforts (surveys, technical notes, dialogues) to support countries in this endeavour. The current dataset now includes 104 Member States that have consistently reported data over the period 2010–2015.

Over this period, more than 60% of countries reported increased government spending on routine immunization relative to their baseline levels: the population-weighted global average increased by 17% from US$ 26.10 to US$ 30.51 per live birth (Annex 8.1). Yet, disaggregated data suggest that the overall global spending growth can be attributed mostly to high-income countries (reporting a growth rate of 102% from 2010 to 2015). Low-income- and Gavi-eligible countries in transition reported modest increases, 8% and 14% respectively in the period 2010–2015. Furthermore, Gavi-eligible countries in transition reported low expenditures per live birth, on average US$ 7–8, relative to the average reported by Non Gavi-eligible middle-income countries, US$ 63–64.

Beyond the global trend, there are high variations and disparities among regions and within regions. WHO is conducting more specific regional and country analyses to understand the drivers behind these disparities and implications of these different dynamics.

WHO and partner institutions (e.g. BMGF, Sabin Institute, the Gavi Alliance) have been supporting countries to strengthen their immunization financing through i) comprehensive assessments and identification of bottlenecks in low- and middle-income settings; ii) development of multi-year plans and budgets for immunization; and iii) advocating for countries to prioritize achieving GVAP goals, including for immunization financing. Such technical support should be maintained and further intensified particularly in the current dynamic landscape: several countries are transitioning out of Gavi support and a larger share of the world's vaccine-preventable disease burden is shifting to middle-income countries receiving very limited or no external financial support for immunization; international agencies also face financial constraints in providing technical assistance

to these countries. Additional detailed information on immunization planning and financing can be found at the WHO website: http://www.who.int/immunization/programmes_systems/financing/en/.

Improving country regulatory environment for vaccine introduction

National regulatory authorities (NRAs) are an integral part of health systems in ensuring the access to safe, effective and high-quality medical products including vaccines. Efficient regulatory mechanisms with streamlined processes and predictable timelines facilitate optimal pricing for vaccines. As of June 2016, WHO reported there were 43 vaccine-producing countries, 37 of which had a functional NRA. At the end of 2015, 22 of the vaccine-producing Member States were producing one or more WHO-prequalified vaccines.

WHO developed a dedicated programme for regulatory systems strengthening within the WHO Essential Medicines and Health Products Department. In recent months, WHO has been developing a new business model of funding and delivery of regulatory systems strengthening programmes, introducing two novel concepts "Global Coalition of Partners" and "Centres of Excellence". The new model was recently piloted in Bangladesh. The global coalition of partners (to be officially launched in September 2016) aims to lead coordinated interventions among all relevant technical and development partners to achieve a sustainable impact on strengthening pharmaceutical regulatory systems. This approach will significantly help to optimize resource mobilization and to enhance greater consistency in standards and approaches. Establishment of centres of excellence contributes to sustainability of high-quality and timely programme outputs/outcomes through decentralizing some steps of benchmarking and capacity-building activities to competent institutions. The programme is also piloting a new WHO global benchmarking tool, which is expected to be released by end 2016.

Among the achievements in 2016 is the assessment of the Russian Federation's NRA that was conducted for the purpose of revaluating the functionality of the regulatory system. The process is ongoing at the time of this report. Assessment of several other countries including Kazakhstan, Serbia and Saudi Arabia has been initiated for 2016.

Even with functional NRAs, inefficient and widely varying processes for registering vaccines, including WHO-prequalified vaccines, create an important obstacle to vaccine introduction, lengthening timelines and driving up costs for countries and suppliers. WHO is working to promote the procedure for collaborative national registration of prequalified vaccines, which will accelerate registration through improved information sharing between WHO and NRAs.

WHO is also developing a comprehensive set of guidelines to support countries in this area, including WHO guidelines for good regulatory practices and guidelines on regulatory preparedness for non-vaccine producing countries in response to pandemic influenza emergency.

Improving and sustaining country vaccine procurement systems

Inefficient procurement is an important barrier to obtaining competitive prices and reliable supply of new and traditional vaccines. To support countries in this area, WHO headquarters is in the process of developing procurement guidelines and a related assessment tool in close collaboration with UNICEF and other immunization partners. The Regional Offices for the Americas, Europe and the Eastern Mediterranean have been providing support to countries on demand-consolidation activities such as demand planning and forecasting, on the harmonization of product requirements across countries and on the improvement of procurement legislation.

Of note, the Regional Office for the Eastern Mediterranean has been encouraging and supporting a number of middle-income countries to procure routine vaccines through UNICEF. The Regional Office for

Europe, in cooperation with the South-eastern Europe Health Network, plans to document, in 2016, the vaccine supply challenges in upper-middle-income countries and to provide evidence-based recommendations regarding areas of action. A Regional workshop on strategic procurement of new medicines is planned for September 2016. The Association of South-East Asian Nations (ASEAN), under the guidance of the National Vaccine Institute in Bangkok, together with the Regional Office for South-East Asia and the Regional Office for the Western Pacific, is leading an initiative on vaccine security, an issue that is in the process of being included in the ASEAN post-2015 health development agenda. A third workshop to discuss progress will be organized in fall 2016. At around the same time, the Regional Office for South-East Asia plans to organize a procurement workshop to support countries in the region experiencing procurement-related challenges. In 2015, the Revolving Fund of the Pan American Health Organization procured, on behalf of 42 countries and territories, 53 different biological products and 21 injection devices worth US$ 545 million from 31 different manufacturers.

Responding to changing market dynamics, the UNICEF Supply Division (UNICEF-SD), one of the major immunization partners active in the area of procurement, has developed new procurement modalities for competitive markets as well as engaged in consultations with industry and WHO to accelerate research and development of vaccines to prevent or respond to public health emergencies (e.g. Zika vaccine and diagnostics). Also, a multi-phase tender was used in the pentavalent market to achieve procurement objectives in alignment with the Gavi Alliance's Healthy Markets Framework: the objective is to more effectively and consistently support development of vaccine markets serving developing countries. UNICEF is also working on the expansion of the Vaccine Independence Initiative (VII), a revolving fund which provides pre-financing support for countries who are transitioning from donor funding. This follows a UNICEF management board decision to expand the working capital of VII in 2015. VII is a platform through which UNICEF has also been providing technical assistance on normative financing matters, including on supply costing, budgeting and forecasting. UNICEF is facilitating country peer learning on procurement through vaccine procurement practitioners exchange forums.

Improving vaccine supply security

Vaccine research and development

During 2015, the R&D Blueprint for Action to Prevent Epidemics has progressed substantially. WHO has published its initial list of priority pathogens likely to cause major epidemics, and will update this on an annual basis. Two key classes of pathogens include filoviruses (such as Ebola) and highly pathogenic coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV). Ebola vaccines have progressed to the stage of regulatory assessment for licensure. For MERS-CoV, WHO has developed a global R&D roadmap and a vaccine is now in clinical testing. Options for funding preparedness and rapid response were identified, pre-publication information sharing was acknowledged by the International Committee of Medical Journal Editors (ICMJE) following recommendations of the R&D Blueprint, and a Material Transfer Agreement capacity building tool is being finalized. WHO is also performing an assessment of potential platform technologies that could be of most assistance in enabling access to diagnostics, therapeutic and preventive interventions for future emergencies.

In 2015 the first malaria vaccine RTS,S/AS01 achieved the equivalent of licensure, a positive scientific opinion from the European Medicines Agency. In January 2016, WHO recommended that pilot implementation of RTS,S occur in parts of 3–5 sub-Saharan African countries, administering 3 doses of the vaccine to children from 5 months of age, with a fourth dose 15–18 months later. At the June 2016 management board meetings of the Gavi Alliance and UNITAID funding agencies, both were supportive with a 50% contribution confirmed by the Gavi Alliance. Providing financing can be secured, the pilot projects will start first vaccinations in Q1 2018. The pilot implementation programme will generate critical evidence to enable decision-making about the potential wider-scale use of this vaccine in 3–5 years.

Technology transfer

Since 2006 WHO has been providing technical and financial support to 14 manufacturers in developing countries to establish seasonal and pandemic influenza vaccine manufacturing capacity. The technology Transfer Initiative within the Essential Medicines Department has been leading this effort and providing overall guidance to Member States on technology transfer for health-related products and vaccines in particular. Over the past 10 years this has resulted in five manufacturers achieving licensure of their influenza vaccines and adding over 300 million doses of capacity to the global pandemic vaccine supply. This capacity will have grown to 500 million by the end of 2017 and 1 billion by 2019.

In particular, during 2015, technical and financial support continued to India, Serbia, Thailand and Viet Nam, to assist manufacturers in these countries to complete the manufacturing infrastructure and bring their influenza vaccines towards licensure. In addition technical support has been provided to a manufacturer in China for the clinical development of a live attenuated influenza vaccine. Sustainability studies have also been conducted in, Indonesia, Mexico, Morocco and South Africa, highlighting the need for coherency between industrial policy and national health security policy.

During 2015 WHO in collaboration with the United Nations Industrial Development Organization (UNIDO) and the African Vaccine Manufacturers Initiative (AVMI) has also conducted an assessment of the needs and potential for vaccine manufacturing in Africa, which was presented at the Ministerial Conference on Immunization in Africa held in February 2016. This work is now being followed up with detailed business plans for vaccine production in five African countries to identify which vaccines should be produced where to provide sustainable production. Requests have been received from Ethiopia and Morocco for technical assistance for vaccine production as well as seed strains. Technical visits have been conducted and plans for further assistance are being scheduled.

Prequalification process

WHO prequalification offers manufacturers a well-established and robust means of accessing markets for products that meet internationally-accepted quality norms and standards. A total of 284 products had been prequalified as of 31 December 2015 compared to 163 in 2010, corresponding to a 74% increase between 2010 and 2015. In 2015, seven new vaccines were prequalified. These represented additional supply sources for BCG, oral cholera vaccine, seasonal influenza and OPV. A guidance document on variations for prequalified vaccines was introduced. This categorized types of variations, the documentation required to be submitted and the time frames for their evaluation. Additionally, the Emergency Use Assessment and Listing (EUAL) Procedure was developed in response to the Ebola outbreak in 2014, and is applicable to future health emergencies.

Several challenges for the WHO prequalification vaccines assessment group were noted: i) where vaccine is not used in country of origin (e.g. whole-cell pertussis; multi-dose presentation with preservative), or only recommended in the national programme for a different age group of schedule of vaccination to that recommended by WHO (e.g. first influenza vaccination for children aged 9 years), clinical data may not be able to be generated in the country of origin; ii) resources were diverted to respond to the Ebola outbreak, negatively impacting routine work; iii) insufficient supply of some vaccines (e.g. BCG, IPV, yellow fever vaccine) creates a need to allocate resources for oversight of supply from existing manufacturers and/or identification of possible future manufacturers.

In the future reporting period the WHO prequalification vaccines assessment group will continue to work in the above-mentioned areas and also focus on revising the WHO EUAL Procedure in light of experiences during Ebola and subsequent health emergencies.

Promoting transparency and dialogue on demand, supply and regulatory matters

Highlights

- A total of 50 countries shared vaccine price information with V3P in 2016, a 25% increase compared to last year (40 countries in 2015).
- The V3P database now provides vaccine price information covering about 70% of the world, both in terms of number of countries and birth cohort (including data provided by PAHO, UNICEF and individual countries).
- The relationship between income level and price is becoming clearer. This relationship is also linked to product preferences evolving with income level.
- Pooled procurement mechanisms manage to secure lower prices than self-procuring countries, except for self-procuring countries purchasing very large volumes.
- WHO and partners remain very active in this area and will look at maintaining price transparency, strengthening the use of pricing data at country level, while key actors will increase their scope of work in the area of market shaping.

Price transparency

In only two years since the launch of the WHO Vaccine Product, Price and Procurement (V3P) project, 50 countries have shared vaccine price information. The majority of reporting countries either procure vaccines themselves, or get them through a mixed procuring system (i.e. through a mix of self-procurement and UNICEF procurement). Data available in the V3P database now cover about 70% of the world's birth cohort and countries (Annex 8.2). This is incredible progress compared the limited transparency that existed on the vaccine market in 2014; while more can be done, it is important to acknowledge that information on vaccine prices now exists thanks to the combined efforts of countries and immunization partners.

Increased dissemination of price information enables transparency of vaccine pricing strategies. For instance, it is now possible to more visibly observe the relationship between price and income levels (with overlapping tiers). Pooled procurement mechanisms continue to secure lower prices, except for self-procuring countries purchasing large volumes. Additionally, there is a small but consistent impact of volume on price for most vaccines. For certain vaccines, such as the pertussis vaccines, the data allow for interesting visualization of market segmentation: product preferences between developing countries and countries with higher incomes with very strong price differentiation.

Moving forward, WHO and partners will focus on strengthening the use of pricing data by countries. Countries can now use information available to inform decision-making for introduction and procurement. In parallel, key actors, such as UNICEF, BMGF, and the Gavi Alliance Secretariat will increase their scope of work in the area of market shaping.

Monitoring vaccine shortages

Over the past couple of years, several countries across WHO regions and income groups have reported being confronted with shortages of vaccines, sometimes causing critical disruptions to immunization programmes. The issue has been reported for several vaccines, many being considered traditional vaccines, including: yellow fever, BCG, a-cellular pertussis (aP)-containing vaccines and IPV. This is a growing issue and Member States have expressed their concerns at several WHO meetings.

To respond to these concerns, a SAGE session was organized on April 13 2016 on "Pre-empting and responding to vaccine supply shortages". To prepare for the session, WHO's Immunization, Vaccines and Biologicals Department collaborated with WHO's Essential Medicines and Health Products Department, key partners, countries and the industry to map main causes behind these shortages, as well as present a global overview of vaccines with known shortages and activities conducted by key international actors to ameliorate them. It was noted that 15 out of 25 vaccines were either in shortage or at risk of a shortage (60%). Also, it was recognized that partners (such as UNICEF, PAHO Revolving Fund, the Gavi Alliance, BMGF) are working collaboratively to outline best practices in mitigating supply constraints when they occur, improving communication with countries at the global level, and applying lessons learned/ strategic considerations to prevent supply constraints. Nevertheless, efforts are focused on certain countries/ vaccines: self-procuring middle-income countries have mixed prospects, with markets in several countries vulnerable to being unable to meet demand.

SAGE recommended that WHO play a key role in setting up an "Exchange Forum", building on existing efforts and helping to collect demand information from all Member States and enhancing supply and regulatory information sharing. The aim is to enhance dialogue between countries, manufacturers and regulators to manage threats to sustainable vaccine supply.

Access to supply in humanitarian emergencies

A nascent and important workstream of WHO's work in the area of sustainable financing and supply for immunization is access to supply in humanitarian emergencies. Despite the available WHO guidance on vaccinating in emergencies and the medical needs, barriers remain to fully operationalizing these tools and realizing the objective of improving vaccination in emergencies. These barriers include supply and procurement obstacles: information on procurement and supply options, difficult forecasting, unpredictable funding and price issues. Rapid availability of needed vaccines at an affordable price poses challenges to countries and global stakeholders. Responding to Member States request for action, partners are working to collaboratively develop solutions. An MSF-WHO co-sponsored event was held in June 2016 and a follow-up discussion is scheduled for October 2016. Potential outputs include the mapping of roles, responsibilities and policies of different actors supplying vaccines in humanitarian emergencies, a quantification of the access problem and concrete proposals for solutions. The Gavi Alliance is currently reviewing its policies for fragile states, including its work in contexts of humanitarian emergencies.

ANNEX 8.1: "All member states commit to immunization as a priority: domestic expenditures for immunization per person targeted (Indicator SO1.1)"

DEFINITION OF INDICATOR	Domestic expenditures for immunization are considered all recurrent expenditures financed by domestic resources (from national and subnational government budgets) for immunization-specific activities carried out for both vaccine procurement and immunization delivery. Supplemental immunization activities are excluded, as are extra-budgetary expenditures from development partners, capital expenditure, out-of-pocket and private expenditures For persons targeted, the number of live births from UN population data is used as a proxy for standard denominator available for all countries
TARGET	Increasing trend in country allocation to national immunization programmes
DESCRIPTION OF DATA SOURCES	The JRF template includes the following immunization financing indicators: 1. Government expenditure on routine immunization 2. Total expenditure (from all sources) on routine immunization 3. Estimated percentage of total expenditure on routine immunization financed by government 4. Government expenditure on vaccines used in routine immunization 5. Total expenditure (from all sources) on vaccines used in routine immunization 6. Estimated percentage of total expenditure on vaccines financed by government

Data quality

There have been steady improvements in the quantity and quality of immunization financing indicators reported by Member States through the JRF since 2010. The current data set now includes 104 Member States that have consistently reported data (at least four of the past five years). This is a significant increase from having 87 Member States fulfil the same criterion at this point last year. In addition, 82 Member States now have a full time-series of data from 2010–2015, representing a richer cohort for data analysis.

It is important to note that all figures are countries' self-reported estimates with varying levels of accuracy. As a preliminary assessment of data quality, the shares of missing and inconsistent data entries are presented for each year in Figure A8.1-1, and disaggregated per region in Table A8.1-1. The assumption is that complete and consistent entries mean higher data quality and more accurate figures.

Figure A8.1-1: Indicators of data quality for immunization financing data

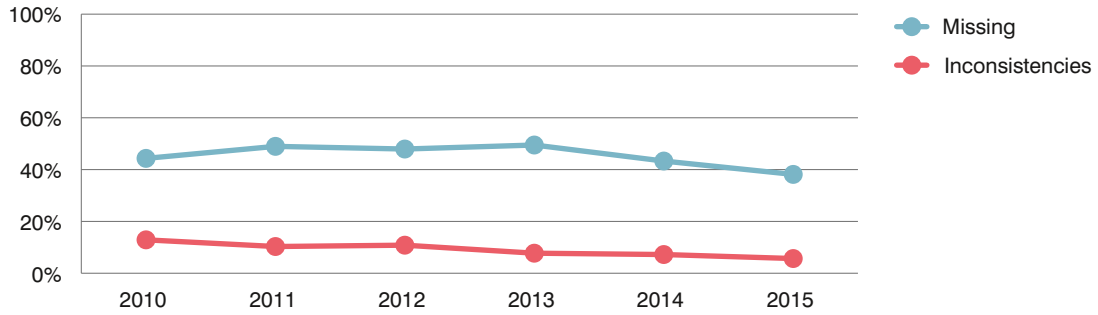


Table A8.1-1: Percentage of countries for which data are missing or inconsistent as reported under the financing indicator on the JRF, 2010–2015

	Percentage of countries with missing or inconsistent data					
WHO region	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
African Region	45	53	57	38	34	34
Region of the Americas	34	29	23	34	26	26
Eastern Mediterranean Region	71	71	81	67	67	52
European Region	77	81	79	79	79	75
South-East Asia Region	73	64	64	45	18	18
Western Pacific Region	56	59	59	59	48	52
Global	**58**	**60**	**60**	**55**	**49**	**47**

With regards to the number of missing and inconsistent data, the entries received from the past six years show a decreasing trend. While this is an encouraging finding, mechanisms to sustain gains in reporting should be strengthened. Efforts to follow-up on missing data are still ongoing which may eventually decrease these numbers in subsequent reports.

To improve quality, data were carefully screened for extreme values that may have been due to typographical or currency conversion errors. Obvious deviations were cross-checked with the prevailing trend from other years and data sources. In certain cases, missing figures were estimated by averaging values reported before and after the year concerned. Different estimation methods were also used if other reliable data sources were available. Reliance on WHO-estimated data has also been consistently decreasing in the past five years, from 36 data points estimated in 2010, to only 12 for the most recent year. For all cases, queries were sent to individual countries through the regional offices for comments, feedback and revisions to strengthen the reliability of reported data.

Countries have also been more responsive to queries and clarifications for data submitted this year. This indicates an increased awareness for the need to monitor financing indicators, and a better understanding of accounting and reporting processes. Nevertheless, there is still a need to strengthen support for countries seeking to build on their technical capacity in monitoring immunization expenditure. This includes efforts by regional offices of WHO and UNICEF to provide support and feedback, while also following-up on potential inconsistencies and missing data.

Methods

For this year's report, the method for comparing the baseline and recent spending figures have been modified to increase the number of countries included in the cohort, thus also improving the reliability of the analysis. The aim is to provide a valid assessment of the changes in expenditure by overcoming the incomplete time series for a number of countries. To be included in the analysis, Member States had to fulfil both of the following criteria:

1. have at least one reported figure for 2010 or 2011;
2. have at least two reported figures from 2013 to 2015.

Last year, reported data for 2010 were used as baseline. Though this would have been ideal had all countries submitted data for 2010, it also has the consequence of excluding all the others that did not, particularly those countries that only reported in 2011. As a solution, the baseline in this year's analysis is calculated as the average of the reported figures for 2010 and 2011 (if the country had both), or the single value in either 2010 or 2011. This serves to include a larger number of countries in the analysis and at the same time, to stabilize the fluctuations observed for some countries, providing a better representation of spending during that period.

These baseline figures are then compared to the three-year averages of the period from 2013 to 2015. Only countries with data from at least two recent years are included. Certain countries only have one data entry for the last three years, sometimes varying wildly compared to the baseline and skewing the average. It was

decided that more reliability could be achieved if at least two recent data points were reported.

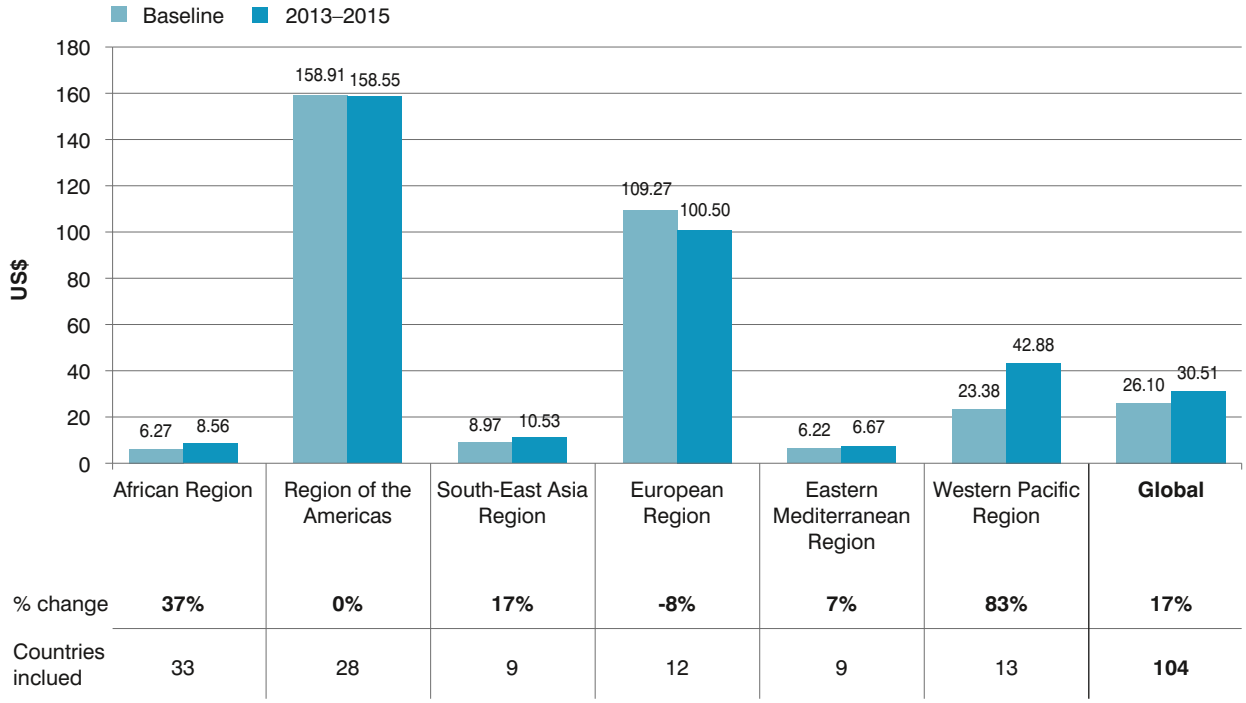
A total of 104 Member States are included in the analysis for this year's report, compared to 92 last year. Countries were grouped and analysed by WHO region and income classification in order to understand the general trends in government spending for immunization. These can be useful in evaluating general strategies and/or targets (i.e. whether to shift focus to a certain region or group of countries). Although concrete steps were taken to improve the analyses, these data should be read cautiously. If possible, countries should be evaluated on an individual basis, along with other indicators.

Results

By WHO regional classification

Of the 104 Member States with sufficient data to be included in the analysis, 33 are from the African Region, 28 are from the Americas, 12 are from the European Region, 13 are from the Western Pacific Region, and 9 each from the Eastern Mediterranean and South-East Asia Regions. Globally, government expenditure on routine immunization increased from a population-weighted average of US$ 26.10 per live birth at baseline, to US$ 30.51 for the period of 2013–2015. This represents an increase of approximately 17% of the global average. Figure A8.1-2 summarizes these findings.

Figure A8.1-2 : Government expenditure on routine immunization (population-weighted average in US$[a] per live birth), by WHO region



[a] Figures shown are in nominal US dollars for each year of observation.

Although the global figures suggest an increase in spending, a closer examination of the regional grouping reveals mixed trends. The Western Pacific Region registered the biggest rise in spending, increasing their baseline figure by 83%. This was mainly driven by spending growth in the Republic of Korea and Malaysia, accounting for a majority of the increase (see Tables A8.1-2–A8.1-7 for country-specific figures). The African Region also reported a remarkable increase of 37%, whereas other Regions such as South-East Asia and the Eastern Mediterranean reported more modest growth rates of 7% and 17%, respectively. Government expenditure on routine immunization remained almost

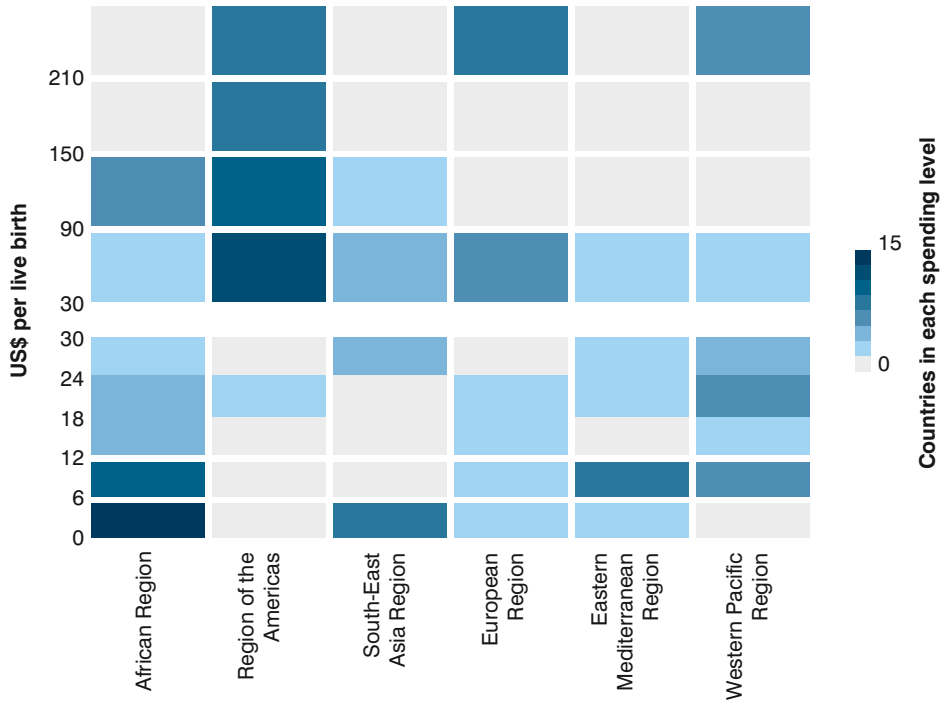
constant in the Region of the Americas, while the European Region reported a decrease in spending (-8%).

Apart from heterogeneous growth, Figure A8.1-2 also illustrates the marked disparity in absolute spending among the different WHO regions. On average, countries in the Regions of Africa, South-East Asia and the Eastern Mediterranean spend on routine immunization about US$ 8.50 per live birth, while those in other regions spend at least five times this amount.

Though the modest growth in these three regions is encouraging, more needs to be done by the governments to assume ownership of their immunization programmes and increase spending accordingly.

Figure A8.1-3 is a modified heat map to visualize the distribution of countries by their recent spending level in each WHO region. The darker shades indicate more countries for that particular spending range, while lighter shades indicate fewer countries.

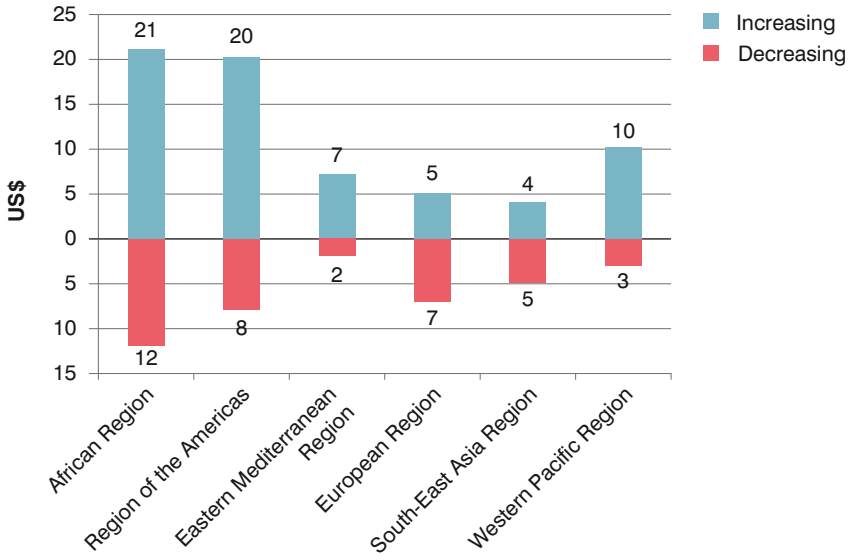
Figure A8.1-3: Country distribution of recent government expenditure on routine immunization, by WHO region



As expected, most of the regions cluster around spending levels close to their reported average, particularly in the African Region and Region of the Americas. However, it is important to note that even government expenditure within regional groups can vary significantly. In the Eastern Mediterranean and European Regions, for example, none of the countries included in the analysis actually spend at the same level as their reported regional average. Apart from helping identify which regions should be prioritized, the figure also presents an overview of the variation in each region and where potential target countries can be found.

Delving deeper into the analysis, Figure A8.1-4 shows the number of countries by region that either increased or decreased their spending. In total, 67 countries reported higher recent spending compared to their baseline, while 37 reported a decrease. The Eastern Mediterranean and Western Pacific Regions had the largest proportion of gainers, which is consistent with the expenditure growth reported above. Interestingly, while the South-East Asia Region also reported an average increase of 7%, most countries in this region actually had decreasing numbers. Closer inspection of the data reveals that Thailand's increase more than compensated for the decreases reported in India and Indonesia, explaining the seemingly contradictory figures for this region.

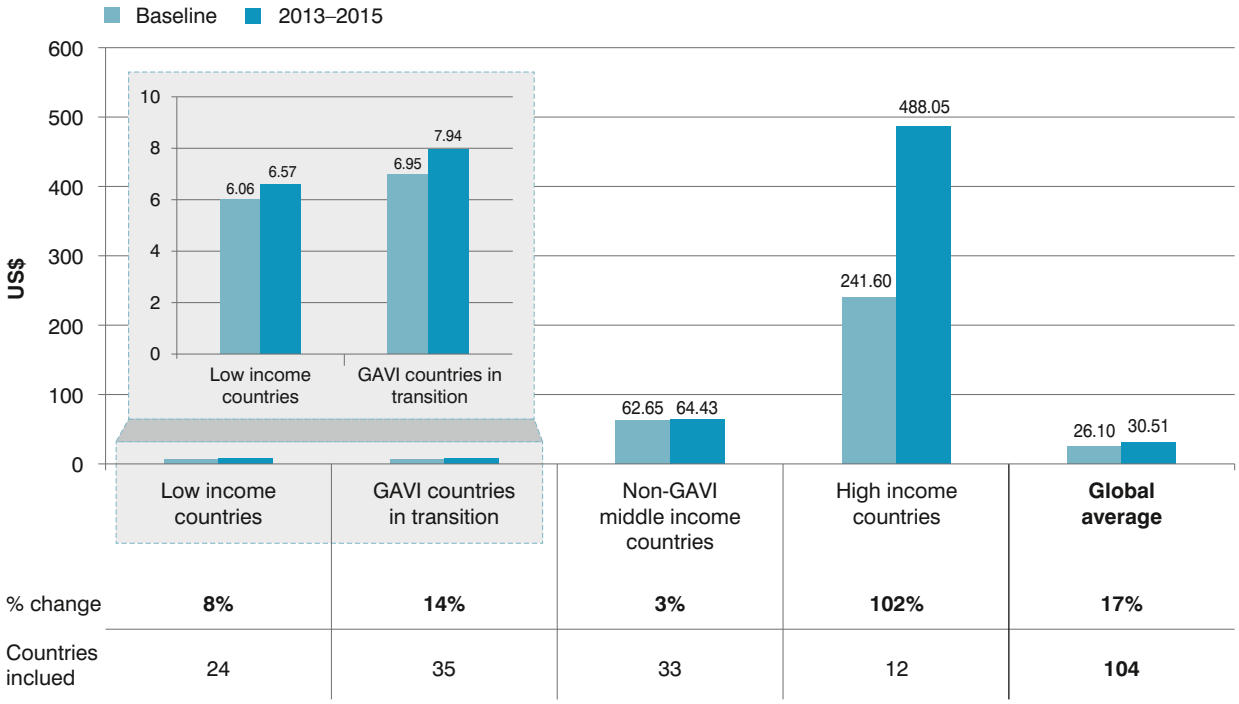
Figure A8.1-4: Trends in government expenditure on routine immunization (number of countries), by WHO region



By income and Gavi classification

When countries are grouped according to their income and Gavi classification[64], some interesting observations can be found. As shown in Figure A8.1-5, all income groups reported increased spending, however in varying degrees. The main driving forces behind the global increase in expenditures were high-income countries, more than doubling their baseline figure. Gavi-eligible countries, that is, low-income countries and those in transition, reported modest growth rates of 8% and 14%, respectively – although relatively higher than the increase reported by non Gavi-eligible middle-income countries of 3%. The absolute spending levels of non Gavi-eligible middle-income and high-income countries are much higher than Gavi-eligible countries.

Figure A8.1-5: Government expenditure on routine immunization,[a] by Gavi Alliance/income classification



[a] Population-weighted average in US$ per live birth.

[64] The Gavi Alliance classifies countries for the co-financing policy into four categories: low income; preparatory transition (phase 1); accelerated transition (phase 2) and self-financing (phase 3). For the purposes of the analysis countries of the three transition phases are grouped together.

Taking a closer look at spending patterns, data regarding government expenditure on vaccines was extracted from a separate JRF indicator. Table A8.1-8 shows the share spent by governments on vaccines as part of their expenditure for routine immunization. Correlating this with the figure above, it appears that in Gavi-transitioning countries the growth in routine immunization spending was propelled by an increase in spending for vaccines. On the other hand, the increase in vaccine spending seems outpaced by non-vaccine expenditures in high-income countries.

Table A8.1-2: Government expenditure on vaccines as a percentage of government expenditure on routine immunization

Classification	Baseline	2013–2015
Low-income countries	46.94%	50.21%
Gavi-eligible countries in transition	54.95%	71.20%
Non Gavi-eligible middle-income countries	84.43%	87.74%
High-income countries	87.62%	78.25%

Conclusion

Of the 104 countries included in the analysis, 67 reported increased government spending on routine immunization relative to their baseline levels: the population-weighted global average increased by 17% from US$ 26.10 to US$ 30.51 per live birth.

Beyond the global trend, regions report different patterns and trends over the period: from high increases reported by the Western Pacific Region to a decrease in the European Region; from relatively low expenditure per live birth in the African Region, South-East Asia and the Eastern Mediterranean Regions to quite high average expenditures in other regions. These disparities would require specific regional and country analyses, in particular to assess if the financial resources allocated to immunization are adequate to achieve the GVAP goals.

Disaggregated data suggest also that the overall global spending growth can be attributed mostly to high-income countries. However, Gavi-eligible countries, low-income countries and those in transition report modest increasing trends of 8% and 14%, respectively. Non Gavi-eligible middle-income countries report a relatively low increase of only 3% over the period.

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Table A8.1-3: Government expenditure on routine immunization by country[a], African Region

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Seychelles	HIC	27.21	20.67	44.19	131.59	222.22	49.45	23.94	134.42	462%
Botswana	UMC	15.93	32.37			63.61	171.69	24.15	117.65	387%
Equatorial Guinea	UMC	1.40	*2.30*			*6.77*	*7.60*	1.85	7.19	288%
Madagascar	LIC	0.55	1.19	1.70	2.67	*3.36*	4.02	0.87	3.35	284%
Uganda	LIC	*1.96*			3.13	9.91		1.96	6.52	233%
Nigeria	LMC	3.68				7.00	16.94	3.68	11.97	225%
Congo	LMC	*3.19*	4.88	9.47	10.48	15.51	11.38	4.03	12.46	209%
Democratic Republic of the Congo	LIC	*0.64*	0.62	1.48	1.62	1.22	0.98	0.63	1.27	102%
Burundi	LIC	0.69	0.74	1.00	1.24	1.67	1.42	0.72	1.44	102%
Guinea	LIC	0.77	*4.09*	*2.98*	3.62	6.71	2.34	2.43	4.22	74%
Sierra Leone	LIC		*3.46*	*2.74*	2.02	6.11	7.56	3.46	5.23	51%
Rwanda	LIC	5.90	*6.41*	*6.92*	7.08	6.80	13.97	6.15	9.28	51%
United Republic of Tanzania	LIC	*4.34*	*5.42*	3.04	2.80	7.62	11.60	4.88	7.34	51%
Côte d'Ivoire	LMC	7.19	4.78	13.12	11.24	*7.55*	*7.43*	5.98	8.74	46%
Mauritania	LMC	*6.48*	*3.87*	*3.22*	*3.15*	12.86	6.22	5.17	7.41	43%
Sao Tome and Principe	LMC	74.16	66.00	102.83	122.15	93.48	58.21	70.08	91.28	30%
Mozambique	LIC	3.68	4.13	4.61	5.82	*5.08*	*4.35*	3.90	5.08	30%
Chad	LIC	6.98	0.64	6.14	5.09	3.39	4.51	3.81	4.33	14%
Mali	LIC	9.66	*6.29*	3.04	*5.23*	7.35	13.70	7.98	8.76	10%
Eritrea	LIC	*2.48*	2.51	2.58	2.65	2.64	2.72	2.50	2.67	7%
Swaziland	LMC	*53.90*	*67.94*	*58.05*	54.97	48.73	90.97	60.92	64.89	7%
Central African Republic	LIC	0.52	1.06	0.41	0.85	*0.97*	*0.43*	0.79	0.75	-5%
Benin	LIC	6.50	5.40	*5.51*	5.62	5.53	5.45	5.95	5.53	-7%
Zambia	LMC	*26.46*	40.11	*40.53*	40.88		17.48	33.28	29.18	-12%
Burkina Faso	LIC	5.78	5.99	*5.27*	4.58	5.00	5.39	5.88	4.99	-15%
Ethiopia	LIC	13.80		1.79	*9.42*	11.54	13.62	13.80	11.53	-16%
Kenya	LMC	4.21	4.29	*4.01*	3.73	3.41	3.11	4.25	3.42	-20%
Zimbabwe	LIC		29.49	*30.43*	16.87	24.77	26.95	29.49	22.86	-22%
Cameroon	LMC	6.76	7.81	3.48	5.33	5.91	5.58	7.28	5.61	-23%
Togo	LIC	18.07	19.50	22.70	21.38	3.63	17.50	18.78	14.17	-25%
Gabon	UMC	*65.36*	30.50	32.47	33.17	25.96	*8.72*	47.93	22.62	-53%
Malawi	LIC	5.60	5.30		*2.10*	2.53		5.45	2.32	-58%
Comoros	LIC	16.15	*12.34*	8.65	4.15	2.02	7.58	14.24	4.58	-68%
						Population-weighted average		**6.27**	**8.56**	**37%**

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

Table A8.1-4: Government expenditure on routine immunization[a] by country, Region of the Americas

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Dominican Republic	UMC	14.07	19.53	27.35	82.59	37.23	37.42	16.80	52.41	212%
Saint Lucia	UMC	26.86	19.45	*29.60*	39.91	26.96	95.20	23.16	54.02	133%
Guatemala	LMC	30.72	31.35	70.41	51.80	60.64	91.19	31.04	67.88	119%
Guyana	UMC	*82.45*	61.61	108.48	133.52	129.67	127.61	72.03	130.27	81%
Barbados	HIC	*144.00*	288.10	96.21		114.97	571.17	216.05	343.07	59%
Argentina	HIC	74.75	254.08	209.21	155.03	244.23	343.00	164.41	247.42	50%
Dominica	UMC	16.11	53.60	57.99	*50.38*	43.07	60.75	34.86	51.40	47%
Saint Vincent and the Grenadines	UMC	26.20	17.51	22.29	24.38	36.95	30.75	21.86	30.69	40%
Paraguay	UMC	58.20	133.99	243.84	*178.15*	112.59	103.31	96.10	131.35	37%
Bahamas	HIC	*128.66*	*105.28*	130.68	123.74	161.52	168.79	116.97	151.35	29%
Venezuela (Bolivarian Republic of)	UMC	51.65	76.84	80.03	72.72	86.81	81.05	64.24	80.19	25%
Colombia	UMC	75.03	129.16	120.64	149.93	132.49	99.56	102.09	127.33	25%
Panama	UMC	249.73	357.95	319.32	*345.84*	*342.13*	*420.20*	303.84	369.39	22%
Nicaragua	LMC	85.44	64.53	66.45	84.84	90.22	96.18	74.99	90.41	21%
Brazil	UMC	214.69	180.06	*157.93*	189.88	279.26	226.23	197.37	231.79	17%
Uruguay	HIC	149.88	172.53	*167.23*	161.79	207.00	185.35	161.20	184.71	15%
Bolivia (Plurinational State of)	LMC	*48.28*	49.87	45.78	40.28	59.80	62.99	49.07	54.36	11%
Cuba	UMC	181.52	174.74	154.84	129.22	224.18	227.52	178.13	193.64	9%
Honduras	LMC	58.49	70.77	48.95	56.00	63.18	81.43	64.63	66.87	3%
Grenada	UMC	53.21	38.16	56.59	36.67	47.41	57.46	45.69	47.18	3%
El Salvador	LMC	113.95	138.03	93.86	105.69	94.38	139.58	125.99	113.22	-10%
Peru	UMC	219.99	146.07	197.98	96.99	114.93	257.63	183.03	156.52	-14%
Saint Kitts and Nevis	HIC	28.18	*22.51*	24.62	30.27	26.08	7.40	25.35	21.25	-16%
Ecuador	UMC	153.21	161.39	146.15	95.98	*130.66*	165.35	157.30	130.66	-17%
Belize	UMC	*54.85*	66.79	37.44	40.96	47.75	55.77	60.82	48.16	-21%
Mexico	UMC	204.48				146.91	85.45	204.48	116.18	-43%
Jamaica	UMC	182.75	69.73	71.16	70.22	33.41	36.66	126.24	46.76	-63%
Suriname	UMC	*117.72*	*116.11*			34.21	26.05	116.91	30.13	-74%
						Population-weighted average		158.91	158.55	0%

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

Table A8.1-5: Government expenditure on routine immunization[a] by country, Eastern Mediterranean Region

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Djibouti	LMC	36.37	31.42	64.58	*73.65*	78.40	82.07	33.89	78.04	130%
Iran (Islamic Republic of)	UMC	12.45	12.33	18.06	18.10	29.20	25.94	12.39	24.41	97%
Lebanon	UMC	44.15	37.12	45.46	55.42	61.40	86.38	40.63	67.73	67%
Sudan	LMC	3.22	2.78	*6.36*	5.46	4.69	3.96	3.00	4.70	57%
Jordan	UMC	*76.24*	*74.28*	*87.28*	*100.28*	*99.35*	*141.44*	75.26	113.69	51%
Tunisia	LMC	*14.39*	*30.78*	29.06	*29.03*	29.18	27.40	22.58	28.54	26%
Yemen	LMC	*4.86*	*5.05*	*6.95*	7.09	7.48	1.26	4.95	5.28	7%
Afghanistan	LIC	*2.15*	*2.28*	*2.51*	1.14	*1.73*	2.31	2.21	1.73	-22%
Pakistan	LMC	8.18		*12.02*	5.81	6.40	4.08	8.18	5.43	-34%
						Population-weighted average		**8.97**	**10.53**	**17%**

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

Table A8.1-6: Government expenditure on routine immunization[a] by country, European Region

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Armenia	LMC	15.27	*20.36*	25.55	*56.58*	88.15	98.55	17.81	81.09	355%
Republic of Moldova	LMC	15.55		*32.16*	49.14	44.60	28.90	15.55	40.88	163%
Uzbekistan	LMC	*4.97*	*9.56*	*9.44*	13.97	12.90		7.26	13.43	85%
Kyrgyzstan	LMC	*5.28*	5.11	5.00	5.31	5.55	14.93	5.19	8.60	66%
Georgia	UMC	35.47	*49.47*	18.58	41.22	62.88	60.07	42.47	54.72	29%
Finland	HIC	383.31	460.53	426.83	404.19	*430.99*		421.92	417.59	-1%
Iceland	HIC	269.80	386.54	441.03	*383.89*	325.03	245.74	328.17	318.22	-3%
Netherlands	HIC	*649.06*	*647.23*	*642.93*	665.94	600.43	533.76	648.14	600.04	-7%
Andorra	HIC	806.44	869.08	808.00	849.34	743.13	553.33	837.76	715.26	-15%
Tajikistan	LMC	5.24	6.23	3.64	*4.03*	4.43	4.91	5.73	4.45	-22%
Bulgaria	UMC	254.37	435.12	346.95	*211.08*	*311.50*	*238.27*	344.75	253.62	-26%
Azerbaijan	UMC	32.49	*30.42*	28.63	28.59	10.88	15.07	31.45	18.18	-42%
						Population-weighted average		**109.27**	**100.50**	**-8%**

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

Table A8.1-7: Government expenditure on routine immunization[a] by country, South-East Asia Region

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Democratic People's Republic of Koreea	LIC	*3.98*	*13.65*	24.87	23.84	23.73		8.82	23.78	170%
Thailand	UMC	*32.18*	*35.04*	*53.78*	*51.00*	46.66	80.07	33.61	59.24	76%
Nepal	LIC	*8.07*	4.79	*3.36*	7.88	3.57	12.35	6.43	7.93	23%
Sri Lanka	LMC	35.06	*9.50*	*25.25*	41.59	18.68	14.82	22.28	25.03	12%
Bangladesh	LMC	7.76	7.39	6.15	5.22	7.58	9.80	7.58	7.54	-1%
India	LMC	3.70	4.07	5.73	3.60	3.89	3.63	3.89	3.71	-5%
Indonesia	LMC	*10.83*	12.99	*12.88*	*12.81*	9.36	11.19	11.91	11.12	-7%
Timor-Leste	LMC	*21.77*	*7.40*	*4.61*	*7.64*	9.26	15.60	14.58	10.83	-26%
Bhutan	LMC	*19.18*	*12.24*	*47.48*		6.75	6.70	15.71	6.73	-57%
						Population-weighted average		**6.22**	**6.67**	**7%**

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

Table A8.1-8: Government expenditure on routine immunization[a] by country, Western Pacific Region

Country	Income	2010	2011	2012	2013	2014	2015	2010–2011 Average	2013–2015 Average	Change
Lao People's Democratic Republic	LMC	1.82	*1.61*	1.41	1.40	25.03	37.69	1.71	21.38	1148%
Republic of Korea	HIC	74.18	142.17		449.50	852.38	1,073.83	108.18	791.91	632%
Malaysia	UMC	84.13	87.21	*90.09*	*92.89*		377.63	85.67	235.26	175%
Mongolia	LMC		22.47	19.42	36.35	*38.08*	*40.14*	22.47	38.19	70%
Papa New Guinea	LMC	5.33	8.10	*15.05*	*10.03*	15.47	5.84	6.71	10.44	56%
New Zealand	HIC	*890.47*	*876.72*	915.75	1,108.63	1,296.51	1,334.67	883.60	1,246.60	41%
Viet Nam	LMC	5.63	6.76	7.25	7.05	8.34	9.65	6.20	8.35	35%
Marshall Islands	UMC	*14.37*	19.17	20.07	*21.07*	22.12	23.22	16.77	22.14	32%
China	UMC	*18.08*	*18.77*	*19.12*	18.52	18.75	*21.86*	18.42	19.71	7%
Philippines	LMC	23.15			19.99	24.10	28.07	23.15	24.05	4%
Vanuatu	LMC	19.03	*17.56*	16.14	17.08	18.03	13.24	18.30	16.12	-12%
Cambodia	LMC	*7.57*	*8.31*	*7.23*	6.16	*6.33*	6.50	7.94	6.33	-20%
Solomon Islands	LMC	*59.70*	59.60	69.98	*44.67*	19.31	11.48	59.65	25.15	-58%
						Population-weighted average		**23.38**	**42.88**	**83%**

[a] Population-weighted average in US$ per live birth. LIC, low-income country; LMC, lower-middle-income country; UMC, upper-middle-income country; HIC, high-income country.

ANNEX 8.2: "Vaccine price report 2016"

Background & Objectives

There are several trends in the vaccine market that are worth highlighting, in order to give some context around the issues of vaccine price affordability and transparency. Confirming the trends of recent years, the vaccine market continues to consolidate, with manufacturers focusing on certain families of vaccines and/or geographies. For some antigens, the demand can also concentrate on one particular product over other options (e.g. 95% of countries reporting rotavirus prices through V3P purchase the same product). Meanwhile, it is worth noting that new product presentations are also arriving on the market, like the PCV 4-dose presentation expected to be available for Gavi-eligible countries in the coming 1–2 years.[65]

In recent years, many countries have been confronted with shortages, as described in the Chapter 7 on vaccines stockouts events of this report. These shortages have happened for several reasons linked to both supply and demand factors. For instance middle-income countries are introducing new vaccines that were until now mostly used in high-income countries, such as aP-combination vaccines.

In this context, WHO Member States have raised the issue of price transparency and vaccine price affordability over the past few years, which was addressed in resolution WHA68.6 *(2015)* specifically the issues of access to sustainable financing, supplies of affordable vaccines for low- and middle-income countries, vaccine price transparency and support for market-shaping initiatives.

Responding to Member States requests and in line with a provision in resolution WHA68.6, the 2016 GVAP price report provides i) an update on the established GVAP price indicators *(2013)* – Table A8.2-1 – and ii) a review of challenges and activities conducted in support of vaccine affordability.

Table A8.2-1: GVAP vaccine price indicators

Indicator	Goal
1 - Number of countries sharing price information through the V3P platform[a] by WHO region	Monitoring country progress in sharing pricing data over time
2 - Annual average or unit vaccine prices as data permit: a. annual weighted average price (WAP) of vaccine, weighted by volume purchased, over time in relationship to procurement mechanism; b. unit prices of vaccines in relationship to country level of income and volume; c. minimum–maximum price range by country level of income	This indicator aims to: • facilitate country planning for the introduction of new vaccines; • and increase country and global knowledge of the vaccine market and price trends

[a] The Vaccine product, Price and Procurement (V3P) project is a platform to provide information on vaccine prices and procurement. The V3P database collects data from participating countries, as well as the PAHO Revolving Fund and UNICEF Supply Division. The V3P website is available at: www.who.int/immunization/v3p.

Reporting on the indicators

It should be noted that comparing vaccine prices is challenging due to the complex nature of vaccine products and markets. Limitations of the V3P price database include: limited availability of historical data (the database was launched in June 2014) with changes in country participation from one year to another; imbalance in the number of countries reporting from each region, which can skew analyses towards trends specific to one particular region; limited collection of variables on procurement systems, which limits the scope of analyses possible to understand factors that may influence prices. Information contained in the V3P

[65] http://www.gavi.org/library/documents/gavi-documents/guidelines-and-forms/pcv-4-dose-vials-faqs/

database is provided by participating countries and/or organizations procuring on behalf of countries that have agreed to share vaccine price and procurement data with V3P; participating countries are solely responsible for the accuracy of the data provided.

Note also: throughout the report and to follow the regular WHO/UNICEF JRF collection process, data collected in 2016 refer to 2015 data. Graphs presented here only use data collected and cleaned before the 30th of June 2016. Prices are given in US dollars per dose. Small discrepancies in prices published may occur due to the use of an exchange rate to convert prices in local currencies to US dollars.

INDICATOR 1: NUMBER OF COUNTRIES SHARING PRICE BY WHO REGION

As of 30 June 2016, 50 countries have shared 2015 data with V3P, with participation registered from five out of six WHO regions (Figure A8.2-1). This is a 25% increase compared to last year (40 countries). The majority of reporting countries are self-procuring or "mix-procuring"[66] (74%), middle-income countries (64%) and either are not eligible for Gavi Alliance support (70%) or transitioning out of it[67] (14%). These are the countries that can benefit the most from price transparency, as they negotiate their own prices or will soon lose Gavi Alliance support.

Data collection is expanding to new geographies: 13 new countries have shared price information for the first time this year. Only 26 non Gavi-eligible middle-income countries (and not benefitting from the PAHO Revolving Fund) remain outside of the V3P platform, including 14 countries that are self-procuring or mix-procuring[68]. Countries in the European and Western Pacific Regions have made great strides to maintain and increase participation in the platform (the former remains the region with the highest participation this year). Countries in the African Region have made an important achievement as well, particularly in the subregions of Eastern and Southern Africa, where 100% of middle-income countries are now reporting price information.

At present, the V3P database – including data shared by individual countries, the PAHO Revolving Fund and UNICEF-SD – covers about 70% of the world, both in terms of number of countries and birth cohort (Figure A8.2-2). This represents incredible progress compared to the limited transparency that existed on the vaccine market in 2013, prior to the launch of the V3P project, when only UNICEF-SD and the PAHO Revolving Fund published data that was easily accessible. Price transparency has been achieved thanks to the willingness and efforts of countries, WHO regional offices and partner organizations.

Reasons for not participating are not known for all countries but are usually connected to two main issues.[69] The first one is the lack of knowledge about the V3P project and database. While linking of the V3P project to the well-known JRF process for data collection has provided great awareness, the project remains relatively new and not always known to countries. Additional communication efforts are required to increase the visibility of the initiative and to enhance country use of data. Sustainable human and financial resources for these efforts are lacking, however. The second issue concerns country inability to share price information. This can be due to procurement being organized outside of the national authorities (e.g. delegated to a third party or decentralized to districts or service providers) or to contractual agreements preventing the disclosure of vaccine prices. On the latter point, efforts should be made to discuss with country governments the risks and benefits of such clauses by vaccine manufacturers.

[66] Countries that both self-procure vaccine and use UNICEF to do so.
[67] Countries that are currently transitioning out of Gavi Alliance support are those that have passed the eligibility threshold of US$ 1580 gross national income (GNI) per capita and are currently in the "accelerated transition phase".
[68] Excludes countries having access to the PAHO Revolving Fund and countries known to procure their vaccines through UNICEF-SD.
[69] In Europe, out of 24 countries not sharing price information, 6 countries reported not being able to do so because of confidentiality issues and 5 countries because procurement of vaccines is decentralized.

Figure A8.2-1: Number of countries reporting vaccine price data by WHO region over time

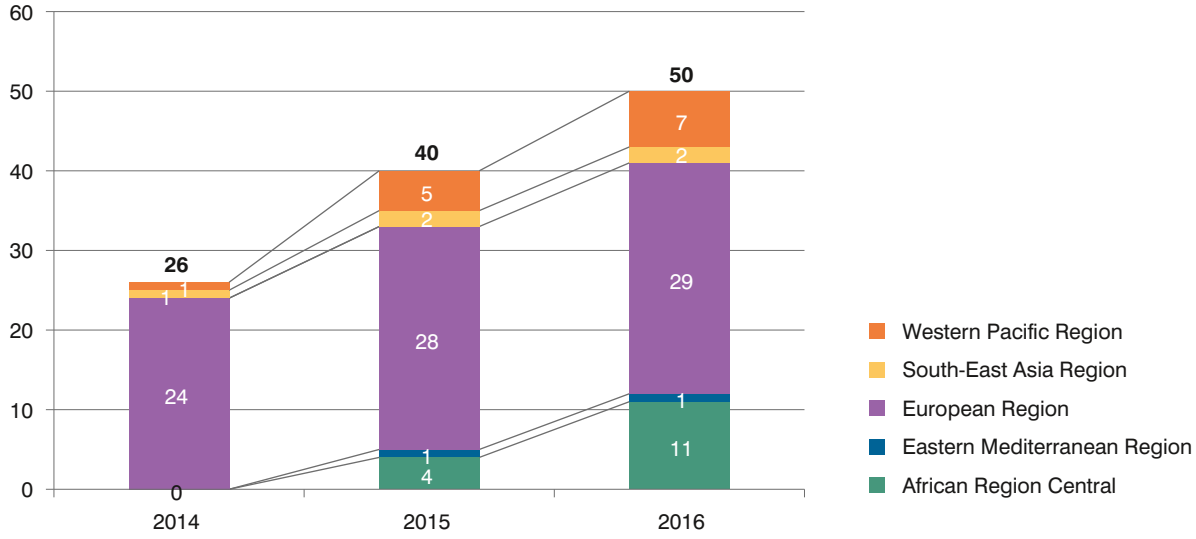
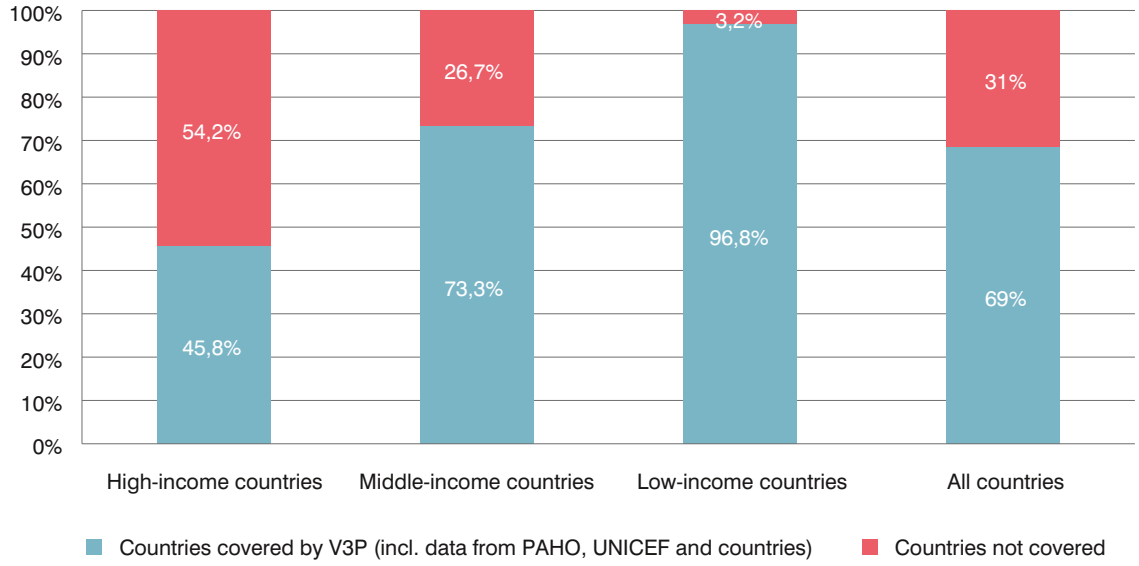


Figure A8.2-2: Coverage of the V3P database, including data shared by individual countries, the PAHO Revolving Fund and UNICEF



INDICATOR 2: ANNUAL AVERAGE OR UNIT VACCINE PRICES AS DATA PERMITS

Note: for all the indicators below, data were selected for one antigen for data visualization purposes. The full set of data is available on the V3P website at www.who.int/immunization/v3p.

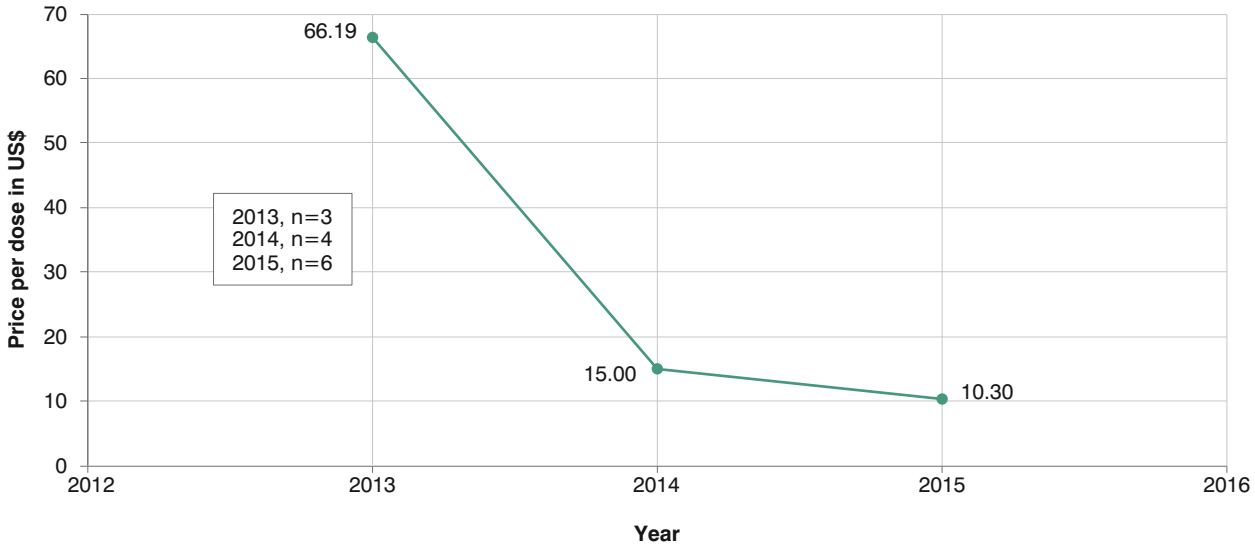
2a - Annual weighted average price (WAP) of vaccine, weighted by volume purchased, over time in relationship to procurement mechanism

With now three years of data available (2013–2015), some analyses of price over time could be conducted, but at this point did not allow for strong conclusions

regarding a potential upward or downward trend in prices. For vaccines with clear increase or decrease in price, these sharp movements could sometimes be explained by changes in the V3P sample (new countries with specific characteristics joining the database) or by the fact that some countries managed to get lower prices through switching products.

The data trend is particularly compelling for the HPV vaccine in middle-income countries (Figure A8.2-3). In 2013, only two reporting middle-income countries had introduced an HPV vaccine and the prices were quite high (range of US$ 54–93 per dose). Large volumes purchased by these countries created a big drop in the average price (WAP from US$ 66 in 2013 to US$ 15 in 2014). During the same time period, the country paying the highest price in 2013 switched from one HPV product to another, lowering its per-dose price from US$ 93 in 2013 to US$ 46 in 2014 (and managed to further reduce the price to US$ 27.5 in 2015). More countries with large purchase volumes joined the database and lowered the price even further in 2015 (WAP at US$ 10.3). A similar trend is seen for PCV (Figure A8.2-4).

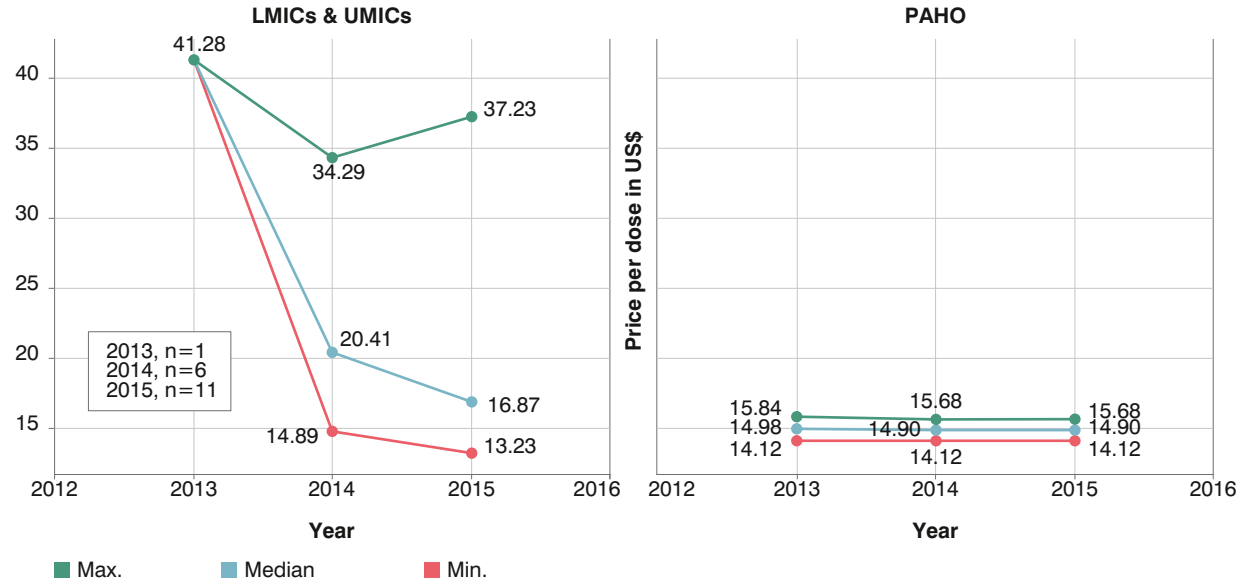
Figure A8.2-3: Weighted average price[a] of the HPV single-dose vaccine in non Gavi-eligible self-procuring middle-income countries, 2013–2015



[a] Price is weighed by volume procured.

Similar to last year, countries procuring through a pooled procurement mechanism get lower prices than self-procuring countries. (However, as new countries with large birth cohorts are joining the database, minimum prices for self-procuring countries get closer to prices obtained by pooling mechanisms such as the PAHO Revolving Fund.) This finding confirms the idea that pooled procurement, either through established mechanisms or by joining volumes with larger countries, is an interesting option for small countries.

Figure A8.2-4: Comparison of min.–max. and median prices obtained by self-procuring middle-income countries and PAHO's Revolving Fund for PCV, 2013–2015

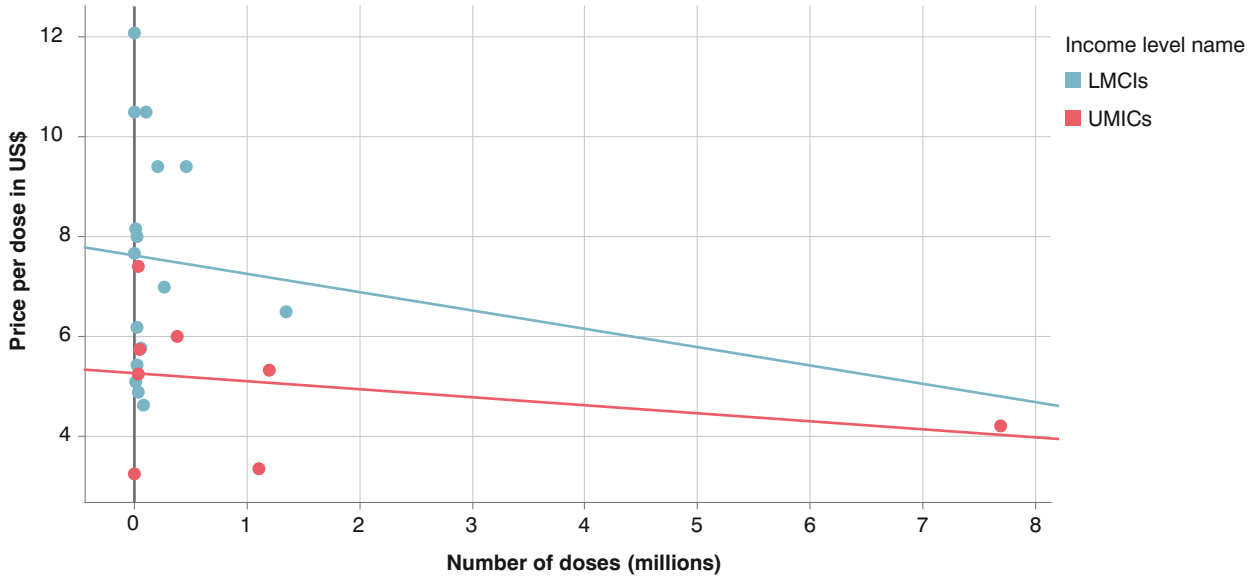


LMICs, lower-middle-income countries; UMICs, upper-middle-income countries

2b - Unit prices of vaccines in relationship to country level of income and volume

As opposed to last year and with new large countries joining the database this year, a small but consistent link can be seen between volume and price for most vaccines (Figure A8.2-5), particularly visible for very large countries procuring several hundred thousand or even millions of doses annually. Indicator 2a even showed that some of these large countries manage to reach a price level similar to what can be obtained through pooled procurement mechanisms. However, the impact of volume on price remains small, and suggests that many other factors besides volumes procured can influence prices of vaccines.

Figure A8.2-5: Price by volume procured for the MMR single dose vaccine in self-procuring countries, 2015

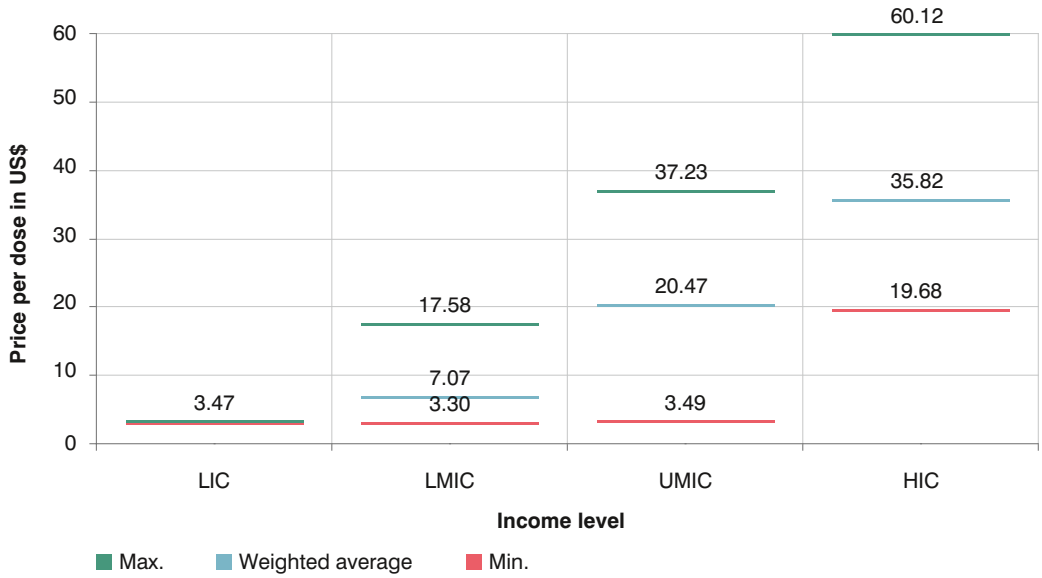


UMICs, upper-middle-income countries; HICs, high-income countries.

2c - Minimum–maximum price range by country level of income

Analyses of the current data show that for most vaccines, the price is higher and the range wider among higher-income countries/groups (Figure A8.2-6) – a similar trend to that seen last year. This is particularly visible in the new vaccines market where the price range can be substantial within and across income groups. This shows that many manufacturers apply a tiered-pricing system that takes income level into consideration. However, price ranges for each income group overlap, which also indicates that some poorer countries pay more than some wealthier countries – and that factors other than income level seem to influence vaccine pricing.

Figure A8.2-6: Minimum, maximum and WAP[a] by income level for PCV, 2015



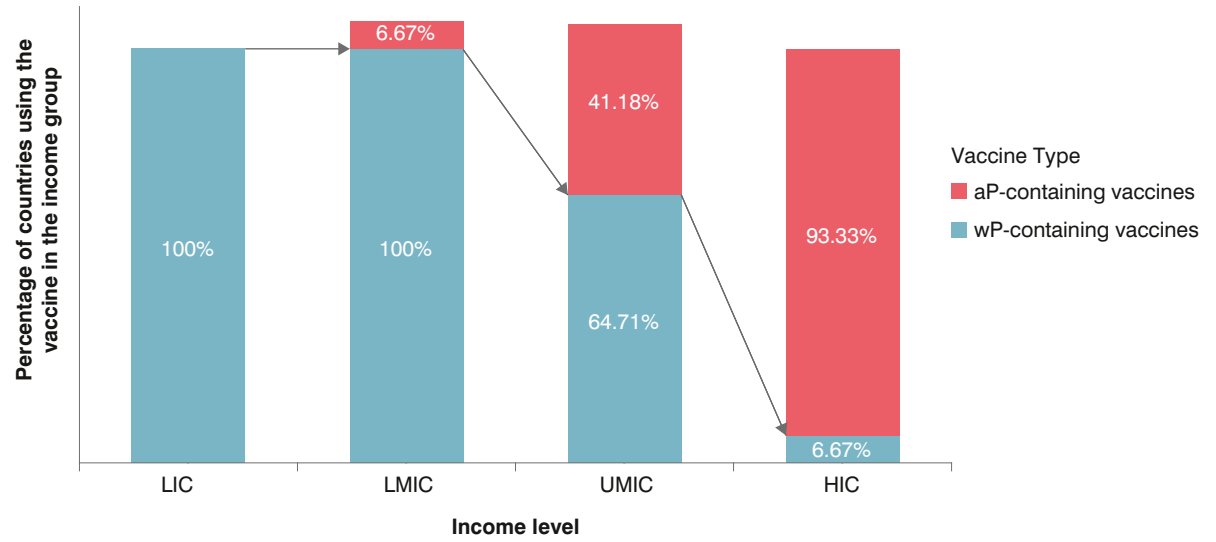
LIC, lower-income country; LMIC, lower-middle-income country; UMIC, upper-middle-income country; HIC, high-income country.

[a] Price is weighed by volume procured.

High product differentiation in some vaccine markets leads to several products co-existing simultaneously with a very wide price range. For instance the pertussis vaccine exists in whole-cell and a-cellular form, and has been combined with other antigens to form combination vaccines. In the V3P database, countries have reported using eight distinct pertussis-containing vaccines (four containing whole-cell pertussis, wP[70] , and four containing a-cellular pertussis, aP[71]). High-income countries tend to use the more sophisticated and expensive products, and middle-income countries are now beginning to introduce these vaccines in their national programmes (Figure A8.2-7). This product differentiation leads to a wide range of prices paid across income groups (Figure A8.2-8) as well as less flexibility in case of shortages (as products may not be interchangeable and not all products are registered in all countries).

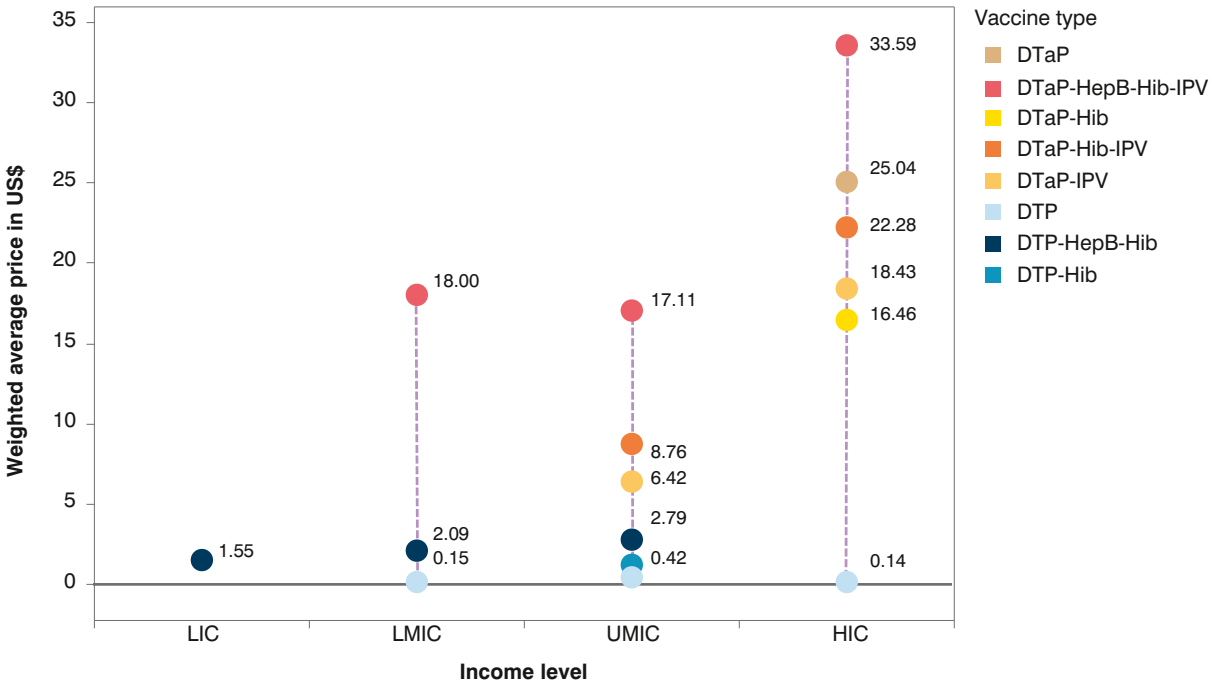
[70] DTwP, DTwP-Hib, DTwP-HepB and DTwP-HepB-Hib
[71] DTaP, DTaP-Hib, DTaP-IPV, DTaP-Hib-IPV and DTaP-HepB-Hib-IPV

Figure A8.2-7: Percentage of countries in each income group using wP- and aP-containing products,[a] 2015



[a] Note that the percentage can be greater than 100% if a country uses both wP- and aP-containing vaccines.

Figure A8.2-8: Comparison of WAP[a] for wP- and aP-containing products by income level, 2015



[a] Price is weighed by volume procured.

Challenges and activities conducted by who and partners in the area of pricing & affordability

Countries face various challenges in order to access affordable vaccines. These have been described in the Middle Income Country Strategy, endorsed by SAGE in April 2015.[72] WHO and partners are active across all the areas described in Table A8.2-2 below.

Table A8.2-2: Ongoing efforts to develop solutions to increase access to price information and to influence market dynamics

Identified issue: Information asymmetry, lack of vaccine price information
Solution: Providing access to price and contract information
• **Impact on affordability:** Better access to price information allows countries to be better equipped for decision-making, budgeting and negotiations.
• **Partners engaged:** WHO (V3P), UNICEF-SD, PAHO (Revolving Fund), MSF (Access Campaign)
• **Examples of activities and impact:** More and more countries are joining V3P and using its vaccine price information. Member States report that price transparency is useful to facilitate country planning, understand what factors may influence prices, make informed decisions regarding vaccine introduction and improve negotiations with manufacturers.[1] At the global level, transparency helps to understand the vaccine market and may be used to monitor the effects of demand & supply-related initiatives (e.g. market shaping initiatives). WHO continues to manage the V3P database and disseminate information to Member States, with data being contributed by partners UNICEF-SD and the PAHO Revolving Fund (both partners publish vaccine price information directly on their websites as well[2]). For example, a workshop was organized in Europe in December 2015 to help countries make use of the price information available to them.
• **Direction:** Work on price transparency needs to be continued to maintain and increase country participation. Communication about and advocacy for V3P must be strengthened, so Member States are made aware of these price transparency mechanisms and can make use of the data in V3P. To that end, WHO regional offices are encouraged to organize workshops on procurement and sustainable access to vaccines that can inform countries on how price data can translate into actions. In the future, WHO would like to continue coordinating activities in this area at the regional and global levels, not only for vaccines but for medicines as well. To that end, WHO is currently working on the organization of a "fair pricing of medicines" forum for 2017.
• In line with its global commitment to transparency, UNICEF regularly publishes historic, current and future awarded prices for all vaccines for which it has established long-term arrangements with suppliers. In order to allow for more informed decision-making especially in non Gavi-eligible middle-income countries, UNICEF is stepping up its efforts to publish additional information on country-specific procurement transactions conducted outside of long-term arrangements.
Identified issue: high prices for new vaccines and lack of competition
Solution: Influencing market dynamics to reach security and affordability of supply
• **Impact on affordability:** Market dynamics play a fundamental role in setting the price and availability of vaccines. A healthy market with a strong manufacturer-base is a key element of affordable vaccines and availability of supply.
• **Partners engaged:** UNICEF, BMGF, Gavi Alliance
• **Examples of activities and impact**: The Gavi Alliance has met and exceeded its goals fixed for 2011–2015, as efforts to improve vaccine markets have led to increased competition and diversification of the manufacturing base: in 2015, 17 manufacturers were producing WHO prequalified vaccines suited to the needs of Gavi-supported countries, from only five Gavi vaccine suppliers in 2001. These efforts have increased vaccine security in some markets (particularly visible on the pentavalent market) while reducing the price of several vaccines such as pentavalent, PCV and rotavirus vaccines.[3, 4] The evolved market dynamics have allowed UNICEF to also negotiate supply arrangements for pentavalent vaccines on behalf of non Gavi-eligible middle-income countries at significantly reduced prices and, most recently, at parity with those prices paid by Gavi.
• Gavi has also developed the Access To Appropriate Pricing (ATAP) framework in collaboration with partners in order to ensure that countries transitioning out of Gavi-support would get access to "Gavi prices" for some vaccines[5] and for a certain period of time after they become fully self-financing, thus supporting the sustainability of programmes in these countries.[6]

[72] http://www.who.int/immunization/programmes_systems/sustainability/mic_strategy/en/

Identified issue: high prices for new vaccines and lack of competition

Solution: Influencing market dynamics to reach security and affordability of supply

- The BMGF continues to focus on providing research and development funding to increase competition and the supply base for key vaccines – with a particular emphasis on newer vaccines or vaccines with large impact profiles within the Gavi Alliance's portfolio. Vaccines of particular interest include PCV, rotavirus, IPV, HPV, measles, and a number of pipeline vaccines not yet part of Gavi's portfolio. In most cases, development funding is tied to global access terms for Gavi-supported countries. In certain cases, BMGF uses innovative financial instruments to enable lower pricing in collaboration with other partners involved in market dynamics work.[7]
- **Direction:** In response to changing market dynamics, innovation in procurement will be done by UNICEF (e.g. multiphase tenders). The Gavi Alliance is paying attention to the impact that its market-shaping activities may have on other countries and will be monitoring this in the future.[3] Some clarification and communication work may be needed to make sure that ATAP translates into predictable pricing for Gavi-transitioning countries.

1 For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).
2 For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).
3 This refers to the 75 countries where more than 95% of all maternal and child deaths occur (including the 49 lowest-income countries) according to the Countdown collaboration (http://www.countdown2015mnch.org).
4 The database can be found at: http://apps.who.int/gho/data/node.main.HE-1540?lang=en.
5 The tool can be found at: https://whoequity.shinyapps.io/HEAT/.
6 For more information about the JRF and WUENIC coverage data, please refer to GVAP Secretariat Report 2013, Annex 1 "Understanding immunization coverage data: WHO-UNICEF JRF and WUENIC", pp. 133–37 (http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1).
7 Based on the weighted average of coverage of a set of eight preventative and curative interventions; the CCI gives equal weight to four stages in the continuum of care: family planning, maternal and newborn care, immunization and case management of sick children. The weighted average for a group (e.g. a country or a wealth quintile) is calculated as FPS is family planning needs satisfied, SBA is skilled birth attendant, ANCS is antenatal care with skilled provider, DPT3 is three doses of diphtheria–pertussis–tetanus vaccine, MSL is measles vaccination, BCG is BCG (tuberculosis) vaccination, ORT is oral rehydration therapy for children with diarrhoea, and CPNM is care seeking for pneumonia. More information at: http://www.countdown2015mnch.org/documents/2015Equity/2015_CD_equity_profiles_all.pdf.

As stated above, and aligned with previously mentioned resolution WHA68.6 on the GVAP and in the GVAP price report 2015, there are other factors that influence the price of vaccines and these are presented under the "Sustainable financing and supply for immunization" section of the report. These areas are interrelated and actions in every areas are necessary in order to have a significant positive impact on sustainable access to vaccines in all countries.

Conclusion

Access to vaccine price information has been perceived as an important element to ensure access to affordable vaccines by all countries, and in particular countries that self-finance their vaccines.

This year, 50 countries have shared vaccine price information (+25% compared to last year) and combined data from all sources included in the V3P database (UNICEF-SD, PAHO Revolving Fund and individual countries) now cover about 70% of the world. While progress can still be done to improve the transparency of the market, it is important to acknowledge that information on vaccine prices now exists. Moving forward, efforts will need to concentrate on ensuring countries make good use of available price information to inform their introduction and procurement decisions.

Increase in price sharing participation, particularly from large countries, has allowed WHO to refine the findings of last year. For instance, it is now possible to more visibly observe the relationship between price and income levels. Pooled procurement mechanisms still manage to secure lower prices than self-procuring countries, except for self-procuring countries purchasing large volumes. There is also a small but consistent impact of volume on price for most vaccines. For certain vaccines, such as the pertussis vaccines, the data allows for interesting visualization of market segmentation and product preferences between developing countries and countries with higher incomes – with very strong price differentiation. WHO and partners remain very active in this area and will look at maintaining price transparency, strengthening the use of pricing data at country level, and key actors will increase their scope of work in the area of market shaping.

Acknowledgments

The analysis of the vaccine price report has been prepared by Melissa Malhame & Samya Mandal (Gavi Alliance), Oleg Benes, Tania Cernuschi, John Fitzsimmons, Stephanie Mariat, Claudio Politi & Daniel Rodriguez (WHO), Suerie Moon (Harvard School of Public Health), Greg Widmyer (BMGF), Kate Elder (MSF), Aurelia Gasca (UNICEF-SD) and Shawn Gilgrist (independent consultant).

References

1. EURO workshop December 2015; ASEAN vaccine security workshop August 2015; MIC pilot missions.
2. UNICEF SD vaccine price list: http://www.unicef.org/supply/index_57476.html; PAHO Revolving Fund prices: http://www.paho.org/hq/index.php?option=com_content&view=article&id=9561:revolving-fund-prices&Itemid=40714&lang=en.
3. Gavi Supply and Procurement Strategy 2016-2020. Report to the Board, June 2016.
4. By tracking the number of products offered in response to tenders for Gavi-supported vaccines, vaccine supply security can be measured.
   The number of products offered as a percentage of the 2015 target increased to 104% in 2015, from 88% in 2014.
5. Commitments have been made by manufacturers regarding the following vaccines: HPV, PCV, rotavirus, pentavalent DTP-HepB-Hib, yellow fever and cholera.
6. Gavi support for Access To Appropriate Pricing (ATAP) for Gavi graduated countries. Report to the Board, June 2015.
7. Details of specific investments can be found at www.gatesfoundation.org.

ANNEX 8.3: "Immunization programmes have sustainable access to predictable funding, high-quality supply and innovative technologies: number of vaccine delivery technologies (devices and equipment) that have received who prequalification (Indicator SO6.5)"

Highlights

- A total of 284 products had been prequalified as of 31 December 2015 compared to 163 in 2010, corresponding to a 74% increase between 2010 and 2015.
- A freeze protection testing protocol was developed and published in 2015, which enables the classification of devices according to their ability to prevent freezing. Appliances are graded A, B or C (grade A being the best performing and grade C being the poorest performing). This protocol has been incorporated into the specification and verification protocol for ice-lined refrigerators (ILRs) and solar direct-drive (SDD) refrigerators.
- Specifications have been developed for freeze-free vaccines carriers and cold boxes as well as for energy harvesting controls for SDD devices.
- Specifications for refrigerated vehicles have been drafted and contact with industry is ongoing to enable inputs for finalization.
- A generic field evaluation protocol was published in 2016. This protocol serves as a template for field testing new technology. The aim is to provide a minimum amount of field-performance data before full prequalification for new technology.

DEFINITION OF INDICATOR	The number of products (cold-chain equipment, injection devices and others) that have been prequalified by the WHO performance, quality and safety (PQS) system as of 31 December 2015, as compared to the number of prequalified products on 31 December 2010, which was 163 products The indicator does not take into account the number of products that might have entered the list and been withdrawn in the interim period. Therefore, it is just the difference between two data points
TARGET	None specified
DATA SOURCES	The WHO PQS programme database
COMMENTS ON DATA QUALITY	Data reflect the difference of the number of products that were listed in the PQS as prequalified on 31 December 2010 and those as of 31 December 2015. The record of the date after each change of a product's status ensures the quality of data

Background

The performance, quality and safety scheme for the prequalification of equipment selects immunization equipment to be purchased by UN agencies. It requires the industry to comply with criteria of performance, quality and safety based on an assessment by independent, WHO-accredited laboratories. For more

details please refer to the GVAP Secretariat report 2015, referenced elsewhere in this document, or to the PQS website: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/.

Results

Innovation: The WHO Prequalification Team (PQT) responsible for the PQS Catalogue and PQS working group partners have been exploring the need for large cold rooms (> 40m^3) to store vaccine in countries with significantly large populations. PQT partnered with UNICEF-SD to provide advice to the Democratic Republic of the Congo during development of the specifications for their super large cold room (400m3). In the same light PQS is working with PATH and UNICEF to develop specifications for solar cold rooms.

In 2015 a new field evaluation protocol was published by PQT to enable the collection of a minimum of data on performance for new technologies (where PQT had no prior experience of their performance) in order to make informed decisions before final prequalification.

In 2014, a multipartner PQS specifications WG was established with WHO, UNICEF, PATH, Clinton Health Access Initiative, Solar Electric Light Fund (SELF) and the Gavi Alliance, with the objective of developing target product profiles (TPPs) for innovative solutions and the revision of existing specifications. This WG met four times in 2015 and has already met twice in 2016. From 2015 to 2016 this group worked on the following:

- standard definitions for net volumes and gross volumes to be included in the Vaccine Management Handbook[73];
- development of standards for freezing capacity calculation for SDD freezers;
- specifications for freeze-free vaccine carriers and cold boxes;
- specifications and verification protocol for voltage stabilizers;
- development of specifications for energy harvesting controls for SDD refrigerators;
- began revising the specifications for safety boxes.

Products: Procurement agencies today can choose between 284 PQS prequalified products from 75 manufacturers. This is a 74% increase from the 163 products that were available 31 December 2010. Availability of products has been increasing steadily since 2008 (Table A8.3-1 and Figure A8.3-1).

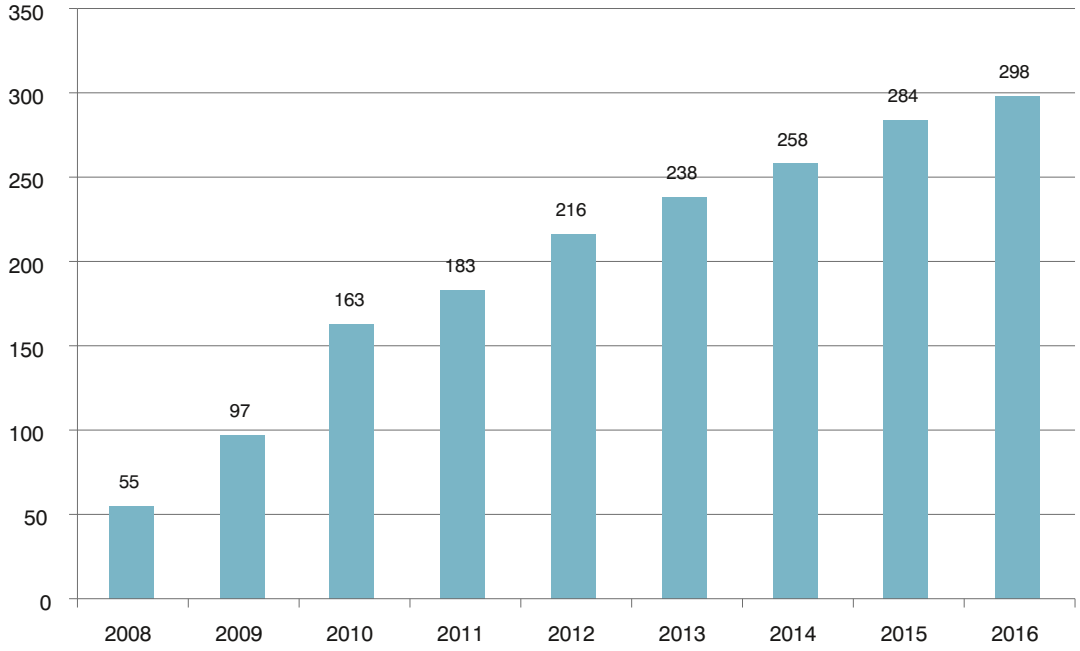
Table A8.3-1: Number of prequalified products per year and per category, 2008–2016[a]

Description	Number of products							% increase
	PQ 2010	PQ 2011	PQ 2012	PQ 2013	PQ 2014	PQ 2015	PQ2016	2010–2015
Cold rooms and related equipment	3	3	3	3	3	4	4	33.3%
Refrigerators and freezers	14	23	33	36	44	51	63	264.3%
Cold boxes and vaccine carriers	31	32	34	37	39	41	42	32.3%
Waterpacks	15	16	18	17	17	17	17	13.3%
Temperature monitoring devices	11	12	17	22	24	31	32	181.8%
AD syringes for immunization	30	27	29	33	36	39	39	30.0%
Waste management equipment	10	10	10	10	11	12	12	20.0%
Therapeutic injection devices	49	60	72	80	84	89	89	81.6%
Total	**163**	**183**	**216**	**238**	**258**	**284**	**298**	**74.2%**

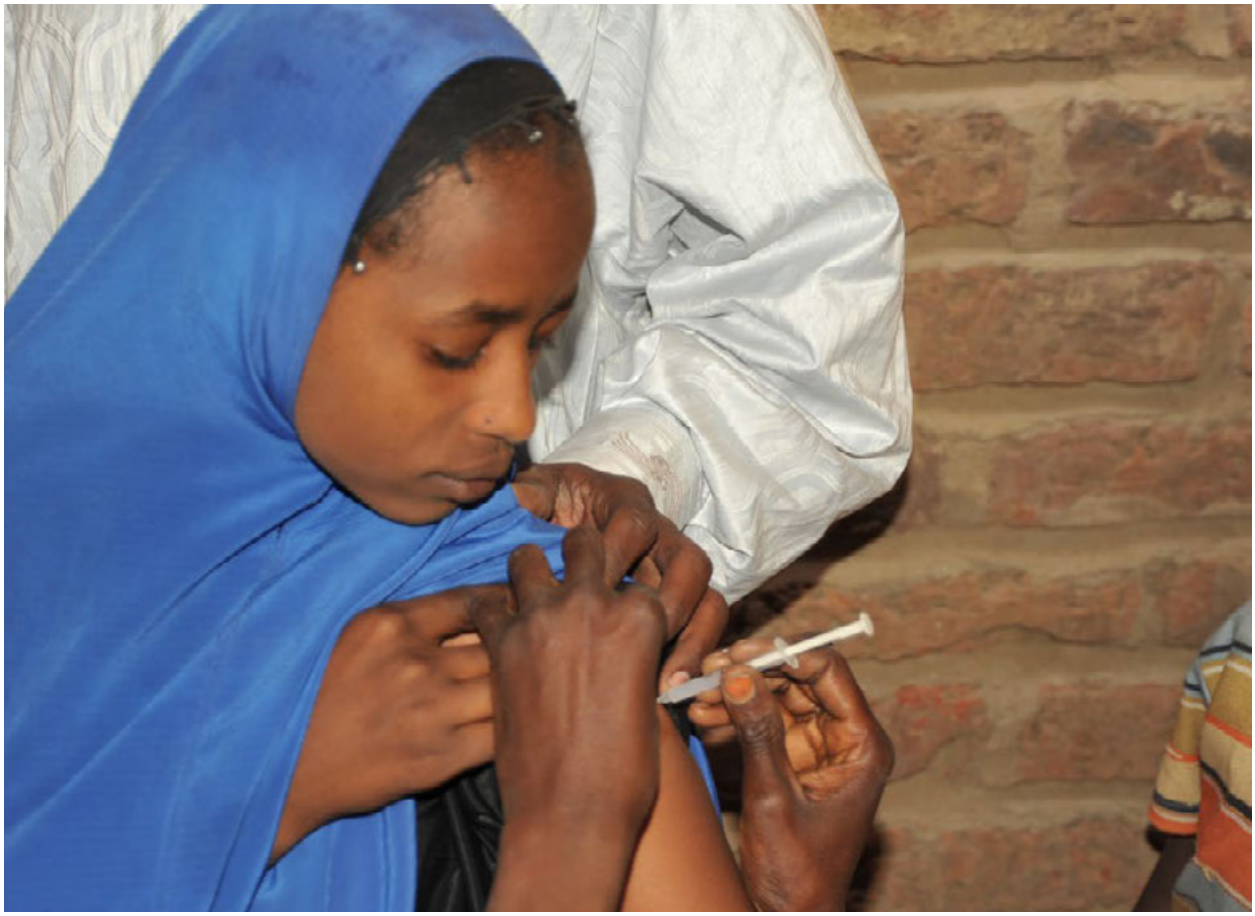
PQ, WHO prequalification.
[a] As of 30 June 2016.

[73] http://www.who.int/immunization/programmes_systems/sustainability/mic_strategy/en/

Figure A8.3-1: Cumulative number of prequalified products per year, 2008–2016[a]



[a] As of 30 June 2016.



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ANNEX 8.4: "Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies: percentage of doses of vaccine used worldwide that are of assured quality (Indicator SO5.1)"

Highlights

- Two WHO international consultations on policy, methodology and a tool to assess (benchmark) NRAs were convened in Geneva in 2015. The consultations welcomed WHO efforts and activities on regulatory system strengthening including harmonization and convergence among different medial product streams including vaccines and medicines. Furthermore, the consultations provided valuable recommendations for finalization and piloting of the WHO global benchmarking tool, expected to be released by end 2016.
- In April 2016, the Russian Federation's NRA met the vaccine indicators required by WHO following its assessment in 2015 that the NRA was suboptimal. The NRA's functionality being restored will significantly help ensure there is a sufficient quantity of high-quality yellow fever vaccine worldwide.
- In early 2016, WHO piloted a new business model of regulatory system strengthening in Bangladesh. Following the success of this pilot project, WHO is organizing a meeting in September 2016 for inauguration of the global coalition with extension of the model to other Member States. Afghanistan will be the next Member State to benefit from joining the coalition.
- Assessment of several countries including Kazakhstan, Saudi Arabia and Serbia has been initiated for 2016. WHO hopes to see these countries join the coalition of countries with functional NRAs by end 2016.

DEFINITION OF INDICATOR	The proportion of vaccine doses used globally by national immunization programmes that are of assured quality. Vaccines of assured quality include vaccines produced in a country with a functional national regulatory authority (NRA), including vaccines prequalified by WHO[74]
TARGET	100% of vaccine doses by 2020
DATA SOURCES	WHO database of prequalified vaccines WHO-UNICEF joint reporting forms (JRFs) (for number of doses used) WHO assessments of NRAs Additional information from vaccine manufacturers, NRAs and national control laboratories, and national immunization programmes

[74] http://www.who.int/immunization/programmes_systems/supply_chain/evm/en/index5.html

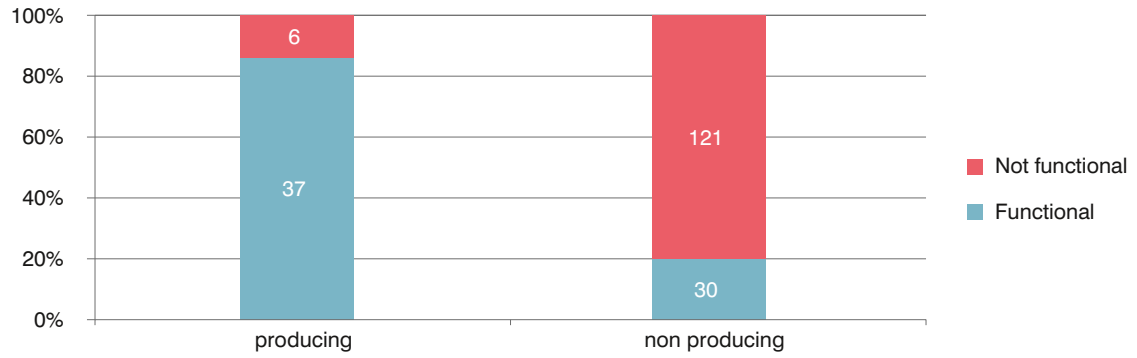
Data sources, availability and quality

No additional information was available at the time of the current report; please refer to the 2014 GVAP Secretariat report for more information on data sources availability and quality.

Results

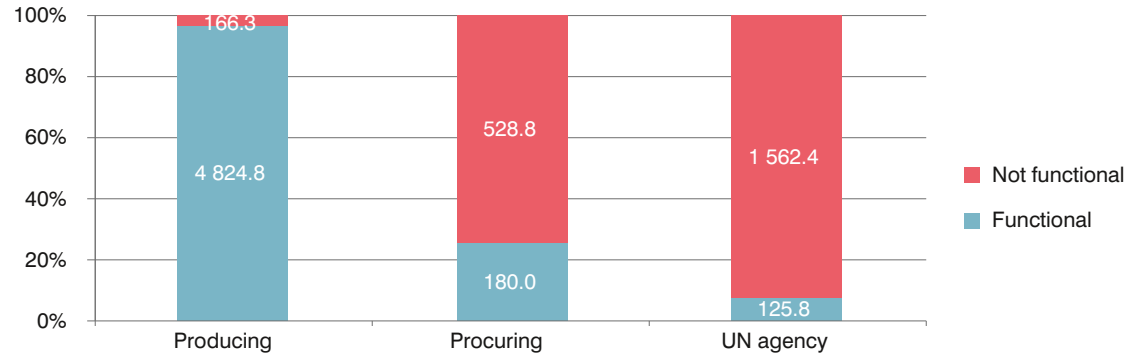
As of June 2016, WHO reported there were 43 vaccine-producing countries[75], of which 37 had functional NRAs, as assessed by WHO (one more compared to June 2015) (Figure A8.4-1). Twenty-two of the vaccine-producing Member States were producing one or more WHO-prequalified vaccines by the end of 2015 (vs 24 in 2014).

Figure A8.4-1: Number and percentage of Member States (vaccine-producing and non-producing) with an NRA assessed as functional as of June 2016



In terms of global population, there was no significant change compared to 2014 as 69% (5.13 billion people) still live in the 67 countries, both vaccine-producing and non-producing, where there is direct oversight by a functional NRA. However, Figure A8.4-2 shows that even in the countries without functional NRAs, where 31% of the world's population lives, people have access to WHO-prequalified vaccines through their national immunization programmes, as the vaccines offered are produced in countries with functional NRAs.

Figure A8.4-2: Proportion of the global population living in countries with functional regulatory oversight for vaccine in 2016 (millions)



Producing: Main source of vaccine comes from a vaccine-producing country.
Procuring: Main source of vaccine is self-procurement.
UN agency: Main source of vaccine comes through a UN agency.
Source: WHO Health Systems and Innovation, as of July 2016.

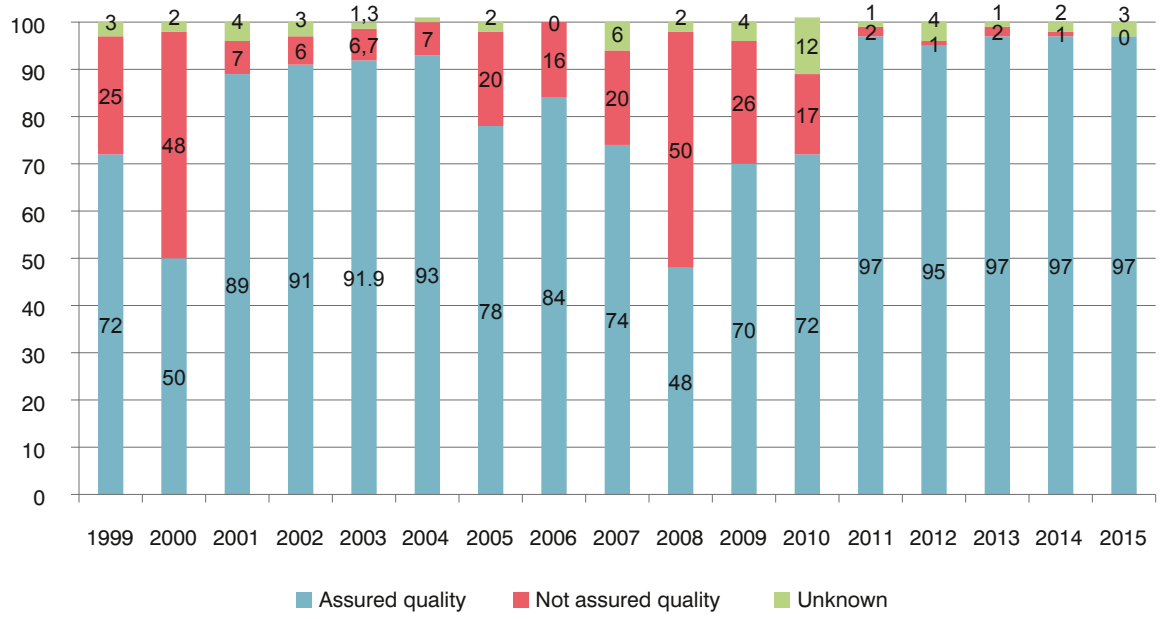
Overall, 97% (same figure of the year 2014) of the global doses of vaccines used in national immunization programmes are of assured quality (Figure A8.4-3). This is well on the way to meeting the target of assured

[75] WHO has defined "vaccine producing country" as a country that is able to produce human vaccine for at least 5% of national demand.

quality of 100% of vaccine doses used by national immunization programmes by 2020.

The Russian Federation is one of only a few countries producing yellow fever vaccine. WHO assessed the Russian Federation's NRA in April 2016, and documented process improvements, which led to its functionality being restored. Viet Nam's NRA has now been functional since June 2015 and four to five more vaccine-producing countries are expected to achieve WHO functionality status by the end of 2020, which makes it likely that the target for this indicator will be achieved by 2020. It worth mentioning that several low- and middle-income countries recently showed interest in producing vaccines in the near future. Should this materialize and these NRAs be prequalified by WHO, this would increase the number of vaccine producing countries.

Figure A8.4-3: Percentage of assured (blue) versus non-assured (red) quality vaccines used worldwide, 2015[a]



[a] Doses of vaccines reported mainly from country's lot release and WHO/UNICEF JRF.

Source: WHO/Essential Medicines and Health Products, as of May 2016.

References

1. Global Vaccine Action Plan. Monitoring, evaluation & accountability: Secretariat annual report 2014. Geneva: World Health Organization; 2014 (http://www.who.int/entity/immunization/global_vaccine_action_plan/gvap_secretariat_report_2014.pdf?ua=1, accessed 11 July 2016).

9. VACCINE SAFETY

Highlights

- This is a new indicator to the GVAP Secretariat report. It has been proposed by the Global Advisory Committee on Vaccine Safety (GACVS) following a request by the SAGE DoV WG to include vaccine safety in the GVAP monitoring framework.
- Safety surveillance is progressing in WHO Member States. By 2015, 84 of 105 countries reporting adverse events following immunization (AEFI) registered 10 or more annual reports per 100 000 surviving infants. This compares to 80 of 99 countries in 2010.
- A majority of countries from the Americas and European Regions meet the AEFI indicator, whereas in the African, South-East Asia and Western Pacific Regions one third or fewer countries meet the indicator.

DEFINITION OF INDICATOR	Number of AEFI reported by country per 100 000 surviving infants. The target is currently set at a ratio of 10 based on an empirical analysis of JRF data since 2000
TARGET	No target set
DATA SOURCES	WHO-UNICEF JRFs
DATA AVAILABILITY AND QUALITY	Please see below

Background

The SAGE Decade of Vaccines WG requested the DoV Secretariat to include a specific indicator on vaccine safety in the GVAP monitoring and evaluation framework. Indeed, vaccine safety is mentioned several times in the GVAP:

- Strategic objective 5: Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies.

"…each country should develop the capacity to monitor and assure the safe use of vaccines, in line with the strategy defined in the WHO Global Vaccine Safety Blueprint initiative" (1).

- Strategic objective 6: Country, regional and global research and development innovations maximize the benefits of immunization.

"The challenge is considerable in achieving understanding of the adverse effects, finding ways to avoid them and yet not compromising the known efficacy of the existing product—and without incurring the costs of developing, testing and registering a new product" (1).

Therefore the DoV WG solicited the GACVS to propose an indicator to be included in the annual reporting process. Following the proposition of several options by the GACVS, the SAGE DoV WG validated the inclusion of the indicator, defined as follows: "Number of AEFI reported by country per 100,000 surviving infants per year and per country" *(2)*.

Data limitations

As this indicator is based on a ratio, the numerator and denominator do not reflect the same populations. AEFI can be reported at any age, yet the denominator is restricted to the population aged less than 1 year. This choice reflects the fact that in a majority of countries, the largest number of vaccine doses are administered before 12 months of age. However, depending on immunization schedules and coverage, the number of vaccine doses administered per year in a country can vary substantially for the same number of surviving infants. The numerator can also include AEFI from people vaccinated outside the infant age group. However since the purpose of this indicator is to encourage reporting of AEFI particularly from lower-middle-income countries where there is hardly any reporting, this indicator provides an indication that at least a significant level of reporting is accomplished. The following points should also be considered.

- This indicator may include data from both passive and stimulated reporting components of the national AEFI surveillance system.
- The numerator does not distinguish benign and serious AEFI nor does it report data related to routine immunization activities from those obtained through supplementary activities.
- At this point, WHO is not in a position to review the completeness of AEFI reports nor can it verify if or how serious AEFIs are being investigated.
- Performance across the country (in all districts) should be relatively homogeneous (e.g. at least 80% of districts should report 10 AEFI per 100 000 surviving infants or more). Variations in this rate indicate the need for strengthening activities if lower, and potentially even lessons that could be transferred to other areas/localities if consistently higher compared to others districts. However, this cannot be assessed with the current JRF data.

At its December 2014 meeting, GACVS proposed that one general indicator be used to assess the volume of AEFI reporting. This indicator is the ratio of all AEFI reports divided by the number of surviving infants per year *(2)*. The number of AEFI reports is communicated through the WHO-UNICEF JRF. Based on an empiric analysis of JRF data, it appears that countries that have established a sustainable passive vaccine safety surveillance system record at least 10 reports per 100 000 surviving infants per year. The distribution of countries that report AEFI by reporting ratio is presented in Figure 9.1, which illustrates that a good majority of those that have AEFI reports exceed the cut-off of 10 per 100 000 surviving infants. Figure 9.2 and Figure 9.3 show the change in AEFI reporting between 2010 and 2015.

Results

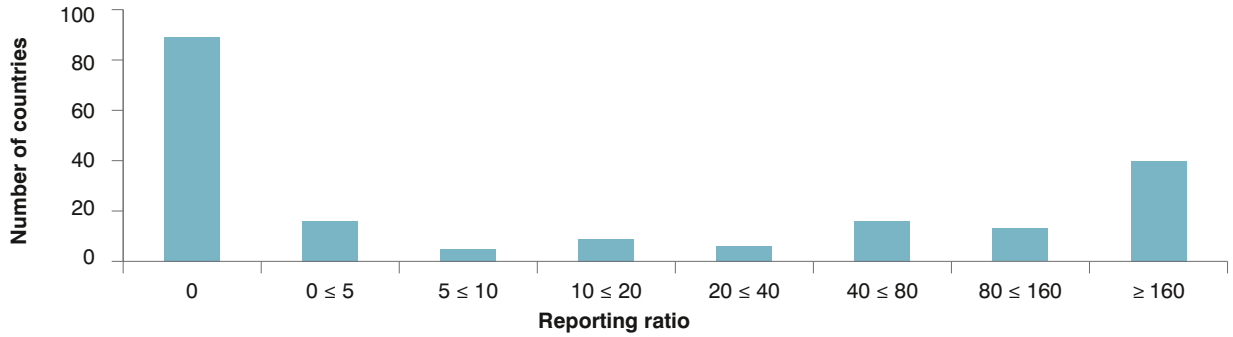
Since the number of AEFI reported annually was introduced into the JRF, there has been a steady increase in the number of countries that indicate they monitor AEFI. This reflects increasing attention to vaccine safety monitoring and progress made in several middle-income countries from Asia and Latin America in particular. Based on those successful experiences, WHO has developed a capacity-building package that includes tools, guidance documents and training packages for use by Member States. The Global Vaccine Safety Blueprint *(3) launched in 2012 is implemented through a collaborative partners network the Global Vaccine Safety Initiative (GVSI). The current indicator focuses on the first Blueprint strategic objective, ensuring minimal capacity in all WHO Member States.*

AEFI reporting has historically been weak in most countries where immunization coverage is limited. Recently, through a concerted effort with NRAs and immunization programmes, several vaccine-manufacturing countries have strengthened AEFI reporting and investigation and provided valuable experience for implementing it in resource-limited countries. The capacity-building model is based on a five-step process that includes benchmarking, assessment, work planning, implementation and evaluation. Through the GVSI, WHO and partners provide assistance to Member States; since 2014, a particular focus has been placed on supporting countries from the African Region.

In addition to establishing minimal capacity for vaccine safety monitoring, the GVSI also supports specific active surveillance projects. Those projects cover a broad spectrum of activities, from the monitoring of specific safety concerns for newly introduced vaccines (e.g. rotavirus vaccines in several parts of the world), to the development of collaborative mechanisms for testing new hypotheses related to safety signals identified by passive surveillance systems, and even the documentation of background rates of conditions of special interest in populations where vaccines have

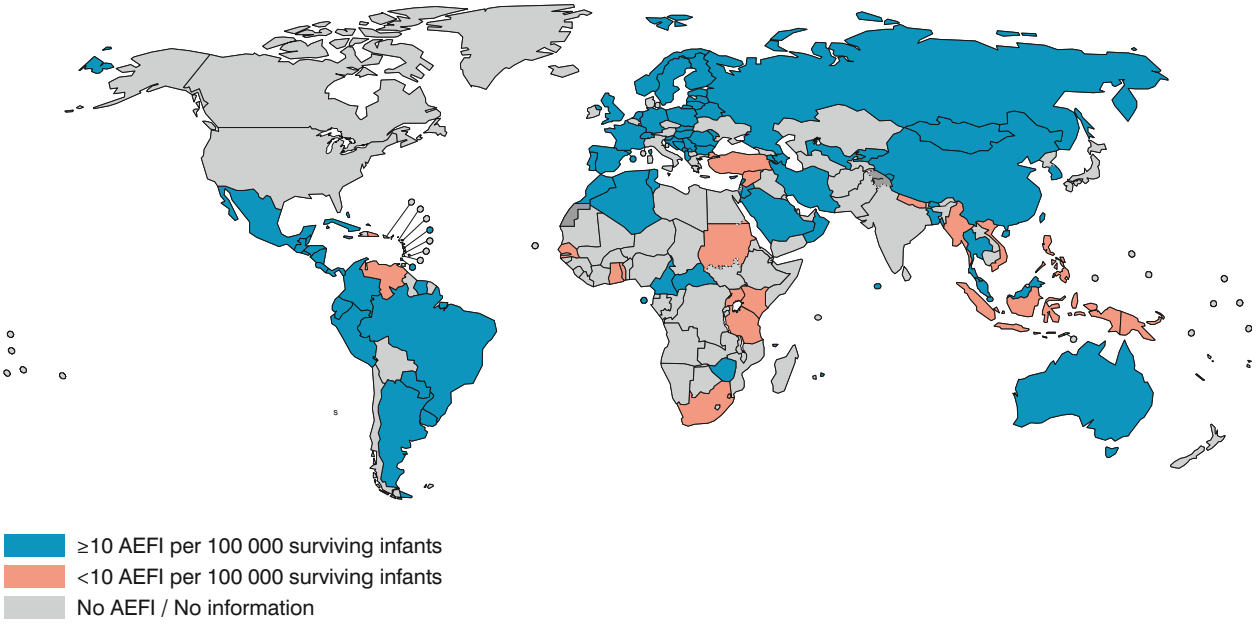
been newly introduced. GACVS at its June 2016 meeting reviewed two recent projects, a proof-of-concept for multi-country collaborations and the background rate of serious AEFI in South India *(4)*.

Figure 9.1: Distribution of Member States by reported numbers of AEFI per 100 000 surviving infants, 2015



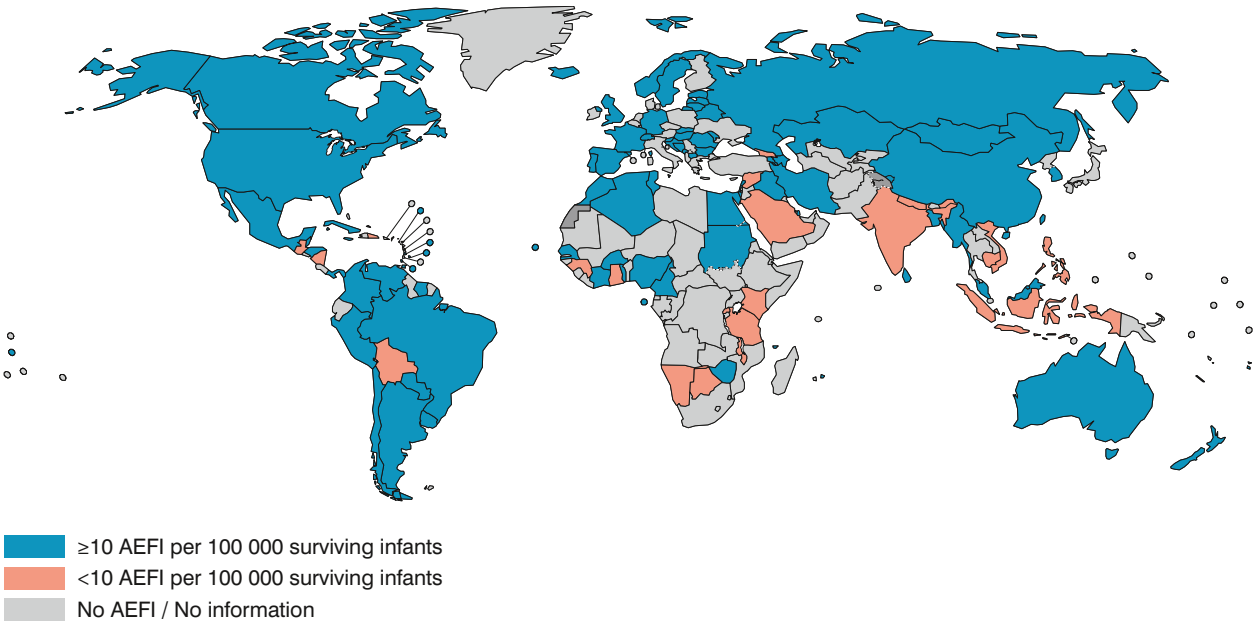
Source: WHO/UNICEF database, as of July 2016.

Figure 9.2: Number of AEFI reported by country per 100 000 surviving infants by Member State, 2010



Source: WHO/UNICEF database, as of 24 June 2016.

Figure 9.3: Number of AEFI reported by country per 100 000 surviving infants by Member State, 2015



Source: WHO/UNICEF database, as of 24 June 2016.

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2. Global Advisory Committee on Vaccine Safety, 3–4 December 2014. Wkly Epidemiol Rec. 2015; 90*(49)*:17–24.
3. Global vaccine safety blueprint. Geneva: World Health Organization; 2012 (WHO/IVB/12.07; http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf?ua=1, accessed 25 August 2016).
4. WHO, Global Advisory Committee on Vaccine Safety, 15 July 2016. Wkly Epidemiol Rec. 2016; 91(28/29):341–348.

10. RESEARCH AND DEVELOPMENT

Progress towards development of tb vaccines (Indicator SO6.1)

Background

In March 1993, WHO designated tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis* (Mtb), a global public health emergency. In 2014, TB killed more than 1.5 million people, making Mtb responsible for more deaths worldwide than any other single infectious agent. Nearly one billion people have died of TB over the past centuries – an astounding number. Ninety-five per cent of the TB cases and deaths occur in low- and middle-income countries that comprise 85% of the world's population, and represent a leading cause of death in HIV-infected individuals and women of childbearing age. The epidemic of TB in sub-Saharan Africa has been fuelled by HIV disease, while the increasing incidence of diabetes in Asia further threatens attempts at TB control.

One of the highest priorities of TB research is to develop vaccines that are more efficacious for preventing TB and interrupting the cycle of TB transmission than the *Mycobacterium bovis*-derived BCG, the only vaccine available to protect against TB *(1)*. Several vaccine-based strategies have been envisioned to better control TB; these include vaccines that protect individuals from initial Mtb infection, prevent those infected from progressing to active TB disease, or prevent recurrent disease in persons who have recently completed drug treatment for active TB.

Efforts also are under way to improve the safety and efficacy of BCG vaccine, which is widely administered to neonates. Different vaccines may be required to induce immune responses in different populations, such as infants versus young adults, those already infected with Mtb and those co-infected with HIV. Experts in TB prevention and control mostly agree that mass vaccination of adolescents/young adults in high-burden countries, regardless of their infection status, even with a vaccine that is only 60% efficacious, would have the greatest public health impact in preventing Mtb transmission and subsequent TB disease. Such a vaccine could prevent an estimated 30–80% of incident TB cases in high-burden settings during the first 35 years after its introduction, depending on the type of protection the vaccine affords *(2)*. This impact would save millions of lives.

Overview of current efforts

BCG is a live, attenuated vaccine that is widely administered to infants in most areas endemic for TB. BCG has been shown to be moderately effective for the prevention of more serious extrapulmonary tuberculosis in infants and young children, such as tuberculous meningitis and miliary tuberculosis *(3)*. A meta-analysis of prospective trials and case–control studies determined the efficacy against pulmonary TB in infants and adolescents at about 50% with a range from 0 to 80% *(4)*. When delivered to neonates, however, BCG is not effective in preventing adult pulmonary TB, which constitutes the bulk of the global morbidity and mortality disease burden.

Most successful, licensed vaccines available today induce neutralizing antibodies that provide protective immunity; however, animal studies suggest that a robust cellular immune response is required for protection against Mtb infection and disease *(5, 6)*. For this reason, the majority of current clinical TB vaccine candidates are based on a variety of vectors, adjuvants and antigens that induce classical TH1 cytokines such as IFN-γ/

TNF-α from either $CD4^+$ or $CD8^+$ T-cells. At least sixteen of these candidates have moved forward into clinical studies in the past 10 years, including 13 current candidates *(7)*.

These clinical candidates encompass a variety of vaccine categories such as inactivated mycobacterial whole cell or whole-cell extracts (live recombinant BCG vaccine VPM1002, Mycobacterium w, Vaccae, DAR-901, RUTI, MTBVAC and *M. smegmatis*) *(8–10)*, viral-vectored candidates (vaccinia-based MVA85A, adenoviral-based AERAS-402 (Ad35Ag85A,B + TB10.4) and AdAg85A and influenza-based TB:FLU-04L) *(11–15)*, fusion protein subunits with TH1-inducing adjuvants (M72 + AS01E, H1:CAF01, H1:IC31, H4:IC31, H56:IC31 and ID93 + GLA-SE) *(16–23);* see Table 10.1. DNA vaccines to prevent TB are still in preclinical development and have not yet entered into human clinical trials *(24)*. To date, clinical trials characterizing candidate vaccines have included studies of safety and immunogenicity in diverse populations, including healthy, TB-naive adults and infants, latently infected adolescents and adults, HIV+ adults, and patients undergoing drug treatment for TB.

BCG vaccine is the most widely administered neonatal vaccine worldwide. Due to this widespread use and its relatively short duration of protection, most of the new candidate vaccines are being studied as adolescent/adult or infant boosters following a priming immunization with BCG *(25)*. In parallel, however, recombinant BCG and MTBVAC vaccines are also being studied as replacements for BCG to improve its safety in HIV-exposed infants and to induce a more efficacious and/or longer duration immune response.

An initial, phase IIb proof-of-concept efficacy trial randomized 2797 BCG-vaccinated infants to receive either ontrol or a viral-vectored vaccine boost containing one Mtb antigen (MVA85A) did not show better efficacy than BCG alone against TB disease or infection *(26)*. A large, phase IIb trial in 3573 HIV-uninfected, latently Mtb infected adults in Africa assessing safety, immunogenicity and TB disease prevention with the GlaxoSmithKline-Aeras M72 + AS01E adjuvanted fusion protein vaccine completed enrolment in 2015 and is ongoing.

In addition to these large-scale, proof-of-concept trials, new human studies are under way, based on the use of innovative trial designs intended to evaluate the biologic activity of vaccine candidates using smaller, more focused populations. The first of these new trial designs is testing whether a novel vaccine (H4:IC31) or the use of BCG re-vaccination can prevent sustained infection (as opposed to disease) by Mtb. The trial uses novel blood tests in which BCG vaccination does not interfere with the result – a common obstacle with the long-time, standard diagnostic test, the tuberculin skin test. This study concept requires only 330 subjects per arm rather than the two thousand or more that would be needed in classic, proof-of-concept trials. The second innovative trial design would be to study the ability of a vaccine to prevent the 4–6% relapse and/or reinfection rate typically observed following successful treatment of active TB. A prevention-of-TB recurrence trial is being planned to evaluate ID93 and will likely require approximately 400 subjects per arm.

Opportunities and challenges

Despite recent advances in the field, developing a TB vaccine for any chosen population is fraught with considerable obstacles. Most importantly, there is no identified correlate of protection that can guide vaccine design or animal experiments, or that can be used as a credible end-point in early human studies. In addition, without a known efficacious vaccine that effectively prevents pulmonary TB, it is impossible to validate an animal model as a potential surrogate. Prior sensitization to mycobacteria (immune priming) is also confounding. Lastly, due to the relatively low regional incidence of TB, despite the high worldwide prevalence, true proof-of-concept trials that use clinical end-points are by necessity very large (1000 to 35 000 subjects) and expensive (US$ 10 to 50 million).

There are no clear models upon which to identify the "best" Mtb antigens for use in a vaccine, as many TB vaccine animal models have a narrow dynamic range of responses that do not allow for easy differentiation among candidates. This limitation is being addressed by refinement of mouse, guinea pig and non-human primate models to better approximate natural infection by Mtb and better mimic human disease. The use of low-dose challenges, sophisticated imaging techniques and novel vaccine candidates (such as H56, ID93 + GLA-SE, cytomegalovirus-vectored and aerosolized adenovirus-vectored vaccines) have recently shown that the non-human primate model may potentially be useful to delineate the true correlates of vaccine-induced protection.

In human biomarker studies, gene expression patterns of inflammatory bio-signatures have correlated with both the risk for TB disease progression and the extent of radiographic involvement in both active and latent TB cases *(27)*. In response to these data, TB vaccine developers are pursuing a systems immunology approach in which gene expression signatures are compared in samples from various time points. These signatures are then correlated to either specific measures of immunogenicity, or to protection in efficacy studies. This method allows for a broader, less biased net to be cast in assessing immune responses.

Current promising leads, strategies and technologies

A rational approach for selection of TB vaccine candidates for future studies is required *(28)*. There is a need to ensure that candidates in the global portfolio are testing a broad variety of immune hypotheses. Tools are needed to rationally identify optimal candidates early in the development process, among those that are likely to induce similar magnitude and phenotypes of immune responses. From candidates that have similar target profiles, head-to-head comparisons of candidates in animal and early human studies would be optimal, and mechanisms and incentives (such as support from funding agencies) to do such comparisons are needed. This approach also implies the need for a diverse and robust pipeline of candidates: not just a set of minor improvements, but truly novel approaches that test different immunologic hypotheses.

To this end, the field of TB vaccine research and development is rapidly changing from one of product development based on a single hypothesis to an exploration of multiple immunologic approaches based on novel technologies. The adjuvanted protein approaches, used as a boost during adolescence following infant BCG, have shown promise in non-human primate models and, as mentioned above, are being tested in innovative clinical trial designs that will provide more rapid results over the next few years. If any of these prove promising, then there will be momentum to carry one or more of these into larger prevention of disease efficacy studies.

Other leads that will be aggressively pursued over the next five years will be the use of aerosolized adenoviral candidates, either alone or in combination. Of note, the combination of aerosolized adenoviral vectored vaccines followed by a modified vaccinia Ankara-vectored vaccine has been especially promising in an early human trial. In addition, cytomegalovirus (CMV) candidates will move forward in both the TB and HIV area, as they induce prolonged and high levels of effector T-cells at the mucosal location at which the pathogen first encounters the human host. Other promising leads include intranasal attenuated para-influenza viruses for induction of mucosal immunity, self-replicating RNA candidates and electroporated DNA vaccines. The value of a number of novel BCG replacement strategies will also become clearer. Systematic study of combinations using harmonized common antigen sets to elucidate the role of antigen delivery platforms is now under way for many of these approaches.

A variety of highly novel candidates are being developed by expert consortia, utilizing a number of approaches such as focusing on prevention of infection through antibody-mediated mechanisms, as well as selecting optimal glycolipid constructs and adjuvants that induce responses via the CD1 system. These are both high-risk and high-reward approaches to expand the immunologic response space being probed by TB vaccine candidates. Testing of these novel candidates is being facilitated by the concurrent development of novel animal models of natural transmission. The models include human-to-guinea pig transmission, as well as novel macaque-to-macaque transmission. The current lead approach involves non-human primate to guinea pig transmission in a closed setting. While these programmes progress, efforts are under way to build a safe bacterial construct that can be used in a TB human challenge model, which would open wide the field of early clinical vaccine assessment. The strain of Mtb used for this construct will need some degree of low-level replication, a fail-safe “kill switch” and a second attenuation mechanism to help ensure safety. In addition, the strain will need to be modified so that the bacterial burden can be easily measured, for example, through the imaging of a luminescent marker or by measuring a soluble, secreted marker in blood or urine.

Future directions

A. Short-term goals (within two years)

- Evaluate vaccine candidates (obtain preliminary results) from pre-proof of concept trials (early safety and immunogenicity assessments) and proof-of-concept clinical trials that may include as end-points prevention of infection in adolescents, prevention of recurrence in recently-treated TB patients and prevention of TB disease in latently-infected individuals.
- Test aerosol vaccine strategies in humans in phase I to IIa studies.
- Develop improved animal models, specifically a low-dose non-human primate challenge model, a non-human primate to non-human primate transmission model and a natural transmission guinea pig model.
- Identify one to two antibody-based candidates to move into animal challenge studies to establish proof of concept for a role of antibody in modulating disease.
- Identify optimized glycoprotein candidates and adjuvants and design their preclinical and clinical development path.
- Identify the most promising combination platforms in preclinical models, using a harmonized common antigen set, and test immunogenicity and safety in humans.
- Determine the role of non-tuberculous mycobacteria exposure on TB vaccine responses.
- Build the first prototype human challenge strains and test them in animals for further re-iterations.
- Identify novel protective antigens that are "unnatural or not immunodominant during latency or treatment.
- Build a consensus for a global portfolio advisory capability that can influence the overall portfolio and resource allocation.

B. Mid-term goals (by 2020, end of the DoV)

- Determine whether the M72 vaccine candidate protects against TB in latently-infected adults.
- Determine whether the novel BCG replacement candidates are more safe and/or effective than BCG in HIV-unexposed and exposed infants.
- Determine whether H4 and/or BCG and at least two other candidates protects against sustained Mtb infection in adolescents in a high risk of infection setting.
- Determine whether H56 or ID93 vaccination, in adults who have recently completed successful treatment for drug-sensitive pulmonary TB, protects against recurrent TB disease.
- Have established a reproducible non-human primate model and use it to identify a potential correlate of protection.
- Have advanced a candidate demonstrating proof of meaningful biological activity (in a non-human primate model, a prevention of infection trial or a prevention of recurrence trial) into phase IIb prevention of TB disease efficacy trials.
- Have a global consortium that influences the overall portfolio and resource allocation.

C. Long-term goals (beyond 2020, if applicable)

- Licensed vaccine by 2027 for prevention of TB disease.
- Longer-term: additional candidates licensed and phase IV studies conducted in multiple populations and geographic areas (e.g. HIV+, diabetic; China, India, Asia Pacific, Latin America, etc.).
- Have established a human challenge model for rapid identification and advancement of the most promising candidates emerging from refined animal models.
- Have novel vaccine candidate platforms in clinical development (e.g. electroporated DNA, RNA, antibody-based vaccines such as polysaccharide conjugates, glycolipids, etc.).

Discussion

Presentations at the 2016 Global Vaccine and Immunization Research Forum (GVIRF) focused on the current pipeline of TB vaccine candidates as well as key challenges and controversies in the field of TB vaccine research and development. Major challenges highlighted were the lack of an immune correlate of protection, inadequate funding, poor predictive power and lack of standardized animal models that reliably predict human clinical outcomes, the lack of a reliable and reproducible functional assay, and the lack of a human challenge model. As a result of the recent failure of MVA85A in the first efficacy trial of a novel TB vaccine candidate and a greater global emphasis on the need for a vaccine, the TB vaccine field has become more ambitious to meet these challenges. For example, the choice of antigens and platforms being tested has broadened,

and there are efforts to develop more relevant animal models and to evaluate different modes of prevention. Other encouraging developments include increasing investigation of subdominant antigens/epitopes, antigens from different stages of the mycobacterial life-cycle and a renewed look at the role of B cells and non-protein antigens, and efforts to transform current animal models into models that better represent human Mtb exposure and disease.

In addition, the Human Challenge Consortium has been formed to develop a human challenge model. The consortium's objectives are significant and varied. They include development of a safe challenge strain (e.g. using auxotrophs and genetic kill switches), development of reporter methodology (e.g. via bloodborne substrates, volatile aromatics, or other related approaches) and integrating regulatory guidance to move the human challenge model into clinical development.

Significant challenges in the field span the gamut of vaccine development activities – from funding and resource allocation to understanding and modifying the effects of key co-factors (e.g. diabetes mellitus, non-tuberculous mycobacteria exposure) on vaccine response and the role of small animal models (mice, guinea pig, rabbit) in vaccine candidate evaluation.

These and other questions must be addressed during vaccine development to create an efficacious TB vaccine that can be utilized effectively worldwide. To begin addressing these issues, multiple new endeavours have begun, including studies of TB epidemiology in various regions of the world as well as efforts to sequence and analyse non-tuberculosis mycobacteria strains from diverse geographic TB-endemic areas.

In addition, the challenging and changing nature of the global TB vaccine landscape has prompted an initiative to form a neutral, expert advisory group (the Global Portfolio Advisory Committee, GPAC) to assess the progress of TB vaccines in, or progressing towards the clinic. Discussions on the membership, terms of reference and scope of activity for the GPAC are under way with an international working group, with the goal of establishing the GPAC as a functioning team within a year.

Although the chances for licensure of a new TB vaccine by 2020 have been significantly diminished by the wide range of challenges faced by TB vaccine developers, the new advances and momentum in TB vaccine research and development suggests that the probability that the world will have a viable and effective TB vaccine by the year 2030 has never been better.

Table 10.1: Development status of current vaccine candidates

Candidate name/Identifier [research partners]	Phase I	Phase IIa	Phase IIb[a]	Phase III
Ad5 Ag85A [McMaster University, Tianjin CanSino Biotechnology Inc.]	X			
Dar-901 [Dartmouth College, Aeras]	X			
TB/FLU-04L [Research Institute for Biological Safety Problems]	X			
ChAdOx1.85A/MVA85A [University of Oxford, University of Birmingham]	X			
MVA85A/MVA85A (intradermal, aerosol) [University of Oxford]	X			
MTBVAC [TuBerculosis Vaccine Initiative, Zaragoza, Biofabri]		X		
ID93 + GLA-SE [Infectious Disease Research Institute, Wellcome Trust, Aeras]		X		
H1/H56:IC31 [Statens Serum Institut, Aeras, Valneva]		X		

Candidate name/Identifier [research partners]	Phase I	Phase IIa	Phase IIb[a]	Phase III
RUTI [Archivel Farma, S.L]		X		
H4:IC31 [Serum Institute of India, Sanofi Pasteur, Aeras]		X		
M72 + AS01E [GlaxoSmithKline, Aeras]			X	
VPM1002 [Max Planck, Vakzine Projekt Management, TuBerculosis Vaccine Initiative, Serum Institute of India]			X	
M. Vaccae [Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.]				X

[a] Phase II comprises studies of a candidate vaccine that are intended to result in efficacy data in the target population to whom the vaccine would be administered should it eventually by licensed. A programme of phase II studies usually defines the preferred dose, route and schedule of immunizations that are eventually evaluated for efficacy. Phase II studies also provide an expanded population assessment of the safety of the product.

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Progress towards development of malaria vaccines (Indicator SO6.1)

Background

According to the latest WHO estimates, there were 214 million malaria cases and 438 000 malaria deaths in 2015 *(1)*. The vast majority of clinical cases (80%) and deaths (90%) continue to occur in sub-Saharan Africa, with children aged under 5 years and primigravid pregnant women most affected.

Opportunities and challenges

In 2015, WHO published two preferred-product characteristics documents specifying the preferred profiles of malaria vaccines to achieve the new strategic goals laid out in the WHO preferred product characteristics for malaria vaccines roadmap *(2)*.

The evaluation of non-clinical models and assays, in the context of a search for correlates (i.e. back validation), has recently been informed by asexual blood-stage controlled human malaria infection studies. Two AMA1-based vaccine approaches, associated with induction of immune responses displaying relatively strong in vitro biological activity against blood-stage parasite growth (as measured by the growth inhibition assay) failed to impact parasite replication rates in vivo *(3, 4)*. These results suggest that careful assessment of the reliance on such in vitro assays to support vaccine development efforts is warranted.

Promising leads, strategies and technologies

Pre-erythrocytic vaccines

In 2015, the final phase III study results for the RTS,S vaccine candidate, which analysed vaccine efficacy, immunogenicity, safety, and impact of RTS,S/AS01 over a median of 38 and 48 months of follow-up (post-dose 1) in infants and young children, respectively (including the effect a fourth dose of vaccine) were published *(5)*. Vaccination with the three-dose primary series reduced clinical malaria cases over the length of the study by 26% in young children aged 5–17 months at first vaccination (over a median follow-up of 48 months after first dose across trial sites). Among young children administered a fourth dose of RTS,S 18 months after completion of the primary series, vaccine efficacy against all clinical malaria cases was 39% over the entire study period. These results were achieved on top of existing malaria interventions, such as insecticide-treated nets, which were used by approximately 78% of the trial participants *(5)*.

Adverse events after vaccination included local reactions (such as pain or swelling) and fever, the latter observed more frequently after RTS,S administration compared to the control vaccine (31% versus 13% in the older 5–17 month-old age category) *(5)*. In some children fever resulted in febrile reactions which were accompanied by generalized convulsive seizures, but all those affected fully recovered within seven days. The rates of serious adverse events seen in the trial (mainly medical events requiring hospitalization, regardless of whether they were considered to be caused by the study vaccine) were comparable between the trial's RTS,S candidate vaccine recipients and those receiving a control vaccine – except for cases of meningitis, which were reported in low numbers. In those cases, AEFI were seen more often among young children receiving RTS,S compared to the control, including a small number of new cases reported after the fourth dose.

In 2014, GlaxoSmithKline submitted an application for a scientific opinion on the RTS,S/AS01 candidate vaccine to the European Medicines Agency (EMA) under its Article 58 procedure. The EMA's Committee for Medicinal Products for Human Use (CHMP) evaluated data on the quality, safety and efficacy of the RTS,S/AS01 vaccine candidate, and in 2015 adopted a positive scientific opinion for the vaccine, stating that its quality and the benefit–risk balance are considered favourable from a regulatory perspective and that the safety profile of the vaccine is acceptable. However, the EMA

also requested that additional information needs be addressed in future studies, specifically with respect to *(1)* the timing of the fourth dose and evaluation of the safety and efficacy of an earlier fourth dose; *(2)* the efficacy and safety of multiple yearly doses and whether the vaccine predisposes to some degree of hypo-responsiveness to sequential doses; and *(3)* the potential utility of a delayed and fractionated third dose schedule in the target age group (see http://bit.ly/1LgqUfF). Subsequent to the Article 58 procedure, WHO issued formal recommendations in January 2016, calling for large-scale pilot implementations of RTS,S (see http://www.who.int/immunization/research/development/malaria_vaccine_qa/en/).

The recommendations include that the pilot implementations use the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings, with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later. Further recommendations for the pilot implementations are outlined in the WHO position paper (http://www.who.int/immunization/policy/position_papers/malaria/en/).

An alternative regimen of RTS,S/AS01—in which the third dose is delayed by six months and fractionated to one fifth of the standard dose —achieved 87% protection (95% CI: 67–95), compared to 63% (95% CI: 20–80) for the standard full-dose regimen, in a controlled human malaria infection study. Re-challenge showed waning efficacy in both groups, but fractional dose boosting maintained high protection *(6)*. These results were remarkably similar to findings reported in 1997, where 6/7 volunteers were protected with a similar regimen of RTS,S/AS02 *(7)*; this regimen was not pursued at that time, as the results were generally viewed as being a "chance" finding in view of later studies (where the fractional booster dose was not implemented), and the non-alignment with the accepted EPI schedules, for which the vaccine was intended. Further dose/regimen optimization using controlled human malaria infection is planned; in addition, a phase IIb field study, in young African children (aged 5–17 months at first vaccination) is scheduled to start in 2017, to evaluate the potential of the delayed, fractional regimen to prevent naturally-acquired *P. falciparum* infection.

Clinical evaluation of radiation-attenuated *P. falciparum* sporozoites, administered by five intravenous doses, has continued. In 2016, results of a controlled human malaria infection study to investigate durability of homologous protection reported partial (55%; 6/11) protection, one year after immunization with four doses *(8)*. Results from field studies in endemic areas, which will inform on the potential of the vaccine approach to confer heterologous protection in the target population, are expected over the coming years.

Sexual, sporogonic, and/or mosquito-stage vaccines

Initial clinical studies of Pfs25-based vaccines, formulated with aluminium-based adjuvants, have been disappointing; only sporadic induction of high levels of transmission-reducing activity, as determined using the standard membrane feeding assay, has been reported.

Over the next few years, the assessment of combination approaches, employing a second sexual-stage antigen (Pfs230), as well as investigation of more potent adjuvants, are expected to yield initial clinical results.

Future directions

Short-term goals (within two years)

In general, the goals identified in the previous report have been met, although there remains a chronic underfunding of *P. vivax* vaccine development efforts. Challenges remain in defining the development pathway for vaccine approaches where the end-points are reduced transmission at the level of a community (i.e. sexual, sporogonic, and/or mosquito-stage-vaccines interrupting malaria parasite transmission).

Development status of current vaccine candidates

The recently updated WHO "Rainbow Tables", which summarize the status of malaria vaccine development efforts, are available at http://bit.ly/18BbpOE.

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Progress towards development of HIV vaccines (Indicator SO6.1)

Background

The human immunodeficiency virus type 1 (HIV-1) is causing a pandemic, characterized by a progressive loss of $CD4^+$ T-cells and chronic immune activation, acquired immunodeficiency syndrome or AIDS. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2015, 2.1 million were newly infected (a 5% increase from 2014), and 1.1 million died, most of whom were in sub-Saharan Africa *(1)*. HIV can be transmitted via injection of blood; from mother-to-child during pregnancy, delivery or breastfeeding; and most commonly through sexual intercourse *(2)*. Antiretroviral drugs in various combinations can help control the infection *(3)*, prevent onward transmission of HIV *(4)* and protect treated, uninfected persons at risk from infection *(5)*. However, fewer than half of people living with HIV receive treatment and pre-exposure treatment is not widely available *(6)*. Ultimately, the development of a safe and effective HIV vaccine remains a global public health priority that is the best hope for ending HIV/AIDS *(7)*.

Overview of current efforts

Some 250 HIV vaccine candidates/regimens have been clinically tested since 1986 as potential preventive vaccines *(8)*, yet as is now well known, only one has demonstrated modest efficacy a prime-boost regimen of a canarypox vector delivering *gag-pol-env* with a gp120 protein boost (ALVAC-Sanofi; gp120-Vaxgen) *(9)*. This RV144 trial demonstrated for the first time that a vaccine could prevent HIV acquisition, with 31.2% overall efficacy *(10)*. In the over five years of follow-on research into the possible correlates of protection, efficacy was most strongly associated with the presence of non-neutralizing IgG antibodies to the V1V2 region of Env) *(11)*.

The extensive efforts to understand the correlates of protection combined with the complexities of generating new clinical trial material delayed a repeat clinical study until 2015/16. Now, however, a new efficacy trial set to begin in 2016 will test a similar, but clade C-based, vaccine regimen in South Africa. The ongoing HVTN 100 preliminary immunogenicity and safety test of these vaccine candidates has set the stage for HVTN 702 to determine their efficacy. The trial will also include an additional protein boost and potentially more potent adjuvant in order to extend the longevity of the previously-demonstrated protection.

Continuing parallel efforts are developing vaccine candidates addressing the hyper-variability of HIV, aimed at increasing breadth of antibody and T-cell responses or focusing responses to conserved regions of the virus. For example, vaccines based on two different hypotheses to elicit broad cellular immune responses are in development. One focuses immune responses to those regions of HIV that are highly conserved and therefore may be required for viral replicative fitness (University of Oxford, International AIDS Vaccine Initiative, European & Developing Countries Clinical Trials Partnership) *(12)*{Borthwick, 2014 #10;Borthwick, 2014 #13} while the other, termed "mosaic antigens" uses in silico methods (Los Alamos National Laboratory) to design immunogens that represent diverse sequences representing the optimal choice of epitopes from all known HIV strains, for broad coverage of circulating viruses (Janssen Pharmaceuticals, Beth Israel Deaconess Medical Center, National Institute of Allergy and Infectious Diseases, Ragon Institute) *(13)*.

Recent technological advances in B cell immunology, next generation sequencing, bioinformatics and structural biology have facilitated the generation of many potent, broadly neutralizing antibodies (bNAbs). Studies have identified bNAb binding sites on HIV Env, solved structural characterization of Env trimer and Env epitopes with atomic-level precision, and provided a better understanding of the ontogeny of bNAbs in HIV-infected individuals *(14)*. Designing immunogens to elicit these bNAbs remains a major challenge, however, though structural design is now beginning to yield more stable and potent immunogens *(15)*. bNAbs are also being evaluated for passive prophylaxis and treatment *(16, 17)*, and for delivery by gene transfer using adeno-associated virus vectors *(18)*. Updates on additional strategies are presented below.

Current promising leads, strategies and technologies

The HIV vaccine field likely will not see data emerging from the next set of efficacy trials until 2019–2020 (see Table 10.2); current strategies are focused on advancing leading candidates through clinical development, improving vaccine delivery methods and optimizing the next generation of candidates entering clinical development, which include the following.

- HIV Env trimers: Recent resolution of the structure of a stabilized HIV Env trimer will lead to clinical evaluation of immunogens more closely mimicking the native Env glycoprotein. Env trimers are set to enter the clinic in 2017.
- HIV antibody epitope-based vaccines: Recent elucidation of at least five major epitopes on HIV Env that bind bNAbs will lead to the generation of clinical candidates targeting each of these epitopes, including glycopeptides (see also below), computationally derived scaffolds and novel immunogens designed to bind to putative germline ancestors of the bNAbs.
- Sequential immunization with different immunogens: Increased understanding of how bNAbs evolve along with virus evolution in the human host led to hypothesis that sequential immunization with immunogens eliciting germline responses and stepwise evolved antibodies may be required to drive antibody affinity maturation. Several groups are advancing candidates and human clinical safety testing of the first immunogens, eOD-GT8 and CH505, are planned for 2017.
- Replication of competent viral vectors: Replicating adenovirus, poxvirus, vesiculostomatitis virus (VSV) and CMV vectors are in preclinical and early clinical development. Research in this area will focus on vectors generating persistent infection, mucosal delivery and targeting of the gut-associated lymphoid tissues all in hope of mimicking the efficacy of a live attenuated vaccine. CMV-simian immunodeficiency virus and VSV delivery of an HIV Env trimer have recently shown efficacy in preclinical studies and are being advanced to the clinic.
- Antigen presentation systems and novel adjuvants: Several virus-like particle and nanoparticle antigen presentation systems as well as novel adjuvants are in development. They are based on advances in understanding of innate and adaptive immune linkages.
- Synthetic biology technologies: Novel DNA and mRNA vaccines are being explored in efforts to achieve the efficacy of viral vectors while mitigating concerns of anti-vector immunity. Delivery of such genetic vaccines by electroporation has shown promise in clinical trials.
- Glycobiology: Advances in glycobiology are yielding important insights for HIV vaccine research, both in characterization and synthesis of targets recognized by bNAbs, and in strategies to manipulate vaccine-induced Fc-mediated immune responses such as antibody-dependent cell-mediated virus inhibition and antibody-dependent cell-mediated cytotoxicity.

As other proven non-vaccine prevention methods, such as treatment-as-prevention, voluntary medical male circumcision and pre-exposure prophylaxis with antiretroviral drugs become more widely available, it will be more difficult to find appropriate at-risk individuals for vaccine trials. Consultation with involved communities regarding standards of prevention within the trials will be essential, as emphasized in the UNAIDS good participatory practices guidelines[76]. Modelling studies indicate that a preventive HIV vaccine could dramatically reduce the number of new infections, even if coverage is less than 50%, in low- and middle-income countries *(19)*. The best hope for ending the AIDS pandemic is to develop an effective, accessible vaccine that is delivered in the context of a comprehensive prevention strategy.

Table 10.2: Ongoing preventive HIV vaccine clinical trials

Trial	Product	Antigen	Phase	ClinicalTrials.gov identifier
		DNA		
CRO2049/ CUT*HIVAC001	GTU-MultiHIV	Rev, Nef, Tat, p17 and p24 with more than 20 Th and CTL epitopes of protease, reverse transcriptase (RT) and gp160 regions of the HAN2 HIV-1 B clade	I	NCT02075983
HVTN 098	PENNVAX-GP	Gag, Pol, Env B	I	NCT02431767
		DNA + Protein		
CUTHIVAC002	DNA-C CN54ENV; CN54gp140	DNA-C CN54ENV: DNA plasmid containing the clade C gp140 envelope gene from HIV-1 isolate CN54	I	NCT02589795

[76] http://ww.unaids.org/sites/default/files/media_asset/JC1853_GPP_Guidelines_2011_en_0.pdf

Trial	Product	Antigen	Phase	ClinicalTrials.gov identifier
DNA + Adeno				
HVTN 076	VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP	DNA env-A, env-B, env-C, gag-B, pol-B, nef-B; Ad5 Gag-Pol Env A/B/C	I	NCT00955006
HVTN 082	VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP	DNA env A, env b, env C, gag B, pol B, nef B; Ad5 env A, env B, env C, gag B, pol B	Ib	NCT01054872
DNA + Pox				
HVTN 094	GEO-D03; MVA/HIV62	DNA Gag, PR, RT, Env, Tat, Rev, Vpu; Pox Gag, Evn, Pol B	I	NCT01571960
HVTN 106	MVA-CMDR; DNA Mosaic Env; DNA CON-S env; DNA Nat-B env	DNA Nat-B Env, CON-S Env, and Mosaic Env; MVA gag-pol CM 240, env CM235	I	NCT02296541
DNA + Pox + Protein				
UKHVCSpoke003	DNA - CN54ENV and ZM96GPN; CN54gp140; MVA-C	Protein: DNA Gag, Pol, Nef C; MVA Gag, Pol, Nef C; protein Enc C	I	NCT01922284
HVTN 086, SAAVI 103	SAAVI DNA-C2; SAAVI MVA-C; Oligomeric gp140/ MF59	DNA gag, rev, tat, nef, env C; MVA gag, rev, tat, nef env C	I	NCT01418235
DNA + Replicating vector				
HVTN 087	HIV-MAG ; VSV-Indiana HIV gag vaccine	DNA gag-pol B, nef, tat, vif, env B; VSV replicating gag	I	NCT01578889
HVTN 112	rVSV envC; HIV-1 nef/tat/vif, env pDNA vaccine	VSV env C; DNA nef, tat, vif , env	I	NCT02654080
DNA + Replicating vector + Pox				
HVTN 092	DNA-HIV-PT123; NYVAC-HIV-PT1; NYVAC-HIV-PT4	DNA gag, env, nef, pol C; Pox Env gp140, Gag, Pol-Nef C	I	NCT01783977
Protein				
IHV01	Full-Length Single Chain (FLSC)	Env gp120 B fused to N terminus of the two outer domains of CD4	I	NCT02756208
IPCAVD008	Trimeric gp140	Trimeric gp140	I	NCT02304185
RV 328	AIDSVAX B/E	Env B,E	II	NCT01933685
Vectored Immunoprophylaxis				
IAVI A003	AAV1-PG9	PG9 antibody	I	NCT01937455
Viral vector - Adeno				
Ad26.ENVA.01 Mucosal/IPCAVD003	Ad26.EnvA-01	Ad26 Env A	I	NCT01103687
Ad26.ENVA.01	Ad26.EnvA-01	Ad26 Env A	I	NCT00618605
Ad5HVR48.ENVA.01	Ad5HVR48.ENVA.01	Ad5/Ad48 Env A	I	NCT00695877
HVTN 083	VRC-HIVADV027-00-VP; VRC-HIVADV052-00-VP; VRC-HIVADV038-00-VP	Ad35 Env A; Ad5 Env A; Ad5 Env B	I	NCT01095224
HVTN 084	VRC-HIVADV014-00-VP; VRC-HIVADV054-00-VP	Ad5 env A, env B, env C, gag B, pol B; Ad5 Gag-Pol clade B	I	NCT01159990
HVTN 085	VRC-HIVADV014-00-VP; VRC-HIVADV038-00-VP; VRC-HIVADV052-00-VP; VRC-HIVADV054-00-VP; VRC-HIVADV053-00-VP	Ad5 gag-pol/env A/B/C; Ad5 env A, Ad5 env B; Ad5 env C; Ad5 gag-pol	Ib	NCT01479296

Trial	Product	Antigen	Phase	ClinicalTrials.gov identifier
Viral vector - Adeno + Protein				
VAC89220HPX2004	Ad26.Mos.HIV Trivalent; Ad26.Mos4.HIV; gp140 DP	Ad26.Mos.1.Env + Ad26.Mos1.Gag-Pol + Ad26. Mos2.Gag-Pol + Ad26.Mos.2.Env; Ad26.Mos.1.Env + Ad26.Mos1.Gag-Pol + Ad26.Mos2.Gag-Pol; protein gp140 C	II	NCT02788045
IPCAVD010	Ad26.Mos.HIV Trivalent; gp140 DP	Ad26.Mos.1.Env + Ad26.Mos1.Gag-Pol + Ad26. Mos2.Gag-Pol; clade C gp140	I	NCT02685020
Viral vector - Pox + Protein				
HVTN 097	ALVAC-HIV vCP1521; AIDSVAX B/E	Canarypox Env B,E; protein Env B,E	I	NCT02109354
HVTN 100	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/ MF59	Canarypox Env gp120 C, gp41 B, gag B., protease B; protein Env C	I/II	NCT02404311
RV 305	ALVAC-HIV vCP1521; AIDSVAX B/E	Canarypox Env B,E; protein Env B,E	II	NCT01435135
RV 306	ALVAC-HIV vCP1521; AIDSVAX B/E	Canarypox Env B,E; protein Env B,E	II	NCT01931358
HVTN 702 *Scheduled	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/ MF59	Canarypox Env gp120 C, gp41 B, gag B, protease B; protein Env C	IIb	
Viral vector - Adeno + Viral vector - Pox				
PEACHI-04	ChAdV63.HIVconsv; MVA. HIVconsv	ChimpAd63 consensus; MVA consensus; AdCh3NSmut1; MVA-NSmut	I	NCT02362217
Viral vector - Adeno + Viral vector - Pox + Protein				
IPCAVD009	Ad26.Mos.HIV Trivalent; gp140 DP; MVA mosaic	MVA Ad 26 mosaic; protein gp140 C	I/II	NCT02315703
Viral vector - Replicating				
IAVI R001	rcAd26.MOS1.HIVEnv	Oral, replicating Ad26 mosiac Env	I	NCT02366013
PXVX-HIV-100-001	Ad4-EnvC150; Ad4-mgag	Replicating Ad4 Env C; replicating Ad4 Gag	I	NCT01989533
Viral vector - Replicating + Protein				
HVTN 110	Ad4-mgag ; Ad4-EnvC150; AIDSVAX B/E	Replicating Ad4 Env C; replicating Ad4 Gag; protein Env B,E	I	NCT02771730
Passive Immunization				
HVTN 704 AMP	VRC-HIVMAB060-00-AB	VRC01 antibody	IIb	NCT02716675
HVTN 703 AMP	VRC-HIVMAB060-00-AB	VRC01 antibody	IIb	NCT02568215
IMPAACT P1112	VRC-HIVMAB060-00-AB	VRC01 antibody	I	NCT02256631
MB66-01	MB66	VRC01 antibody and HSV8 antibody	I	NCT02579083
VRC01LS	VRCHIVMAB080-00-AB	Modified VRC01 antibody	I	NCT02599896
10-1074	10-1074	10-1074 antibody	I	NCT02511990
MCA-0835	3BNC117	3BNC117 antibody	I	NCT02018510

Source: IAVI's Database of Preventative HIV Vaccine Candidates *(8)*.

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Progress towards a universal influenza vaccine (Indicator SO6.2)

Background

Influenza is an acute viral infection caused by the influenza virus. There are three types of human influenza – A, B and C, but infections with type C are uncommon. Type A influenza viruses are further classified into subtypes according to different combinations of the virus surface proteins haemagglutinin (HA) and neuraminidase (NA). While there are 18 different HA subtypes and 11 different NA subtypes found in nature (primarily in wild bird populations) only two influenza A virus subtypes (H1N1 and H3N2) and two antigenically distinct influenza B virus lineages (Yamagata and Victoria) circulate in human populations.

Influenza epidemics occur yearly during autumn and winter in temperate regions. Worldwide, these annual epidemics result in about 3 to 5 million cases of severe illness, and about 250 000 to 500 000 deaths. Illnesses result in hospitalizations and deaths mainly among high-risk groups (the very young, pregnant women, elderly or chronically ill). Most deaths associated with influenza in industrialized countries occur among people aged 65 or older. In some tropical countries, influenza viruses circulate throughout the year with one or two peaks during rainy seasons. There is a paucity of data on influenza transmission patterns in tropical countries.

Influenza pandemics arise when animal influenza viruses adapt to human hosts. In 2009, the reassortment of several human, swine and avian influenza viruses resulted in the emergence of the pandemic influenza A(H1N1)pdm09 virus. In the 20th century, pandemics occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 1977 (reintroduction of H1N1). During the 1918 pandemic, it is estimated that the global death toll exceeded 20–25 million. The sporadic occurrence of human infection with avian influenza subtypes (e.g. H9, H7 and particularly H5) have led to concerns about the possibility of influenza pandemics with increased morbidity and mortality.

The most effective way to prevent the disease or severe outcomes from the illness is vaccination. Safe and effective vaccines have been available and used for more than 60 years. Among healthy adults, influenza vaccine can prevent 70% to 90% of influenza-specific illness. Among the elderly, the vaccine reduces severe illnesses and complications by up to 60%, and deaths by 80%. However, vaccine efficacy varies greatly from year to year, spurring numerous efforts among the scientific and public health communities to develop novel vaccines with increased efficacy.

Influenza vaccination is most effective when circulating viruses are well matched with vaccine viruses. Influenza viruses are constantly changing, and the WHO Global Influenza Surveillance and Response System (GISRS), a partnership of national influenza centres and WHO collaborating centres around the world, monitors the influenza viruses circulating in humans. WHO annually recommends a vaccine composition that targets the most representative influenza A and B strains in circulation in the northern and southern hemispheres.

Currently approved vaccines and their limitations

There are three broad classes of approved influenza vaccines: a) inactivated virus vaccines which can be whole virion, split virion or subunit vaccines; b) live attenuated influenza vaccines (LAIVs); and c) a third class of vaccines based on recombinant HA. The inactivated and recombinant vaccines function primarily by inducing antibodies to the immune-dominant head region of HA, and function by inhibiting virus entry into cells through preventing the HA binding to cell-surface sialic acid. The live attenuated vaccines stimulate an immune response to influenza virus that more closely mimics natural infection.

There are inherent limitations to the effectiveness of current approved vaccines. The greatest weakness of HA-based vaccines is that the most immunogenic regions of the HA protein are the most variable. The virus HA protein evolves rapidly so that circulating viruses may escape the protective effect of a vaccine within a single season; any mismatch between the vaccine strain and the circulating strain results in significantly decreased efficacy. The rapid evolution of influenza requires global surveillance of influenza viruses and the production of new vaccine every year to match the circulating strains. Moreover, in the event of a sudden emergence

of a novel pandemic strain of influenza virus the process of preparing the new seed strains and reagents adds months to the vaccine production, meaning that vaccines could only become available several months after the pandemic has started.

Because these vaccines are composed primarily of HA, they elicit very little response to other influenza viral proteins, such as the surface protein NA, against which antibodies do afford some level of protection. Additionally, most current vaccines do not expose the host to significant quantities of internal components of the virus such as the matrix or nucleoprotein that do not vary significantly from strain to strain. These more highly conserved viral proteins might induce a useful immune response in the event of a mismatch between the vaccine and circulating HA. Moreover, the HA stem region that is conserved between subtypes does not induce the production of significant amounts of neutralizing antibodies in current vaccines because of the immune-dominant nature of the HA head.

Inactivated vaccines are generally poorly immunogenic in influenza-naive individuals – namely infants who have not been exposed to influenza viruses, or the entire population when a new strain with pandemic potential arises. The efficacy of these vaccines in older adults is also not optimal, and in this population eliciting a cellular immune response may increase the efficacy of influenza vaccines.

Live attenuated vaccines have advantages and disadvantages compared to the inactivated or HA vaccines. Because they are nasally administered they induce mucosal immunity, and since there is some viral replication, they also induce cell-mediated responses to conserved proteins, which may offer some limited protection against infection with a new strain. These vaccines are also very efficacious in children and infants, however their efficacy in adults is less than that of inactivated vaccines. As with the inactivated vaccines, new candidate vaccine virus has to be prepared each season, and in the event of a pandemic will not be available for several months.

A recent notable advance in the field has been the development of heterologous prime boost approaches, in which a live attenuated vaccine is used as prime and an inactivated vaccine as boost. This approach leverages both arms of the immune system and generates a unique immune response that has the potential of being broadly protective and longer lasting. Recently published work includes: *Assessment of immune responses to H5N1 inactivated influenza vaccine among individuals previously primed with H5N2 live attenuated influenza vaccine (1)*, where an LAIV prime was followed 18 months later by an inactivated boost and resulted in highly protective titres when compared to the inactivated vaccine alone. Another study showed that LAIV-primed individuals could be boosted by an inactivated vaccine, up to five years later *(2)*. Additional studies are ongoing *(3)*. While an optimal prime boost strategy has not been identified yet, these studies identify a promising area for vaccine development.

The development of a universal influenza vaccine represents a formidable scientific challenge because the diversity in seasonal influenza strains has largely been driven by immune selection in humans. Therefore, different or new combinations of antigens other than those targeted by seasonal vaccines must be identified and successfully exploited to provide broad immunity in influenza-naïve and influenza-experienced individuals alike. The fact that efficacious strain-specific vaccines based on various approaches are currently available and the recently demonstrated success of prime-boost approaches provides support to the possibility that the right combination of conserved antigens, coupled with a vaccine regimen that elicits a multi-functional, durable immune response, could make the goal of a universal vaccine possible.

General approaches to the development of universal influenza vaccines

Numerous avenues are being explored to develop universal influenza vaccines that expand the breadth of the host immune response and the duration of immunity to the virus. The ultimate aim of a universal influenza vaccine is to provide protection against all strains of influenza for many years without the need for annual vaccine strain changes or annual vaccinations.

The main approaches being explored to develop such vaccines include the following.

1. Vaccines based on the conserved HA stem region. These include prime boost strategies using chimeric proteins and “headless” stem-based strategies.
2. Adjuvants. The use of potent oil-in-water adjuvants in combination with subunit vaccines has shown to increase the breadth of the response. Adjuvanted vaccines have been demonstrated to be effective against strain drift.

3. Vaccine design strategies using bioinformatics approaches to build consensus-based or optimized recombinant HA antigens in the form of proteins or synthetic peptides.
4. Vaccines comprising nucleic acid coding for HA followed by boosting with HA protein, intended to induce antibody response against the common determinants. DNA-based vaccines also include strategies designed to elicit host response against conserved internal proteins.
5. LAIV that elicit a broadly cross-reactive, longer-lasting host response.
6. Vaccines comprising conserved internal proteins such as the nucleoprotein or matrix protein, or fragments of these, in formulations destined to induce cell-mediated immunity. These include highly conserved peptide epitopes or expression of these internal proteins in viral vectors or nanoparticles.
7. Vaccines comprising a plurality of HAs from different strains, intended to provide an antibody response against the common determinants of the HA head.
8. Vaccines that combine multiple strategies, bringing together conserved regions from HA and internal proteins into a single vaccine. These multimeric universal vaccines include virus-like particles, viral vectors or nanoparticle platforms.
9. Testing vaccine combination modalities and prime-boost approaches, including heterologous prime boost strategies.

Opportunities and challenges

Opportunities:

- Recent scientific findings on the role of broadly cross-reactive antibodies providing protection from infection with the pandemic influenza A(H1N1)pdm09 virus demonstrate the potential efficacy of a universal influenza vaccine and provide support for a universal vaccine strategy inducing antibodies to common proteins, and in particular the HA stem.
- Research demonstrating the feasibility of developing monoclonal antibodies with broad cross-reactivity to multiple or all influenza A and B subtypes has provided extensive information on the structure of conserved HA epitopes in the stem, and the receptor binding domain of the globular head domain.
- Promising results from a number of laboratories have stimulated significant interest from pharmaceutical companies interested in developing the next generation of influenza vaccines.
- The urgent public health need for influenza vaccines with improved efficacy and the perception of increased risk of influenza pandemics have spurred increasing government interest in the development of universal influenza vaccines.
- Multiple development strategies can lead to the development of vaccines with enhanced breadth and duration of protection; some approaches may be targeted to enhance the efficacy of current vaccines, or replace seasonal vaccine, whereas others may be useful tools to protect the public against pandemic influenza.

Challenges:

- The availability of a relatively effective annual influenza vaccine creates a barrier for the development and implementation of novel influenza vaccine.
- In natural infection there is only a limited immune response to the conserved influenza viral epitopes such as the HA stem; and it is not clear how conserved regions will respond to increased immune pressure caused by a universal vaccine.
- It is not fully understood how immunity to one viral antigen can affect immune response to a different influenza virus. Vaccine investigators have reported that, during some years, prior influenza vaccination may modify influenza vaccine performance; in some cases prior vaccination is associated with residual protection and in others it is associated with decreased vaccine effectiveness. The potential modification of immune response by prior influenza vaccine exposure is the topic of ongoing investigation by WHO and partner public health agencies.
- Licensure of universal influenza vaccines will require the development and approval of novel assays and correlates of immune protection.
- Potential of a human challenge model for development of universal influenza vaccine needs to be mapped out with the regulatory agencies.
- It is likely that universal influenza strategies will require the use of adjuvants; what are the safety concerns of adjuvants used in coordination with novel antigens?

- Licensure of universal vaccines will require agreement on acceptable outcomes (prevention of infection or severe disease), efficacy of these vaccines and the design of clinical trials and end-points.

Current promising leads, strategies and technologies

Table 10.3 highlights the status of current vaccine candidates. Some of the most promising strategies and their sponsors (non-exhaustive list) include the following.

- Chimeric HA proteins designed to focus the immune response (The Icahn School of Medicine at Mount Sinai/ National Institute of Allergy and Infectious Diseases (NIAID)/ Biomedical Advanced Research and Development Authority (BARDA) and Main School of Science and Mathematics (MSSM)/BMGF/PATH).
- MF59 (Novartis) and AS03 (GlaxoSmithKline) adjuvants have been used in combination with subunit vaccines and have shown increase in the breadth of response.
- Computer optimized HA antigens designed to elicit an immune response to a recombinant consensus HA (Vaccine and Gene Therapy Institute (VGTI)/ Sanofi Pasteur).
- DNA-based vaccines encoding HA followed by protein boost (NIAID Vaccine Research Center, VRC) or coding for a genetic consensus of multiple existing strains of each subtype that is known to cause seasonal influenza (Inovio).
- Immunization with a peptide or protein, which combines several conserved regions of influenza proteins into one molecule. Includes synthetic peptide-containing small regions of the virus which are highly conserved, such as Flu-v (SEEK) and the M-001 vaccine which contain regions from HA and two internal virus proteins (BiondVax).
- Virus-like particles (Medicago, Sanofi Pasteur and VGTI).
- M2e-based vaccines such as M2e fused to TLR-agonists (Vaxinnate).
- Fusion proteins of multiple copies of the M2e region fused to the conserved nucleoprotein and conjugating to these immunostimmulatory oligonucleotides, such as being pursued by Dynavax.
- Novel attenuated influenza viruses (University of Maryland College Park, Codagenix, Vacthera).
- Single-replication influenza virus that is un-attenuated, but unable to shed. Designed to elicit humoral, mucosal, and cell-mediated immunity (FluGen).
- Expressing conserved proteins or sequences in viral vectors such as MVA (University of Oxford) or adenoviruses (Ad3, Okairos; Ad4, PaxVax; Ad5, Altimmune, Vaxart), to induce protective $CD8^+$ T-cell responses.

Future directions

A. Short-term goals

- Consensus on definition, target product profile (interim acceptable and ideal) and roadmap for development of universal influenza vaccines.
- Availability of global platform to coordinate vaccine development efforts.

B. Mid-term goals (by 2020, end of the DoV)

- One or two candidates advanced towards licensure.
- Robust pipeline of vaccine candidates using variety of approaches advanced in preclinical development, ready to move to clinics.

C. Long-term goals (by 2030)

- At least one or two universal influenza candidates licensed.
- Global sustainable support available for roll-out of these vaccines in developing countries.

Table 10.3: Development status of current vaccine candidates

Organization	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licenced
Novartis (Switzerland)	Adjuvant MF59 allows for broader cross-reactivity against viral strains not included in the vaccine.				X	X
	Synthetic, self-amplifying mRNA, delivered by a synthetic lipid nanoparticle (SAM).	X				
GlaxoSmithKline (United Kingdom)	Cross-clade antibody responses demonstrated with split-virion, inactivated, AS03-adjuvanted vaccine.				X	X
Icahn School of Medicine at Mount Sinai (United States) and GlaxoSmithKline (United Kingdom)	Various approaches to target conserved broadly reactive epitopes on HA stalk, such as "headless" HA or functional chimeric HA (comprising non-matched "head" and "stalk") expressed either in the context of whole virus or as rHA.	X				
VaxInnate (United States)	Fusion protein between influenza M2e and bacterial flagellin (TLR5 ligand). Self-adjuvanted. Proposed to be used with conventional trivalent influenza vaccine (TIV).			X		
Medicago (Canada)	Recombinant haemagglutinin (HA) expressed as virus-like particle (VLP) in tobacco plants. Requires adjuvant.			X		
Altimmune (United States)	Nasovax: Adenovirus 5, on PER.C6 cell line for vaccine production.		X			
	Flunsyn. Former Immune Targeting Systems. Long peptides from four core influenza proteins elicits strong T-cell response.			X		
BiondVax Pharmaceuticals (Israel)	Multimeric-001 vaccine: recombinant protein, combination of nine conserved linear epitopes from HA, nucleoprotein (NP), and matrix protein (M).			X		
SEEK (formerly PepTcell) (United Kingdom)	Flu-v: mixture of four chemically synthesized peptides targeting conserved T-cell epitopes present in M1, NP, and M2 (with oil-in-water adjuvant).			X		
Vivaldi Biosciences (United States and Austria)	Replication-deficient influenza virus created by deletion of the interferon-inhibiting NS1 protein.		X	X		
Acambis Inc. (now Sanofi Pasteur) (France)	ACAM-FLU-A fusion between M2e and hepatitis B virus core protein (M2e-HBc) to produce VLPs presenting M2e.		X			
Inovio (United States)	DNA plasmids encoding consensus sequences of HA, NA and NP delivered by intradermal electroporation for eliciting antibody and T-cell responses.		X			
Dynavax (United States)	Fusion protein comprising two highly conserved influenza antigens, NP and M2e, which are covalently linked to a proprietary immunostimulatory sequence.		X			
Antigen Express (United States)	Synthetic peptides derived from conserved B cell epitopes from HA, linked to MHC Class 2 Ii-Key moiety for facilitated Th activity.		X			
PaxVax (Ad4 vector with H5 HA)	PXVX0103 (Ad4-H5-Vtn administered as oral capsules) live adenoviral-based vaccine against avian influenza (H5N1)		X			

Organization	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licenced
Vaxart (hAd5 expressing HA/TRL 3)	Orally delivered vectored vaccine. Non-replicating adenovirus type 5 vector backbone, which expresses HA from avian influenza and a TLR3 ligand as an adjuvant.		X			
Nanobio (Nano-emulsion)	Novel oil-in-water nano-emulsion that can incorporate, deliver and adjuvant multiple antigen types, effective when administered via intranasal, intramuscular or subcutaneous vaccination.		X			
NAIAD (United States)	Fusion protein between self-assembling ferritin protein and full length HA for nanoparticle presentation of HA.	X				
Janssen/Crucell Vaccine Institute and the Scripps Research Institute	A stable trimeric influenza haemagglutinin stem (headless) as a broadly protective immunogen (mini-HAs).	X				
Jenner Institute, University of Oxford (United Kingdom)	Replication-deficient modified vaccinia virus Ankara (MVA) expressing both NP and M1. Designed for strong cross-reactive T-cell response. Self-adjuvanted.	X	X			
	Replication-deficient simian adenovirus expressing both NP and M1. Designed for strong cross-reactive T-cell response.	X	X			
	MVA expressing NP, M1 and conserved portion of HA.	X				
Cytos Biotechnology (Switzerland)	M2 protein linked to a TLR7 ligand yielding high levels of IgG2c antibodies.		X			
Wistar Institute (United States)	Fusion protein between M2e and NP, expressed in chimpanzee adenovirus vector.	X				
Gamma Vaccines (Australia)	Whole virion gamma-irradiated virus for intranasal application. Elicits B and T-cell responses that are cross-protective. Self-adjuvanted.	X				
Sanofi Pasteur and VGTI (United Kingdom and United States)	VLP vaccine with computer-optimized consensus HA sequence (Computationally Optimized Broadly Reactive Antigen, COBRA). Elicits broad antibody response. Alum adjuvanted.	X				
FluGen (United States)	Single-replication influenza virus that is un-attenuated, but unable to shed. Designed to elicit humoral, mucosal, and cell-mediated immunity (REDEE FLU).	X				
University of Maryland, College Park (United States)	Rearranged genome of influenza virus permitting expression of two HAs on the same virus while also being attenuated.	X				
CureVac (Germany)	Synthetic mRNA encoding HA and NP. Temperature-stable product, elicits both B and T-cell response. Self-adjuvanted.	X				
University of Pennsylvania (United States)	Adenovirus expressing broadly-neutralizing monoclonal antibody against HA delivered by intranasal administration.	X				
Georgia State University (United States)	Multiple M2 extracellular domains expressed in a VLP.	X				
Merck Research Laboratories (United States)	Synthetic peptides of M2 extracellular domain conjugated to keyhole limpet haemocyanin or *Neisseria meningitidis* outer membrane protein complex.	X				

Organization	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licenced
Bionor (Norway)	Peptide-based approach targeting conserved epitopes (Vacc-Flu).	X				
VBI (formerly Variation Biotechnologies) (United States)	Unique technology using a mixture of eight to 32 peptides, which represent hypervariable epitopes of HA to elicit polyclonal immune response.	X				
University of Wisconsin (United States)	Modified vaccinia virus Ankara encoding influenza virus HA and/or NP.	X				
Codagenix (United States)	Live attenuated influenza vaccine using Synthetic Attenuated Virus Engineering (SAVE).	X				
InvVax (United States)	Linear invariable epitopes used to construct non-variable influenza virus.	X				
University Of Utah Research Foundation (United States)	Modified HA sequence with mutations that reduce antigenicity of immunodominant/variable epitopes.	X				
Okairos (Italy, Switzerland)	Replication-defective pan adenovirus type 3 vector, expressing a fusion protein of M1 and NP.	X				
University of Ghent (Vlaams Instituut voor Biotechnologie VIB) (Belgium)	Recombinant tetrameric protein, M2e-tGCN4 (modified form of the leucine zipper of the yeast transcription factor GCN4 linked to M2e).	X				
University of Göteborg (Sweden)	Fusion protein based on the CTA1-DD adjuvant and containing tandem repeats of the M2e ectodomain epitope.	X				
Tsinghua University (China)	Synthetic peptide (N-terminus of M2e) coupled to carrier protein.	X				
University of Ottawa (Canada) and National Institutes for Food and Drug Control (China)	Adenovirus vaccine encoding secreted fusion protein (codon-optimized HA2 subunit fused to a trimerized form of murine CD40L).	X				
California Institute of Technology (United States)	Adeno-associated viruses delivered intramuscularly, encoding two broadly-neutralizing antibodies.	X				
Medigen (United States)	Recombinant H7 haemagglutinin forms subviral particles that protect mice and ferrets from challenge with H7N9 influenza virus	X				
KJ Biosciences (United States)	M2e + fusion peptides	X				
Vacthera BioTech GmbH (Germany)	Influenza A-attenuated vector expressing conservative influenza A and B epitopes from the NS1 open reading frame. Influenza A-attenuated vector expressing conservative influenza A and B epitopes from the NS1 open reading frame.	X				

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Progress towards institutional and technical capacity to carry out vaccine clinical trials (Indicator SO6.3)

Highlights

- The Eastern Mediterranean Region remains the region with the lowest number of clinical trials overall and the highest number of countries with no clinical trials occurring at all over a four-year period.
- The regions of the Americas, Europe and Western Pacific report consistently high numbers of vaccine clinical trials. However this hides substantial disparity between countries.
- China has become the country conducting the second highest number of vaccine clinical trials (due to a large increase in trials in 2015–2016), followed by India. It is not certain that the trend in China will continue, however. India has been ranking consistently higher than any European country over the four years of reporting.
- Caution is needed in interpreting these trends, as it is not possible to determine whether they may be due partly or wholly to increased use of clinical trial registries in countries.
- There continues to be a lack of adequate data-quality indicators that can be used at the global level.

The main changes in the landscape for clinical trial activities are summarized below.

In addition to a three-step process for all clinical trials, WHO has advocated for the registry of all clinical trials to prevent underreporting and ensure that the full extent of data from such trials is accessible to Member States and other stakeholders. Other stakeholders (such as the National Institutes of Health, NIH) have also drafted guidelines on dissemination of results and data from clinical trials, as well as forums and networks to increase clinical trial regulatory oversight and responsiveness, particularly in developing countries.

Data

In order to ensure full comparability across the years of reporting all four years of vaccine clinical trial activity has been provided for all Member States globally and by WHO region annually from 2012 to 2016 (using 1 May to 30 April as each 12-month period). The results by country and WHO region are presented in Table 10.4.

Limitations of this indicator

The indicator for monitoring clinical research capacity is the number of trials registered by country over a 12-month period. This indicator is subject to the following limitations.

- The database searched is the WHO International Clinical Trials Registry Platform (ICTRP), which collates data from the following registries: the Australian New Zealand Clinical Trials Registry, the Chinese Clinical Trial Registry, clinicaltrials.gov, EU Clinical Trials Register, ISRCTN registry, the Netherlands National Trial Register, the Brazilian Clinical Trials Registry, Clinical Trials Registry – India, Clinical Research Information Service – Republic of Korea, Cuban Public Registry of Clinical Trials, German Clinical Trials Register, Iranian Registry of Clinical Trials, Japan Primary Registries Network, the Pan African Clinical Trial Registry, the Sri Lanka Clinical Trials Registry, and the Thai Clinical Trials Register. Any clinical trials registered in other registries are not imported into ICTRP.

- The date used for classification is the date of registration of the trial. The date of registration may not reflect the precise start date of the trial. It may be registered after the trial has started (although this is not recommended and not allowed for some registries), either with a later start date or it is possible some registries retroactively provide a date of registration that is earlier than the actual date registered (which could alter the results based on the time the database is searched).

WHO support to Member States and other developments in clinical trials capacity

WHO has proposed a three-step process for all clinical trials.

- Step 1 is universal prospective clinical trial registration using a registry compliant with WHO standards (www.who.int/ictrp).
- Step 2 is public disclosure of results from the clinical trials within 12 months of the completion date for the trial (http://www.who.int/ictrp/results/reporting/en/).
- Step 3 is consideration of sharing of the individual participant data taking into account legal and ethical requirements. WHO does not mandate sharing individual participant data from clinical trials but notes that this is an area where policy is in the development stage. WHO encourages that any sharing of individual participant data should be conducted as a 3rd step building on steps 1 and 2.

Further work by WHO and others regarding clinical trials policy is below.

- WHO published its institutional position on prompt reporting of results from clinical trials in April 2015 (http://www.who.int/ictrp/results/reporting/en/), in addition to the Organization's long standing position that all clinical trials must be prospectively registered (www.who.int/ictrp).
- Audits of the extent of clinical trial registration and reporting are beginning to occur and be made available (http://bmjopen.bmj.com/content/6/3/e009285.full and http://bmjopen.bmj.com/content/5/11/e009758.full). These have shown that substantial non-reporting and even non-registration occurs and underpins major biases in the evidence base. Action is needed by Member States to enforce dissemination of results from clinical trials.
- In its official Statement on Public Disclosure of Clinical Trial Results, WHO has called on stakeholders in funding agencies, ethics committees, industry, academia, regulatory and publishing spheres to take actions to ensure universal registration and reporting of all clinical trials [REF]. Underreporting is equally high for industry sponsored or academic trials.
- In 2015 the National Institutes of Health (NIH) conducted a public consultation on draft new rules promoting dissemination of results of all NIH-funded clinical trials http://grants.nih.gov/clinicaltrials_fdaaa/. The final new rules are awaited.
- In early 2016 the International Council of Medical Journal Editors (ICMJE) conducted a public consultation on plans to mandate sharing of individual participant data within six months of publication of all clinical trials in member medical journals going forward http://www.icmje.org/news-and-editorials/M15-2928-PAP.pdf. The final ICMJE position on data sharing is awaited.

In addition to this, important developments have taken place recently in addressing some of the challenges posed by inadequate clinical trial regulatory oversight and responsiveness, particularly in Africa. The African Vaccine Regulatory Forum (AVAREF) was formed in 2006 as a platform to build capacity for NRAs and ethics committees, to promote harmonization of requirements and practices and to reduce lengthy timelines associated with the review of clinical trials. Building upon earlier success, the AVAREF platform proved critical in the joint and assisted Clinical Trial Assessments (CTA) of candidate vaccines to combat EVD during the Ebola epidemic in West Africa in 2014–15. In an effort to further strengthen and expand AVAREF, an extraordinary meeting was held in Addis Ababa 9–10 June 2016, resulting in a new vision, mission and governance structure with a steering committee composed of heads of NRAs and national ethics committees. The new Forum, whose scope has expanded to include medicines and diagnostics, is designed to serve as a platform for joint reviews of multi-country trials of vaccines and other technologies of public health interest, accelerate clinical review times, promote transparency and facilitate convergence based on the African Medicines Regulatory Harmonization principles of regional harmonization. AVAREF will also serve as the first pan-African regulatory network, providing a vehicle for product development partnerships and companies to discuss development plans and plan multi-country reviews. It is also expected to function as the precursor to the African Medicines Agency.

In parallel, the Developing Countries Vaccine Regulators Network (DCVRN), established in 2004 as an international platform for strengthening the regulatory oversight of vaccine trials, is also revisiting its governance structure with a view to adopting a new operating model during an extraordinary meeting of in November 2016. The Network, composed of the NRAs of developing countries that produce and export prequalified vaccines, has already expanded its scope to include product registration and vigilance. It is proposed that DCVRN expand its responsibilities and activities in a step-wise manner to include a broader range of medical products used for the diagnosis, prevention and treatment of infectious diseases that are endemic in, and of interest to, developing countries.

Table 10.4: Annual[a] vaccine clinical trial activity by Member State and WHO region, 2012–2016[b]

a) African Region

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Burkina Faso	3	0	1	2
Cameroon	0	0	0	1
Equatorial Guinea	0	0	1	0
Gabon	0	1	0	2
Gambia	0	3	1	1
Ghana	0	0	0	5
Guinea	0	0	1	0
Guinea-Bissau	1	0	0	0
Kenya	4	2	1	4
Malawi	0	0	1	3
Mali	0	1	2	5
Mozambique	1	1	0	2
Niger	0	0	1	0
Nigeria	0	1	0	3
Senegal	2	1	0	3
Sierra Leone	0	0	1	2
South Africa	11	14	3	7
Uganda	1	2	2	0
United Republic of Tanzania	1	3	0	1
Zambia	2	3	0	1
Zimbabwe	0	0	1	0
Total clinical trials	**26**	**32**	**16**	**37**

[a] Each 12-month period began on 1 May and ended on 30 April of the following year.
[b] Data as of 30 June 2016. Note that the Comoros and San Marino could not be searched in the ICTRP database.

b) Region of the Americas

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Argentina	5	1	3	1
Brazil	13	9	9	17
Canada	18	33	14	25
Chile	2	8	5	3
Colombia	6	14	10	8
Costa Rica	0	5	3	1
Cuba	4	4	3	8
Dominican Republic	5	5	5	4
Ecuador	1	0	0	0
Guatemala	2	2	1	0
Honduras	3	3	3	2
Mexico	9	5	11	11
Nicaragua	0	0	0	1
Panama	6	10	7	3
Paraguay	0	0	0	1
Peru	4	3	5	2
United States of America	108	120	101	100
Venezuela (Bolivarian Republic of)	1	1	0	0
Total clinical trials	**187**	**223**	**180**	**187**

c) South-East Asia Region

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Bangladesh	7	1	0	2
India	38	40	31	35
Indonesia	2	5	1	0
Sri Lanka	0	0	0	2
Thailand	16	13	11	19
Total clinical trials	**63**	**62**	**44**	**58**

d) Eastern Mediterranean Region

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Egypt	1	2	0	0
Iran (Islamic Republic of)	8	9	8	9
Jordan	1	0	0	0
Lebanon	1	1	0	0
Pakistan	4	2	0	0
Qatar	0	1	0	0
Saudi Arabia	1	1	0	0
Somalia	0	0	0	0
Sudan[a]	0	1	0	1
United Arab Emirates	1	0	0	0
Total clinical trials	**17**	**17**	**8**	**10**

[a] N.B. in the GVAP Secretariat report 2014 Sudan was listed under the African Region.

e) European Region

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Austria	3	5	1	5
Belarus	0	0	1	0
Belgium	19	16	13	11
Bulgaria	2	1	1	2
Croatia	1	1	0	0
Czech Republic	18	9	8	9
Denmark	7	5	6	4
Estonia	11	5	3	8
Finland	19	13	8	13
France	10	15	7	12
Georgia	1	0	0	0
Germany	23	28	16	24
Greece	3	3	2	1
Hungary	6	6	4	3
Ireland	0	0	0	1
Israel	5	7	0	2
Italy	12	12	4	11
Latvia	0	0	2	2
Lithuania	1	1	2	3

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Monaco	0	0	0	1
Netherlands	7	13	5	11
Norway	5	3	2	2
Poland	12	12	8	7
Romania	3	1	2	3
Russian Federation	10	10	6	4
Serbia	0	0	1	1
Slovakia	1	2	2	0
Spain	28	23	10	10
Sweden	14	9	4	12
Switzerland	3	4	5	4
Turkey	6	9	1	3
Ukraine	3	2	2	0
United Kingdom of Great Britain & Northern Ireland	31	36	19	25
Total clinical trials	**264**	**251**	**145**	**194**

f) Western Pacific Region

Country	Number of trials (2012–2013)	Number of trials (2013–2014)	Number of trials (2014– 2015)	Number of trials (2015–2016)
Australia	32	29	25	22
Brunei Darussalam	0	0	0	0
Cambodia	0	0	0	0
China	29	28	30	50
Japan	6	13	5	12
Malaysia	6	6	3	0
New Zealand	8	6	3	3
Philippines	5	18	11	10
Republic of Korea	23	25	27	29
Singapore	3	4	5	4
Viet Nam	1	2	5	8
Total clinical trials	**111**	**131**	**114**	**138**

Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases (Indicator G4.1)

OPERATIONAL DEFINITION OF INDICATOR	Licensure relates to registration by a functional national regulatory authority (NRA). Launch is defined as addition of the vaccine to the national immunization schedule in one or more low- or middle-income countries and sustained for a period of at least 12 months. Excludes use when limited to the private sector only. Includes vaccines in national schedule that may be selectively used in at-risk populations
TARGET	Progress towards licensure/launch of one or more such vaccines by 2020
DATA SOURCE/COLLECTION	Subject matter experts; landscape reviews; clinical trial databases
MILESTONES	Incremental progress (i.e. number of products in phase I, II or III clinical trials) in development to be reported and assessed by SAGE

Background

Goal 4 of the Monitoring & Evaluation/Accountability Framework in the GVAP is to "develop and introduce new and improved vaccines and technologies". Sub-goal 4.1 specifically calls for an assessment of progress towards licensure and launch of vaccine(s) against one or more major diseases, currently not preventable with vaccines. The current status of vaccine development for HIV/AIDS, tuberculosis, malaria and a universal influenza vaccine has been addressed in other sections of this report. A large number of vaccines for other diseases, however, are in research and development globally in both the public and private sectors at the present time. In order to focus efforts in this complex and dynamic area, it was decided to concentrate initially on seven diseases for which vaccines are considered to be highly desirable, candidate vaccines are already in various stages of development, and which represented a broad microbiological spectrum: dengue, hepatitis C, CMV, RSV, group A streptococcus, leishmaniasis and helminth infections. To that end, the GVAP Secretariat consulted with experts, performed a landscape analysis and generated reports for each of the target diseases. The selected candidate vaccines as a group were generally considered to provide a representative indication of the changing state of the science.
The information below represents a high-level overview and emphasizes cross-cutting themes.

The goal is to have one or more vaccines licensed or launched for at least one of the target diseases by 2020. Incremental progress, defined as new products entering or moving through clinical development, will be reported on a biennial basis to SAGE and the World Health Assembly. This chapter provides an update on the current status of vaccine candidates and presents a forward-looking assessment of potential progress in the DoV and beyond.

Overview of current efforts

In 2015, a live recombinant tetravalent vaccine against dengue, Dengvaxia, designed for use in individuals older than 9 years of age, was licensed in Mexico. Since that time, the vaccine has been licensed by NRAs in other dengue-endemic countries. As discussed below, additional dengue candidate vaccines are under development.

Table 10.5 shows the number of candidate vaccines for the seven target diseases currently in active clinical development. As compared to 2014 more candidate vaccines are entering and progressing through the clinical development pipeline for five of the seven target diseases. There are substantial basic research and preclinical development efforts in each of the target diseases. Current efforts encompass a variety of diverse technologies and approaches, ranging from

live attenuated (dengue, CMV, RSV) and inactivated vaccines (dengue, RSV) to subunit-based vaccines (all target diseases). In addition, vaccines are being developed for both prophylactic and therapeutic indications (e.g. hepatitis C, schistosomiasis).

Table 10.5: Number of candidate vaccines against selected diseases currently in active clinical development[a]

Target disease	Phase I	Phase II	Phase III
Dengue	4	1	2
Hepatitis C	3	1	0
Cytomegalovirus	12	6	1
Respiratory syncytial virus	11	2	2
Group A streptococcal disease	4	1	0
Leishmaniasis	2	0	0
Helminth diseases[b]	5[c]	0	1[d]

[a] As of July 2016.
[b] Includes schistosomiasis, hookworm, onchocerciasis and lymphatic filariasis.
[c] Includes two candidate vaccines for *Schistosoma mansoni* infection and three for hookworm infection.
[d] Includes one candidate (therapeutic) vaccine for *Schistosoma haematobium*.

Opportunities and challenges

Substantial opportunities for vaccine development for each of the target diseases derive from recent advances inter alia in genomic sequencing, proteomics, systems biology and structural biology, which are facilitating the identification, credentialing and selection of candidate vaccines. In addition, increasing access to manufacturing capacity enhances process development and shortens the interval from preclinical concept to availability of clinical trial material. Furthermore, technology is offering more and more tools for greater depth of analysis for characterization and quality control of vaccines, and for characterization of relevant immune responses. Priority lists produced by multiple organizations have renewed focus on development efforts for vaccines against diseases included in the GVAP. Public-private partnerships and advances in manufacturing processes provide promise that more cost-effective approaches toward vaccine development may be realized.

Interestingly, several common issues present challenges to vaccine development for a number of the target diseases, such as: an incomplete understanding of the pathogenesis (including immune-mediated disease enhancement) and immunologically-mediated protection; the absence of adequate and/or predictive animal models for pathogenesis or protection; and the lack of correlates of protection/pathogenesis to help guide development. To address these questions, investigators are actively pursuing the development of human challenge models for a number of diseases, including notably dengue and hookworm. The aim of increasingly powerful analytical tools must be to detect and discriminate appropriate signals and identify linkages to relevant biological effects. Defining and measuring crucial analytic characteristics for potency and safety should be an important focus of future efforts. Additional challenges relate to an incomplete understanding of the epidemiology of disease, availability of and access to defined target populations with sufficiently high incidence rates to support efficient and cost-effective clinical trials, and a diversity of clinical manifestations and outcomes depending on the pathogens involved and the target populations. Vaccine hesitancy and perceived safety concerns discourage enrolment and execution of clinical studies; a concerted, evidence-based effort will, therefore, likely also be required to address future delivery and deployment issues. Finally, vaccine affordability should be considered at all stages of the development pathway without compromising quality standards.

Current promising leads, strategies and technologies

As noted above, numerous leads, strategies and technologies are being pursued concurrently. The candidate vaccines in phase III trials, representing the most advanced candidates, are based on recombinant live attenuated viruses (dengue vaccines), DNA vaccines (human CMV vaccine), nanoparticles (RSV vaccines) and adjuvanted recombinant proteins (schistosomiasis vaccine). Candidate vaccines in phase II trials are based on live attenuated virus (RSV vaccine), recombinant live attenuated virus (dengue vaccine), viral-vectored vaccines (hepatitis C, CMV), DNA vaccines (human CMV), adjuvanted peptide combinations (Group A streptococcus vaccine), adjuvanted recombinant proteins (human CMV vaccine) and subunit vaccines (RSV). Internationally-accepted quality standards can be important drivers, especially when identified early in the development cycle, that can support both innovation and subsequent access to affordable, high-quality products. Finally, investigators working at the basic and preclinical level of research for the targeted vaccines as well as in phase I clinical trials are pursuing a variety of antigens, delivery systems and adjuvants to elicit protective B- and T-cell responses. In addition, it is worth noting that for zoonotic diseases such as leishmaniasis and schistosomiasis, veterinary vaccines are also being pursued that may prove useful in future control programmes and may serve as models for future human vaccines for these diseases. Further details of the various approaches being taken are discussed in the references at the end of this section.

Future directions

A. Short-term goals (0–2 years)

In the short term most efforts in the seven target diseases are focused on maintaining momentum and analysing ongoing projects. Of particular note and interest, the recently licensed dengue vaccine will continue to be followed and where applicable, the resulting analysis used to inform licensure of other vaccines against dengue and the other target diseases. Also, results from five phase III trials (for the tetravalent, live attenuated vaccines for dengue; the nanoparticle vaccines for RSV; and the adjuvanted, subunit vaccine for *Schistosoma haematobium* infection) and a phase II trial of a hepatitis C vaccine are expected to be available soon and will warrant careful analysis. In addition, research and development efforts will continue to address some of the research challenges identified above, to prioritize standardization needs, and support advancement of promising candidate vaccines for all seven targeted diseases.

B. Medium-term goals (by 2020, end of the DoV)

In the medium term efforts are focused on post-licensure studies and delivery strategies, notably regarding the licensed dengue vaccine. Support of research and development to address unmet research opportunities and gaps identified above remain high priorities as well as identifying promising vaccine candidates, developing and implementing the required standards, and providing appropriate credentials to advance their development as warranted. Assuming encouraging results in phase I trials, a number of candidate vaccines will advance into phase II trials. It is possible that vaccines to prevent human CMV reactivation and RSV will be licensed in the medium term.

C. Long-term goals (post-2020)

In the long term the goals are to license safe, effective and affordable vaccines for all of the target diseases as needed to fulfil appropriate medical and public health mandates.

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Licensure and launch of at least one platform delivery technology (Indicator G4.2)

DEFINITION OF INDICATOR	New platform delivery technology defined as a new mechanism for delivering vaccines to individuals that facilitates coverage, improves performance or reduces the cost of vaccine or delivery (e.g. jet injectors, microneedles, aerosols). Licensure relates to registration by a functional NRA. A launch is defined as the use of the technology in the national immunization programme of one or more low- or middle-income countries
TARGET	2020: one or more vaccines
DATA SOURCES	Landscape reviews and meeting reports

Background

Innovations in delivery technology have many potential benefits. All are designed to increase access to life-saving vaccines by improving deliverability and thereby accelerating uptake. Some platform technologies can help to facilitate outreach and increase vaccination coverage. Investment in new technologies can simplify delivery in routine immunization and campaigns, helping to achieve the goal of reaching the one out of five children (the "fifth child") who are missed by current immunization efforts. Some can improve the safety of vaccination programmes, for example, by reducing the risk of needle-stick injuries and preventing the re-use of needles and syringes, or avoiding the use of non-potent vaccine. Indeed, innovations such as auto-disable syringes and vaccine vial monitors are now widely used to improve the safety and efficiency of vaccination programmes. New technologies on the horizon could lessen and simplify the workload of health care workers, which could further improve programme capacity and impact. In addition, new delivery technologies can potentially increase efficacy, reduce the amount of antigen required per dose, allow for vaccine access during supply shortages and potential reduce total delivery cost by delivering antigens directly to immunologically active tissues.

Overview of current efforts

Substantial progress has been made in advancing novel platform delivery technologies for vaccines, and this GVAP indicator is expected to be achieved by 2020. Table 10.6 summarizes a number of key platform delivery technologies that have achieved or are advancing towards licensure and launch in low- and middle-income countries within this time frame.

Table 10.6: Summary of progress for key platform delivery technologies expected to achieve launch in low- and middle-income countries by 2020

Technology	Manufacturer	Vaccine application	Licensure (NRA)	WHO prequalification	Anticipated launch in country
Stratis 0.5 mL needle-free jet injector (subcutaneous and intramuscular)	PharmaJet	Clinical study complete with MMR *(1)*	Received USFDA 510(k) clearance in July 2011 and approval in August 2014 for delivery of Afluria influenza vaccine *(2)*	February 2013	Expected in 2017 (relabelling of Serum Institute of India's MMR vaccine for delivery by Stratis)
Tropis 0.1 mL needle-free jet injector (intradermal)	PharmaJet	Intradermal delivery of IPV	CE mark received in June 2016	Expected in 2016–17	Expected in 2017; by GPEI

Technology	Manufacturer	Vaccine application	Licensure (NRA)	WHO prequalification	Anticipated launch in country
Intradermal adapter	Helm/West Pharmaceutical Services	Intradermal delivery of IPV	USFDA clearance received in February 2013 *(3)*	Expected in 2016–17	Expected in 2017; by GPEI
Blow-fill-seal primary containers	GlaxoSmithKline	Oral delivery of rotavirus vaccine	Expected in 2018	Expected in 2018	Expected in 2018
Barcodes	Multiple vaccine manufacturers	All vaccines	NRA approval in at least one LMIC expected by 2020	Critical characteristics on secondary and tertiary packaging by 2020	Continued nationwide expansions expected in 2017
Vaccine vial monitor with threshold indicator (VVM/TI)	Temptime	Potentially all vaccines labelled for controlled temperature chain use	NA	Expected in 2016	TBD

USFDA, United States Food and Drug Administration; LMIC, low- and middle-income country.

It is interesting to note that two of the platform delivery technologies, the Tropis disposable-syringe jet injector and Intradermal the intradermal adapter, are targeted for immediate availability in low- and middle-income countries for polio outbreak control due to the limited supply of IPV. These technologies offer means for dose sparing (fractional dose) by delivering the vaccine intradermally resulting in adequate immune responses at lower doses. WHO has recommended that countries consider intradermal delivery of fractional doses of IPV in the routine immunization schedule and these devices are intended to enable that recommendation *(4)*. There are a number of studies supporting the use of such technologies delivering intradermal fractional dose IPV, which would facilitate the introduction of fractional dose of IPV *(5)*.

GPEI has recently finalized purchasing agreements with PharmaJet and Helm/West Pharmaceutical Services for the Tropis and the intradermal adapter respectively for use in intradermal delivery of fractional dose IPV in support of polio eradication. The initial purchase orders comprise 4.1 million intradermal adapters with Helm autodisable syringes, 5000 Tropis devices and 5 million needle-free Tropis syringes for use by Q1 2017. Launch of both technologies in low- and middle-income countries is expected to begin this year in places with poliovirus outbreak. In addition, there are other intradermal-capable technologies (the MicronJet hollow microneedle from NanoPass and the intradermal syringe from Star Syringe) that may also potentially be available for low- and middle-income country use by 2020 depending upon successful modifications of both technologies to meet programmatic suitability and usability requirements.

It is important to note that given the current supply shortages for yellow fever vaccine, fractional dose subcutaneous delivery of this vaccine has also been recently recommended by WHO *(6)*. Currently WHO is procuring a new safety syringe with a fixed 0.1 ml dose and a suitable needle size and length for subcutaneous delivery.

In the case of the PharmaJet Stratis, an MMR study conducted in India by the Serum Institute of India was recently successfully completed which will ultimately lead to relabelling of Serum Institute of India's measles-containing vaccines for delivery with disposable-syringe jet injectors. Programmatic interest in using the Stratis has been expressed by MSF in particular, for measles vaccine delivery, dependent upon the results of the Serum Institute of India MMR study.

Blow-fill-seal is an alternative aseptic fill/finish process in which polymer containers are formed, filled, and sealed in a single operation. It offers an advanced degree of sterility assurance in comparison to conventional filling equipment, and has the potential to allow for comparable manufacturing costs to multidose vials but in multiple single-dose formulations. Blow-fill-seal also enables greater flexibility in primary container design, including the potential to reduce cold-chain volume through compact, stackable shapes. Blow-fill-seal is commonly used for packaging a variety of licensed pharmaceuticals, and is in development for vaccines. GlaxoSmithKline is leading the vaccine field, and has invested in a pilot blow-fill-seal manufacturing facility in Boronia, Australia for Rotarix vaccine *(7)*. GlaxoSmithKline's Rotarix vaccine is expected to be available in blow-fill-seal containers as an improved product presentation in the South Asian/Pacific

region in 2018 as well as through eventual UNICEF procurement. Additionally it should be noted that Rommelag, a major blow-fill-seal equipment company, is developing a parenteral-capable blow-fill-seal design that is intended to meet the requirements for a compact prefilled auto-disable device.

Barcodes represent a technology that has been broadly utilized in a number of fields, to include assessment for use with vaccines. Improved supply chain and inventory control has been demonstrated with this technology class. Currently barcodes are being utilized on a limited scale for vaccines and other health care commodities in a few low- and middle-income countries. To reduce the barriers to improved traceability, a multi-faceted approach is being supported. The United Republic of Tanzania, Pakistan, Ethiopia, and Nicaragua have all completed pilot projects of the use of barcodes on secondary and tertiary packaging. The United Republic of Tanzania is completing a cost–benefit analysis of barcode use to justify scaling the programme nationally. Furthermore, Nigeria and the Democratic Republic of the Congo are making plans to require barcode labelling in the next few years. Work is also advancing to increase the availability of automated identification and data capture functionality within country systems. Bar code functionality was added to the logistics/vaccine information management system (OpenLMIS/VIMS) in the United Republic of Tanzania with an accompanying guide describing how to recreate and reuse the barcode library. Pakistan has built barcode functionality into their vaccine logistics management information system, and Ethiopia has similarly added it into their supply chain management system. Nicaragua extended the pilot software from the United Republic of Tanzania and replicated an end-to-end traceability test there.

The vaccine vial monitor with threshold indicator (VVM/TI) is being advanced as an option for the monitoring of vaccines used in a CTC setting. The VVM/TI will provide indication when the vaccine has been exposed to a temperature higher than 40°C. The interpretation of a VVM/TI is designed to be the same as the current VVM; so additional training would not be required. To date, VVMs with separate prototype threshold indicators have been used in CTC MenAfriVac vaccine introductions. The VVM/TI is currently undergoing WHO laboratory and field prequalification. Availability in low- and middle-income countries will be dependent on pricing, WHO recommendations/ requirements for use and demand from countries distributing vaccines in a CTC.

Opportunities and challenges

Over the past two years, there has been an increased desire from manufacturers, policy-makers and procurement agencies for a tool that will enable evaluation of the trade-offs between the impact that product innovation may have on vaccine development cost, vaccine price and delivery cost. Such a tool would facilitate the prioritization of public and private sector investments in key platform and delivery technologies applied to specific vaccine products. WHO and PATH are currently co-leading a delivery technology working group comprising subject matter experts from WHO IPAC member institutions, as well as representatives from the International Federation of Pharmaceutical Manufacturers and Associations and the Developing Country Vaccine Manufacturer's Network with a mandate to provide guidance on new primary container and delivery technologies, and to help inform how best to develop a tool to evaluate the potential programmatic utility and cost-effectiveness of these new innovations (see "future directions"). The delivery technology WG reports directly to WHO's IPAC.

In addition, concerted efforts are being undertaken to advance strategies that can serve to bring improved vaccine products to low- and middle-income countries for existing vaccines. For example, in December 2015, the Gavi Alliance's management board endorsed a new strategic framework for 2016 to 2020, which expands Gavi's strategic goal on market shaping to include other immunization products in addition to vaccines. By working with other stakeholders in the market-shaping community, the Gavi Alliance can help to provide greater clarification and focus on promising areas for product innovation with timelines beyond 2020, thereby informing strategic investment decisions in product development.

Work to advance barcodes on vaccine packaging has benefited from the efforts of a barcode WG formerly under the Vaccine Presentation and Packaging Advisory Group (VPPAG) and supported by GS1. Despite the expected benefits derived from barcode technology, its path to adoption is hindered by a series of divergent standards for barcode use; and the need for continued alignment of participants across the supply chain ecosystem including WHO, UNICEF, vaccine manufacturers, and countries. The combined power of WHO prequalification activities, UNICEF purchasing coordination and manufacturer advancements in their packaging activities greatly accelerated the pace and coverage of barcodes. However, the barcode WG currently lacks involvement from WHO and UNICEF

after reorganization of the VPPAG and may therefore disband. If this occurs, work to advance barcodes on vaccines will likely be ad hoc, without the opportunity to coordinate activities and share lessons learned; should this occur, it will set back the deployment of barcode capabilities within countries by several years.

Current promising leads, strategies and technologies

In addition to the key platform delivery technologies (listed in Table 10.6), work is advancing on a number of other platform technologies – though these are unlikely to launch in low- and middle-income countries by 2020.

Microarray patches (previously referred to as microneedle patches) consist of an array of small projections containing a dry formulation of a vaccine or pharmaceutical. When applied to the skin (like a plaster) the vaccine dissolves into the upper layers of the skin. Potential advantages of this method of delivery include increased thermostability, ease of delivery, reduction in sharps waste, and the possibility of increased efficacy or dose sparing. The development of microarray patches is a rapidly evolving field with upwards of 40 developers. To date, microarray patches have been evaluated in clinical research for influenza vaccine and parathyroid hormone, and are in preclinical development for vaccines such as IPV, MR, rotavirus, HPV and malaria *(8–18)*.

Novel primary containers are in development as well, which may reduce or simplify the storage and delivery of vaccines. The blow-fill-seal manufacturing process, which is being advanced for packaging oral vaccines, is also in development for delivery of parenteral vaccines. Potential designs that are currently being evaluated for suitability include polymer blow-fill-seal vials, ampoules and compact prefilled auto-disable devices. Other alternative primary containers which may be available in the future include integrated reconstitution technologies, in which the dry vaccine and diluent are packaged together or as an integral system and mixed within the device before delivery, potentially simplifying the logistics of transportation, the process of preparing vaccines and reducing the risks of reconstitution errors that can result in adverse events following immunization.

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2016 Global Vaccine and Immunization Research (GVIRF) Forum: Meeting Report

Highlights

- "Positive opinion" received from EMA under Article 58 for first anti-parasitic vaccine, RTS,S/AS01, to protect children from malaria.
- Licensure of the first dengue vaccine has been achieved.
- Ebola candidate vaccines have been developed with unprecedented speed through global collaboration.

Introduction

Research on the discovery, development and delivery of vaccines is an integral part of the GVAP and essential to achieving the vision of the DoV. WHO, the National Institute of Allergy and Infectious Diseases (part of the NIH) and BMGF convened the second GVIRF in March 2016. This GVIRF aimed to track recent progress of the GVAP research and development agenda, identify opportunities and challenges, promote partnerships in vaccine research and facilitate the inclusion of all stakeholders in vaccine research and development. Leading scientists, vaccine developers and public health officials from around the world discussed scientific and technical challenges in identification, credentialing and development of candidate vaccines, manufacturing and regulatory issues and research to improve the impact of immunization. This section summarizes the discussions and conclusions from the forum participants.

Progress and lessons learned

Malaria vaccines

Reflecting the global burden of malaria, development of vaccines against this parasitic infection continues to be an active area of investigation, with numerous candidates advancing in both preclinical and clinical development. In light of recent successes in reducing the prevalence and incidence of malaria worldwide, discussions are now evolving to include not only vaccines to prevent infections and reduce the burden of disease, but also to prevent malaria transmission. A variety of approaches, including subunit recombinant proteins, vectored vaccines and whole-parasite vaccines, as well as prime-boost combinations are being pursued. In addition, the need to ensure adequate research capacity in endemic areas, and the use of controlled human malaria infection studies to provide preliminary indications of safety and efficacy of candidate vaccines in endemic populations, were discussed.

Recent results from a large, multicentre phase III clinical trial of the most advanced candidate vaccine, RTS,S/AS01 (MosquiRix), demonstrated modest efficacy in infants and young children (18% in infants, 26% in young children) over a three- to four-year follow-up period after receiving three doses of vaccine; efficacy could be boosted with a fourth dose of vaccine. Although the EMA issued a "positive opinion" following review of the data, SAGE recommended further pilot studies to assess the feasibility of delivery and potential impact of this vaccine under field conditions prior to widespread deployment.

Vaccines in integrated disease control

The potential role that new vaccines with modest efficacy might play in integrated disease control generated thought-provoking discussion. Studies of pneumococcal and rotavirus vaccines have highlighted

the influence of geography, pathogen heterogeneity and clinical syndrome-based end-points on assessments of vaccine efficacy. Vaccines with modest efficacy can have a significant impact on reducing disease, especially in high-burden settings; and in situations where herd immunity exists they can produce substantial benefits in "non-target" populations. Moreover, such vaccines can complement other interventions. For example, the lack of complete protection using currently available tools and the emergence and spread of antimalarial drug and insecticide resistance, indicates that malaria vaccines with modest efficacy could enhance control efforts and potentially reduce the spread of drug resistance, which supports the inclusion of such vaccines in any package of malaria control interventions. Similar arguments were advanced for development of vaccines against bacteria exhibiting antimicrobial drug resistance. Finally, although numerous interventions exist to prevent HIV, a modelling case study of an HIV vaccine with modest efficacy in conjunction with other interventions, illustrated that such an approach could substantially reduce the number of new infections and deaths by 2050 and that targeting the general population provides a greater impact than targeting only high-risk groups.

Immunization in the second year of life and beyond

The vaccine landscape has been exceptionally dynamic in recent years, and several vaccines that have entered public health programmes require additional immunization contact points. Similarly, the immunization schedules of commodity vaccines have been re-assessed. Implementation research to assess the complexity of adding new immunization contact points is needed. Policies designed to introduce vaccines into new age groups have not necessarily translated into changes in immunization practices and have highlighted the complexities of adding a healthy child visit in the second year of life. The challenges in delivering MCV2 apply to other vaccination contacts for children > 1 year old, including MenAfriVac (serogroup A meningococcal vaccine), RTS,S, and other vaccines given to older age groups. Further research is needed to clarify how to introduce a new visit successfully and use resources productively.

Progress toward measles control and eradication

Even mature interventions and well-established control strategies need regular scrutiny: progress, challenges and opportunities were discussed for the measles and rubella elimination agenda. Despite the availability of a highly-effective vaccine, approximately 250 000 cases occur annually, and this is considered an under-estimate. At least 95% coverage is needed to sustainably control the diseases, and this level of coverage must be global in order for eradication to become a reality. Achieving this level of coverage is particularly challenging in hard-to-reach, remote, and migrating or itinerant populations, and in areas of civil unrest. As has been the case with polio vaccines, any strategic innovation that enables measles vaccine delivery by house-to-house vaccination rather than fixed or mobile post campaigns would increase measles vaccine coverage. While the economic benefit of measles eradication is compelling, little investment is made into innovations to achieve this goal. Microarray patches were discussed as a novel, and potentially game-changing, strategy to increase coverage of measles vaccine by enabling house-to-house campaigns. Such innovative approaches can help to overcome significant challenges on the road to measles eradication, and may have positive repercussions beyond measles.

Progress in regulatory strengthening

Regulatory authorities are responsible for protecting the public, including clinical trial subjects, from unsafe medical products while simultaneously facilitating the development and delivery of products with important public health benefits. In low-income countries, regulatory bodies face many challenges, including weak capacity, poorly-defined processes and limited pharmacovigilance. Manufacturers must grapple with disparate requirements and processes across countries, a lack of guidance documents, inconsistent communication and poor transparency. AVAREF was launched in 2006 to tackle these issues, by facilitating joint reviews with stringent regulatory authorities; supporting adoption of common application documents, approval guidelines and timelines; and promoting cross-learning. In the past decade reviews and approvals of clinical trial applications for products such as MenAfriVac, RTS,S, and TB vaccines have accelerated. AVAREF will be expanding its scope to include medicines as well as vaccines and adopting a regional approach.

Regional vaccine manufacturing capacity

Vaccine manufacturing capacity is unevenly distributed over the world. Today, Africa represents 14% of the world population (projected to increase to 25% in 2050), but has virtually no manufacturing capacity. Also, many African countries will be graduating from Gavi

Alliance support over the coming years, thus increasing demand for low cost, high-quality vaccines.
The African Union has taken steps to increase African pharmaceutical development and production capacity, with the dual goal of empowering African health systems to respond to the health needs of their people, and to contribute to overall socioeconomic development. Following this lead, the African Vaccine Manufacturing Initiative is expanding its pharmaceuticals strategy to vaccines.

Vaccine demand and hesitancy

A cornerstone for increasing the impact of vaccines is acceptance of vaccination. The overall high coverage rate of vaccination, the call for vaccines in the context of emergencies and the recent attainment of disease control targets, are encouraging signs that overall vaccine acceptance is high. However, vaccine hesitancy has emerged in many communities and is having a profound impact on programme performance. Vaccine hesitancy is complex and context-specific, varying across time, place and vaccine. It includes factors such as complacency, convenience, confidence and trust. Addressing vaccine hesitancy requires an understanding of the magnitude and setting of the problem, diagnosis of the root causes, tailored evidence-based strategies to address the causes, impact evaluation to gauge if the intervention has affected vaccine acceptance and ongoing monitoring. Comprehensive tools to assess and address hesitancy have been developed and successfully used, with the promise that hesitancy can be addressed.

Emerging technologies and insights

Novel approaches to discovery and development

The GVIRF provided a forum to illustrate a variety of novel approaches to better understand discovery and development of vaccines. In recent years, a convergence of advances in structural biology, molecular immunology and computational biology has created new opportunities to design novel immunogens for vaccines against "hard-to-target" pathogens. Leading scientists presented studies showing how these approaches are now being applied to construct novel vaccines to induce protective immune responses to dengue (and potentially other flaviviruses), RSV and HIV. In addition, the possibility to design highly specific "cage-like" protein nanoparticles capable of potent multivalent display of antigens and targeted delivery to appropriate cell types was illustrated.

Evolution of a systems perspective

A major lesson from the GVIRF relates to the need for broad systems perspectives in conceptualizing, developing, prioritizing and implementing vaccine innovations. At the outset, the global vaccine community focused on making vaccines developed for high-income markets available to those in poorer countries. However, many diseases primarily affect populations in low-income countries, whose needs cannot be fully met by vaccines originally designed for use in the developed world. To address this issue product development partnerships were created to develop vaccines for low-income countries. Such an approach has led to the development of malaria vaccines and MenAfriVac. These new vaccines must be designed with delivery in resource-constrained environments in mind. This has led to a greater emphasis on preferred product characteristics and target product profiles as a way to ensure user needs are factored into product development decision-making. Although still a work in progress, total systems effectiveness (TSE) represents the next step in this trajectory. TSE blends quantitative and qualitative analysis of five factors influencing the performance of a new intervention: efficacy, coverage, safety, product-cost efficiency and operational-cost efficiency. To inform priorities, the TSE framework can be used to compare the potential benefits of alternative approaches.
To inform adoption decisions, the TSE framework can be used to compare the current state with a post-intervention future state. The TSE framework is currently being piloted by WHO and PATH to understand where it can add most value. This breadth of perspective requires greater collaboration across more stakeholders, but can result in greater efficiency in the development and delivery of new interventions.

Influence of the human microbiome

Recent data have demonstrated the profound influence of microbiomes on immune responses. Microbiomes from different locations (e.g. nasal tract, gut, vagina) vary in composition. In addition, microbiomes can vary according to age and geographic background of an individual, suggesting they may contribute to differences in vaccine responses. Microbiomes have been implicated

in nutritional uptake as well as control of inflammation, and interactions between the host and microbiome are bidirectional, thus offering insights into pathogenesis as well as opportunities for intervention. In some cases, pathogens exploit the microbiome to colonize hosts. Studies of the nasopharyngeal microbiome have demonstrated that external perturbations, such as viral infections or vaccines, can promote alterations in the composition of the microbiome. Thus, a better understanding of the relationships between changes in the microbiome and vaccine responses has great potential to lead to better vaccination strategies.

Monoclonal antibodies for passive immunization

In recent years the feasibility of identification, economical production and facile characterization of monoclonal antibodies (mAbs) that protect against infection have generated considerable interest in the use of mAbs for passive immunization. Nevertheless, significant regulatory hurdles remain, especially for rare or emerging diseases. GVIRF presenters illustrated some of the benefits as well as the challenges of mAbs and highlighted: improvements in technologies that can extend antibody half-life, thus allowing for longer intervals between dosing; the use of gene-based in vivo expression systems to allow for rapid and sustained expression of broadly-neutralizing antibodies; and some of the ethical and regulatory challenges associated with development of mAbs as an alternative to rabies immunoglobulin.

Vaccine market dynamics

Just as vaccine development is evolving, so too is our understanding of the vaccine marketplace. Demand, supply and financing are closely interconnected and their interactions can be positive (virtuous) or negative (vicious). A vicious cycle results from uncertainty in demand. Manufacturers limit their capacity investments, restricting supply and elevating prices. High prices mean poor cost–effectiveness, so funding does not materialize and demand lags. Overall, the market fails to achieve the promised health impact or profits. In contrast, in a virtuous cycle, clarity on demand leads to appropriately-sized production and lower costs. This improves value, attracts financing and stimulates demand. Growing demand leads to investment in capacity, leading to a mature market that serves more people with greater health impact.

In areas of public health interest, several mechanisms have been used to promote healthy markets and the virtuous cycle. Evidence on avertable burden of disease and cost–effectiveness can help attract financing. Product development investments, termed "push funding", can bring new suppliers to a market, increasing total supply and creating price competition. Advance market commitments, advance purchase commitments and other "pull mechanisms" serve to lower downstream risks for manufacturers and align supply and demand. Demand forecasts can lower risks for manufacturers by allowing them to appropriately size production and maximize efficiency, thereby lowering costs. Pooled procurement, for example through UNICEF or the PAHO Revolving Fund, consolidates demand and streamlines procurement. Recent events, however, such as the consolidation of the vaccine industry, and an increasing number of vaccine stockouts, are potential indicators of market fragility. Healthy markets, which sustainably meet the needs of manufacturers, purchasers and consumers, and provide incentive for innovation while maximizing health benefits, remain an ambitious objective.

Persistent and new challenges

Choosing intervention strategies and vaccine targets

In the initial plenary session recounting updates on progress against HIV, malaria and TB, several themes in vaccine development were identified that recurred in other sessions throughout the GVIRF. The first theme was the importance of identifying a specific target indication for particular vaccines. Doing so informs not only the clinical trial end-points, choice of assays and go/no go criteria, but also the desired vaccine characteristics, which in turn can inform upstream research and development efforts, and the utility of including a vaccine as part of an integrated disease control strategy. As was pointed out for TB, there may be multiple outcomes of interest, e.g. prevention of infection, prevention of primary disease or prevention of recurrent disease. For malaria, outcomes of interest may include prevention of infection, prevention of disease and interruption or prevention of transmission. Different vaccines may be required to achieve these different outcomes. With respect to HIV prevention,

diverse interventions have already been identified (e.g. adult male medical circumcision, treatment and pre-exposure prophylaxis), and thus, as was demonstrated in a recent modelling study, an opportunity exists to combine an HIV vaccine (even one with modest efficacy and modest population coverage) with these other interventions to improve the overall rate of prevention.

Down-selecting among candidates

Given the overall attrition rate in the vaccine development pipeline and the associated costs, the ability to down select efficiently to choose the most promising candidates for advancement was also identified as a recurrent theme. In some cases (e.g. TB) standardized animal models are lacking or if available, have uncertain predictive power to identify candidates likely to have the desired product characteristics in humans. In contrast, the use of human challenge models employing well-characterized strains (e.g. for malaria) is being investigated for their ability to provide relevant insights and predict responses in small groups to allow for appropriate down selection of candidates prior to launching large-scale, labour intensive, and costly field trials.

More shots on goal

Another recurring theme was the importance of maintaining a robust portfolio of vaccine candidates. Given the attrition rates of candidate vaccines, the probability of success in developing a vaccine for any given disease is likely to be greater if there are more diverse candidates available for development. Advancing candidates into clinical studies is an important step; when designed and conducted appropriately, clinical trials provide significant learning opportunities to inform vaccine research and development, even when a candidate may fail to achieve its original objectives. If every candidate has to be taken completely through phase III trials, however, the costs can be prohibitive. Thus, the importance of predictive preclinical or early clinical studies to predict later stage success becomes critical, and careful attention must be devoted to developing and validating such assays, systems and models.

Emerging infectious diseases

Over the past few years, emerging infectious disease threats have been a prominent theme on the global public health agenda. The epidemics of Ebola, Zika and the growing threat from pathogens resistant to current antibiotics, pose major challenges to public health, and raise expectations for vaccine-based interventions. In response, WHO launched an effort to develop an R&D Blueprint for priority diseases for which medical countermeasures currently are lacking. The development and implementation of this roadmap will build on multiple partner efforts. The blueprint entails five workstreams, one of which is the prioritization of pathogens. Others address the development of platform technologies, research and development roadmaps, governance and coordination as well as financing options.

The Ebola epidemic also revealed deficiencies in regulatory preparedness. While many countries today have clinical trial legislation in place and follow International Council for Harmonization guidelines, specific measures for public health emergencies are often lacking. These are urgently needed to give regulators a framework within which to operate and convey acceptable levels of flexibility in an emergency situation. Regional harmonization and collaboration, such as promoted by AVAREF, need to be further developed. In addition, to insure developers against undue financial risks, a sustainable market for vaccines developed against emerging disease threats is needed.

Antimicrobial resistance

As pointed out by speakers in a workshop at the GVIRF, the emergence and spread of antimicrobial resistance (AMR) not only limits effective treatment options for significant infectious diseases, but also imposes substantial economic costs on health care systems. As a result, various public health agencies have developed comprehensive response strategies. Licensed vaccines already play an important role by preventing both bacterial and viral illness that might otherwise lead to consumption of antibiotics. Presenters in the workshop reviewed the current status of vaccine development efforts against methicillin-resistant *Staphylococcus aureus (MRSA)*, antibiotic-resistant Neisseria gonorrhoeae and hospital-acquired antibiotic-resistant bacterial infections. In addition, considerable discussion took place in other sessions around other pathogens, such as *Clostridium difficile*, X/MDR-TB and malaria. A key message that emerged from these discussions was the important role that effective vaccines can play not only in preventing emergence but also spread of AMR, thereby preserving the current therapeutic armamentarium. Such vaccines would also be expected to have substantial economic impact. For vaccines in development, therefore, the threat posed by AMR for a given target disease may be an important consideration in determining prioritization of effort.

Conclusion

At the midpoint of the DoV, much has remained the same in vaccine research and development. We continue to see steady progress in the development and licensure of new vaccines, and continue to build expertise in designing and deploying innovative technologies for vaccine research, development and delivery. Nevertheless, challenges persist: as noted above, HIV and TB vaccine development continues to lag, and immunization rates still fall short, as each year, 19.4 million children still do not receive the basic vaccines they need.

But much has changed, and the value of vaccines has never been more apparent. Polio is on the verge of eradication. Economic analysis has projected that each US dollar invested in vaccines in this decade saves US$ 16 in treatment costs and productivity losses. When broader economic and social benefits are included, this rises to US$ 44 saved per US dollar invested *(1)*. Each emerging health threat, first Ebola and then Zika, has triggered calls for new vaccines. Innovation is needed to meet these challenges, and to ensure that vaccines reach all those who need them most.

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II

Tracking resources invested in immunization: report on health account activities

Background

As per the Monitoring and Evaluation/Accountability (M&E/A) Framework presented to the Sixty-sixth World Health Assembly in May 2013, resources invested in immunization will be tracked and monitored on a yearly basis throughout the decade using the framework of the Organisation for Economic Co-operation and Development (OECD)/Eurostat/WHO System of Health Accounts 2011 (SHA 2011). The SHA 2011 is an effort to create a single platform for collecting and analysing all of a country's health expenditures including those for priority programmes such as immunization. Since January 2013, a total of 10 regional Health Accounts introductory training workshops have been held around the globe. These workshops have provided 99 countries with the knowledge and training required to begin their own SHA 2011 reports.

Results

Fifty-four Member States[77] have produced at least one SHA 2011 report by the end of June 2016 – up from 33 at the same period last year, representing an increase of 63% over the abovementioned period. Of these countries, two thirds *(34[78])* – up from 22 last year – have included specific information on the topic of expenditures on vaccine-preventable diseases and immunization. Besides, an additional 31 countries or areas[79] – all including information at immunization's granularity level – are currently producing their first SHA 2011.

Despite this relatively good implementation success rate, challenges remain in terms of easy access to data. Yet, only half of the countries have made their data publicly available nationally arguing the report has to be officially cleared for publication by senior management first. Moreover, the WHO Health Accounts Team is reviewing the data before international publication as some estimates have been flagged as needing further examination. As a matter of fact, findings are discussed with disease programmes at WHO and cross-checked against databases from global health initiatives such as the Gavi Alliance[80]. Sustainability wise, each year WHO convenes Health Accounts Peer Learning Meetings gathering country health accountants and policy-makers, with the goal of increasing the ownership of the data by reviewing and refining, where needed, the SHA2011 country-produced data.

The first set of disease information, including details on specific programmes such as immunization, is scheduled to be released on the WHO website[81] in June 2017.

[77] Bahrain, Belarus, Benin, Bhutan, Bolivia (Plurinational State of), Bosnia and Herzegovina, Burkina Faso, Burundi, Cambodia, Cameroon, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Egypt, Fiji, Gabon, Gambia, Ghana, Haiti, Iraq, Kazakhstan, Kenya, Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Mali, Mauritania, Mongolia, Morocco, Mozambique, Namibia, Niger, Nigeria, Paraguay, Philippines, Papua New Guinea, Sao Tome and Principe, Serbia, Seychelles, Sierra Leone, Sri Lanka, Sudan, Tajikistan, Thailand, Timor-Leste, Togo, Tunisia, Uganda, United Republic of Tanzania and Viet Nam.

[78] Benin, Burkina Faso, Burundi, Cambodia, Cameroon, Chad, Comoros, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Egypt, Gabon, Gambia, Ghana, Haiti, Kenya, Lao People's Democratic Republic, Liberia, Malawi, Mali, Mauritania, Namibia, Niger, Philippines, Sao Tome and Principe, Seychelles, Sierra Leone, Sri Lanka, Tajikistan, Togo, Tunisia, Uganda, United Republic of Tanzania and Viet Nam.

[79] Afghanistan, Armenia, Bangladesh, Botswana, Cape Verde, Chile, Colombia, Costa Rica, Dominican Republic, Ethiopia, Georgia, Guinea, Guinea Bissau, India, Kosovo, Kuwait, Kyrgyzstan, Maldives, Micronesia (Federated States of), Oman, Saudi Arabia, Senegal, South Africa, South Sudan, Suriname, Swaziland, United Arab Emirates, Uruguay, Uzbekistan, Zambia and Zimbabwe.

[80] In fact, only four countries with available immunization expenditure data are not Gavi-eligible countries: Gabon, Namibia, Seychelles and Tunisia.

[81] On the Global Health Expenditure Database, updated annually: http://www.who.int/health-accounts/ghed/en/.

III

Documenting and monitoring commitments for immunization: the partnership for maternal, newborn and child health 2015 accountability report

No report submitted in 2016.

IV

Case studies and report from the GAVI CSOs constituency

CIVIL SOCIETY CASE STUDIES

Gavi CSO Constituency
for Immunisation and Stronger Health Systems
Helping to reach Every Child with Immunisation and Health Services

I. AFGHANISTAN: CIVIL SOCIETY LEADERSHIP KEY TO NATIONAL SUCCESS IN IMMUNIZATION COVERAGE

In Afghanistan, civil society organizations (CSOs) are major players in the implementation of the Ministry of Public Health's Basic Package of Health Services (BPHS). The BPHS contracts out to CSOs for the bulk of health services provision, including immunization in all 34 provinces in the country. This arrangement of relying on CSOs to take on immunization and health service delivery has been key to success for a country ravaged by war, and is an important and unique example of an effective partnership between the government and CSOs.

In 2012, the Afghanistan government declared emergency status for polio eradication, a landmark decision that mobilized resources to curtail the disease. The Ministry of Public Health initiated a successful "polio eradication is my responsibility" campaign, asking every Afghan to support this important issue. In 2014, the government revised its National Emergency Action Plan, concentrating efforts in the Southern Region's highly endemic areas, with a focus on district-level activities.

For the polio eradication campaign, deepened civil society involvement was central to ensure access to children in times of conflict in the Southern region. District polio teams worked with CSOs to gain access to areas occupied by armed opposition groups. Equally important, CSOs have been critical partners in the actual delivery of vaccines and other health services. HealthNet TPO-- one of the largest health-focused NGOs in the country, and a key partner of the Ministry of Public Health-- runs the health system in three provinces using an approach grounded in community participation, support and ownership. Using its network of over 100 facilities and thousands of community volunteers, it participates in polio eradication campaigns, vaccinating children through fixed centres, outreach and mobile services. HealthNet TPO also piloted a public-private partnership approach to deliver vaccines alongside reproductive health services in Uruzgan province, proving it is feasible to reach insecure and difficult-to-access villages. The initiative, supported by the government and Gavi, has expanded to other provinces, including Helmand in the south. The success of these activities has bolstered acceptance of polio vaccination. The dedicated efforts of community health workers, especially female vaccinators who regularly visit households, have played a key role in pushing polio out of the Southern Region.

Despite these successes, the country still faces many challenges. Sadly, Afghanistan remains one of only two countries in the world, along with Pakistan, that has not yet eradicated polio. New cases have emerged in the Eastern Region near the border with Pakistan where several vaccinators, mostly female, have been attacked and some killed.

Synchronized polio eradication campaigns between Afghanistan and Pakistan have been an encouraging sign that political commitment to eradicating polio remains high. The role of CSOs in educating parents, traditional and community leaders, and government officials on the benefits of the polio vaccine and other vaccines in preventing death and disease is more critical than ever.

Sources: "Cornering polio in Afghanistan" special article for the Vancouver Sun, 1 January 2014, by Dr. Abdul Majeed Siddiqi, Chair, HealthNet TPO Afghanistan and Pakistan; "Pakistan and Afghanistan join forces to wipe out polio" article in The Guardian, 5 April 2016; additional input from Dr. Muhammad Naseem, Managing Director, HealthNet TPO Afghanistan, July 2016

II. CHAD: INNOVATIVE ACCOUNTABILITY APPROACH THROUGH REGIONAL COMMUNITY HEALTH OBSERVATORIES

Established in September 2013, the "Plateforme des Organisations de la Société civile pour le Soutien à la Vaccination et à l'Immunisation au Tchad" (POSVIT), or the national civil society immunization and health systems platform, is a success of the Gavi CSO Constituency Country Platforms project. POSVIT operates in six of 23 regions in the country and serves a critical function in immunization leadership and

accountability through a range of activities implemented by member civil society organizations (CSOs).

The main strategy used by POSVIT to ensure accountability is the establishment of Regional Community Health Observatories, which have been established in four regions of the country - Guera, Logone Occidental, Mayo Kebbi Est (East) and Mayo Kebbi Ouest (West). The main activities devolved to the regional community health observatories are to inform, sensitize and raise awareness of communities about their right to health by:

1. Collecting information from health service providers, patients and the public about issues, concerns and gaps in health services at the local level. Areas of information include issues affecting access to services; the efficiency of structures involved in quantification, procurement and delivery of drugs, vaccines and consumables; the effectiveness of implementation and enforcement of certain health policies and measures; issues affecting quality of care such as stigma, discrimination and equity.
2. Producing reports on access to health care and services, with a focus on the availability of services and inputs (vaccines), the availability of health personnel, and the sufficiency and functionality of equipment at facilities, especially related to the vaccine cold chain. Compliance with current provisions governing the cost and quality of services is also tracked and reported on.
3. Sharing reports with stakeholders and decision makers to help resolve issues.

The Observatories are meant to serve as structures for educating communities about immunization, health more broadly, and their rights, as well as for communities to take greater ownership of health services. The Observatories also help to identify needed improvements and solutions to bottlenecks and gaps in the provision of immunisation and health services. They are meant to bring communities, health officials and political authorities closer together toward a common goal of better health for all.

While Regional Community Health Observatories are still in their infancy, an evaluation conducted in late 2015 by the Ministry of Planning shows that POSVIT's capacity in immunization and health has been strengthened and overall, the concept of the Regional Community Health Observatories has the potential to support significant improvements in the efficiency and effectiveness of the national immunization and health program.

Source: Responses from immunization stakeholders in Chad to the Gavi CSO questionnaire used in the preparation of the 2016 Civil Society independent submission to the 2016 GVAP Secretariat report

III. INDIA: COMMUNITY ACCOUNTABILITY AND OWNERSHIP TO STRENGTHEN ROUTINE IMMUNIZATION

In recent decades, healthcare services have measurably improved in India, however, significant challenges remain, especially in rural parts of the country. Access to better healthcare facilities and immunisation services remain major concerns in the rural areas of the country. One approach used by communities to monitor the immunization status of children has been through the use of USAID's "My Village My Home" (MVMH) tool. Developed in India, the MVMH tool is essentially a large chart that is posted on the wall of a health center or in a routine immunization site. Community health workers record on the chart the names and identifying information for all newborns in a particular village. The dates of vaccinations for each child are included and used to help health workers explain to mothers the benefits of each vaccine and the importance of keeping to the immunization schedule. The chart is available for the community as a whole so that at-a-glance, anyone from the community can see the immunization status of all children in the village.

In the states of Jharkhand, Rajasthan and Uttar Pradesh, member civil society organizations (CSOs) of the Alliance for Immunization in India (AII)—the Gavi CSO supported platform-- have adopted the tool. These CSOs were trained on the use of the tool during workshops on routine immunization organized by AII.

One rural-based community organization, the Rajasthan Catholic Diocesan Social Service Society (RCDSS) has been working in the district of Ajmer to mobilize communities around routine immunization. RCDSS used the tool in 15 Aanganwadi village centers within the blocks of Arai, Jawaja and Srinagar in Ajmer district. These government-run centers provide basic maternal and child health services and are staffed by Aanganwadi

workers who are chosen by the community. RCDSS teamed up with the Aanganwadi centers and workers and used the tool to track the numbers of children who were regularly vaccinated, those who were due for vaccines, and those who were not vaccinated. This information allowed RCDSS to do the necessary follow up with those in need of immunizations; carry out further sensitizations; and ensure that communities and individualsget back on track. In one year alone, RCDSS has seen a significant change – the percentage of children who have completed their regular immunizations has increased from 76.16% in 2014 to 90.95% in 2015.

Overall, AII member organisations that have used the tool have cited similar encouraging results. Through the use of the MVMH tool, CSOs can mobilize communities more effectively to increase immunization demand, and communities are able to hold themselves accountable for their children's health. Communities have gained greater ownership of the health status of their families and neighbors.

Sources: Alliance for Immunization in India (AII) booklet; USAID/MCHIP "My Village My Home: A Tool to Optimize Immunization Coverage – Guidance Note for Using the MVMH Tool" June 2014; CSO case study on AII website "A Tool Which Can Ensure Access to Better Health".

IV. NIGERIA: COMMUNITY ACCOUNTABILITY AND OWNERSHIP TO STRENGTHEN ROUTINE IMMUNIZATION

Nigeria is the largest country in Africa, both in terms of population and the economy, with a consistent economic growth rate of over 7% per annum over the decade ending in 2014. However, the country's economic growth has not translated into improved living standards for much of the population. High unemployment has limited socio-economic development, with detrimental consequences for the nation's health sector. These development challenges have affected coverage and equity in the provision of immunization services for Nigerian communities. In addition, the lack of political will and commitment, paucity of funds, poor community participation and limited scaling-up of cost effective interventions have further challenged efforts to improve immunization coverage.

Civil Society in Malaria Control, Immunization and Nutrition (ACOMIN) serves as the Secretariat of the national Civil Society Platform on Health (CSPH) and has helped to coordinate efforts among CSOs working in the health sector, with immunization as an entry point. CSPH member organisations play various roles in the health sector at the community level in states across Nigeria. These roles include: 1) advocating for supply and availability of vaccines; 2) advocating for and supporting sufficient numbers of skilled personnel in the community; 3) increasing knowledge and awareness of immunization; and 4) promoting innovation and ownership of health interventions at the community level.

In surveys carried out from 2013 to 2015, it was found that knowledge-building activities run by CSOs have led to increased awareness of vaccine preventable diseases among frontline health care workers, nursing mothers and community members in hard-to-reach areas of the country. This greater awareness has helped to strengthen community participation and ownership of immunization efforts and to increase vaccine uptake. These CSO-led activities complement government efforts and help to bridge the service-availability gap.

CSPH member organizations use the evidence of what works in communities to hold the government accountable for investments in the immunization program and health systems. These accountability efforts have included stimulating and leading debates for better government involvement in immunization activities at all levels; advocating for solutions to identified problems in the vaccine supply chain; and highlighting equity issues related to immunization delivery. This has led to increased coverage and equity in immunization and improved health care systems at the state level.

However, as with any organization, successes have not come without challenges. Lack of funding for CSOs to expand their educational activities to cover the entire country has left communities in hard-to-reach and conflict areas with poor knowledge of the benefits of immunization. This, coupled with difficulties in the government-managed vaccine delivery logistics system, has continued to hinder progress to get vaccines to these communities. For example, Immunization Plus Days held in January 2015 at Adamawa state in North-Eastern Nigeria were successful in most areas, but not without issues. At Gella, Hajjia Bintu Konto, the CSOs reported that insurgencies and persistent communal clashes often hampered the delivery of vaccines to health facilities.

Despite the challenges, CSPH and its members continue to do what they can to meet the need for immunization in communities. Developing partnerships with immunization-related government agencies, using evidence to advocate effectively and continuing to raise awareness based on best practices have been important activities to ensure that the immunization program stays accountable to the people it is intended to serve.

Sources: Adapted from ACOMIN article "Immunization and civil society in Nigeria: a challenge of scale" by Njoku Chinwendu.A. posted on Vaccineworks.org; additional input from Ayo Ipinmoye, chair of ACOMIN, July 2016

V. UGANDA: COMMUNITY LEADERSHIP AND ACTION TO INCREASE IMMUNIZATION COVERAGE

In Uganda, decades of budget and staffing shortfalls, coupled with the challenges of reaching the country's remote rural communities, have made national immunization efforts difficult. Faced with those challenges, the Malaria and Childhood Illnesses NGO Secretariat (MACIS), a national network of over 281 health-focused civil society organizations (CSOs) supported by the Gavi CSO country platforms project, is taking a leadership role by extending the reach of the national immunization program and mobilizing areas underserved by the national campaign, while also informing national immunization policy. MACIS' wide civil society network links vaccinators, advocators and reporters for better coordination, coverage, and policy advocacy.

The model used by MACIS is fully grounded in the community. After first identifying the CSOs in the best position to help, MACIS provides training to CSO focal persons who in turn train community health volunteers to boost their skills in data collection, advocacy and report writing. MACIS, through its partners, then establishes these volunteers as the first link in the information chain, and to immunization and health services. Through community outreach efforts, each volunteer links up with hundreds of children each month, ensuring that no child is missed. At the same time, volunteers collect critical information on immunization gaps, staffing shortages and supply problems and then pass that information on to one of the 103 District Immunization Champions also identified and trained by MACIS. The Champions' role is not only to gather and process the information they receive, but to engage government District Health Officers on key issues within their mandate and to task them to report directly to national policy makers. Realizing the important role of the Champions, the District Health Officers now include them in planning and review exercises.

Passed on from the district level, information gathered locally then reaches the regional level through what are called Regional Nodes. These Nodes receive reports from all of the districts in their region, addressing any gaps with government health officials. At this point, information is reviewed to see what goes to the national level and what requires intervention by the Regional Nodes.

National-level MACIS representatives are the last link in the information chain. Equipped with monthly reports passed on from the Regional Nodes, MACIS meets regularly with government health officials to inform national policy. And while challenges around timely access to information still exist, the community-to-national information, reporting and accountability flow is showing good results. MACIS reports that overall immunization coverage in areas where they operate has increased by over 20% on average and there have been more improvements in coordination between CSOs and government structures in terms of information sharing, social mobilization, accountability, transparency, responsiveness and reduction in duplication of activities.

To ensure long-term sustainability, MACIS collaborates with the national immunization effort, working closely with district level health officials and advocating for increased immunization funding at the national level. As a sign of the success of that effort, MACIS was included in the 2015 budget for the national polio immunization campaign, as the government recognized the valuable role that civil society plays in mobilizing local communities and providing oversight on service delivery at all levels.

Sources: Catholic Relief Services, USA, June 2015 publication; additional inputs by Fred Chemuko, Regional Node coordinator for Eastern Uganda and National Chair of MACIS Regional Nodes Forumt

GAVI CSO CONSTITUENCY STAKEHOLDERS' REPORT

Gavi CSO Constituency
for Immunisation and Stronger Health Systems
Helping to reach Every Child with Immunisation and Health Services

July 2016

I. INTRODUCTION

Despite progress made over the first half of the Decade of Vaccines (2010–2015), the 2015 Assessment Report of the Global Vaccine Action Plan (GVAP) by the Strategic Advisory Group of Experts on Immunization (SAGE) concluded that achievements have not been consistent across countries and for all vaccines. The SAGE cited inadequate funding and weak accountability systems as the main reasons for progress being off track. Reflecting on the contributions of civil society to immunization efforts at the country level as reported by CSOs and development partners who fund CSO activities, a similar picture emerges. Funding for civil society is more often insufficient and/or inflexible to cover the need, leading to stifled innovation, overstretched staff, lack of consistent monitoring of activities and poor documentation. At the same time, the information and stories that do emerge, including the example in the 2015 SAGE assessment report on community leadership in India, are encouraging. These examples further demonstrate the need to view and support civil society as an equal and valued partner in immunization efforts at all levels to ensure that every child is reached.

In keeping with the leadership and accountability theme of the 2016 GVAP Secretariat report, the independent submission from the Gavi CSO Constituency and Steering Committee focuses on the role that civil society organizations (CSOs) play in ensuring that leadership and accountability are in place at all levels. Aligning with the focus countries chosen by SAGE for the 2016 assessment report, this year's civil society report looks at 10 countries from three WHO regions:

- African Region – Chad, Democratic Republic of the Congo (DRC), Ethiopia, Kenya, Nigeria and Uganda
- Eastern Mediterranean Region – Afghanistan and Pakistan*
- South-East Asia Region – India and Indonesia

The Gavi CSO Constituency has prepared an independent civil society report since 2014 for inclusion in the annual GVAP Secretariat report. The purpose of this year's independent civil society report is to:

1. Share examples of strategies used by CSOs in ensuring leadership and accountability from the local to the global level
2. Highlight the results of these leadership and accountability strategies
3. Describe the extent to which civil society capacity has been strengthened in order to respond to and sustain participation in leadership and accountability processes for immunization- and health-system strengthening and immunization equity, etc.

II. METHODOLOGY

Similar to the 2014 and 2015 independent civil society submissions to the annual GVAP Secretariat reports, the Gavi CSO Constituency Coordinator and the 20-member Gavi CSO Steering Committee directed and oversaw the work of an external consultant who prepared this report. The consultant's work was funded by the World Health Organization Immunization, Vaccines and Biologicals (WHO/IVB) Department.

The consultant carried out a desk review of civil society documents, reports and national immunization plans pertaining to activities and strategies in 2015. The desk review was supplemented by responses from a sampling of current and former SAGE and SAGE Decade of Vaccines (DoV) working group members as well as country-level stakeholders in each of the 10 focus countries. Time zone issues between the consultant and focus countries as well as inconsistent phone network services in several countries made it quite difficult to reach individuals by phone, therefore the greater part of the information contained in this report was gathered using an email-based questionnaire.

For country-level stakeholders, 3-4 individuals in each of the 10 focus countries were asked to complete the short questionnaire. These individuals included:

* Pakistan was originally included in the group of focus countries, however, due to sensitivities between civil society and the government, it was determined that information from country stakeholders would be better placed in the main GVAP Secretariat report rather than in the civil society report.

a) one representative from the national civil society immunization platform or network; b) one national-level government representative; c) one sub-national/community-level government representative; and d) one community resource person or community leader.

The number and type of individuals to interview was determined by the Gavi CSO Steering Committee. The questionnaire was developed in English and French by the consultant and approved by the Gavi CSO Steering Committee prior to conducting the interviews.

III. LEADERSHIP AND ACCOUNTABILITY BY CIVIL SOCIETY

For the purposes of this report, leadership can be defined as civil society proactively using evidence to resolve bottlenecks and improve progress towards the achievement of results. Accountability includes the establishment and enforcement of accountability systems to measure results and hold governments, partners and civil society accountable for reaching targets. In other words, leadership is about making informed decisions and taking action while accountability focuses on monitoring the results of those decisions and actions. To achieve the GVAP goals, leadership and accountability activities are required at the sub-national, national, regional and global levels.

The Gavi CSO Constituency Steering Committee provided the following examples of civil society roles in leadership and accountability (Table 5), according to the six GVAP Strategic Objectives (SOs).

Table CSO 1: CSO roles in leadership and accountability by the GVAP SOs

SO 1 All countries commit to immunization as a priority
• Building policy consensus, disseminating policy positions based on evidence
• Enhancing public support for evidence-based immunization policies
SO 2 Individuals and communities understand the values of vaccines and demand immunization as both their right and responsibility
• Building informed public choice on immunization based on evidence
• Mobilizing and organizing to increase immunization demand and coverage
• Helping to shift social attitudes around the benefits of immunization
SO 3 The benefits of immunization are equitably extended to all people
• Promoting equity and pro-poor immunization policies
• Raising community preferences in resource allocation
• Giving voice to marginalized groups to increase access to immunization
• Facilitating community interactions with immunization services
SO 4 Strong immunization systems are an integral part of a well functioning health system
• Negotiating immunization standards and approaches
• Delivering immunization services
• Monitoring responsiveness and quality of immunization and health services
• Building health worker morale and support
SO 5 Immunization programs have sustainable access to predictable funding, quality supply and innovative technologies
• Financing immunization services where government / donor resources do not reach
• Mobilizing and organizing community co-financing schemes
• Building public accountability and transparency in raising, allocating and managing resources
SO 6 Country, regional and global research and development innovations maximize the benefits of immunization
• Implementing and using immunization-related operational research findings

IV. ROLES OF CIVIL SOCIETY IN COMPREHENSIVE MULTI-YEAR NATIONAL IMMUNIZATION PLANS

In order to understand the country-specific contexts in which civil society is working, comprehensive multi-year national immunization plans (cMYP) in effect in 2015 for the 10 focus countries were reviewed for mention of key words related to civil society's various roles:

- "civil society"
- "CSO" (civil society organization)
- "NGO" (non-governmental organization)
- "CBO" (community-based organization)
- "FBO" (faith-based organization)
- "community"

The review revealed a commonality in several types of civil society-led immunization activities. These included activities in advocacy and communications; social and community mobilization; and demand creation. Table 6 includes a summary of CSO activities that are described in national immunization plans.

Table CSO 2: Country cMYPs in effect in 2015 where civil society roles are noted

Country	cMYP timeframe	Roles of civil society organizations
African Region		
Chad	2015-2017	• Demand creation, awareness-raising / communication, community social mobilization activities
Democratic Republic of the Congo (DRC)	2015-2019	• Social mobilization, awareness-raising / vaccine promotion • Reinforce structures for community participation and local community organizations in the national program • Resource mobilization • Advocacy at the community level • Strengthen links between health services and the community
Ethiopia	2011-2015	• Community-based Vaccine-Preventable Disease (VPD) surveillance • Communication and social mobilization to increase demand for immunizations and educate communities on immunization schedules
Kenya	2011-2015	• Provision of immunization and health services via non-governmental and faith-based organizations • Increase community demand for immunizations
Nigeria	2011-2015	• Advocacy, community education and mobilization to create awareness and increase immunization demand at community level • Resource mobilization • Communication on importance of completing immunization schedules • Community surveillance
Uganda	2012-2016	• Resource mobilization, education on the value of vaccines, advocacy / communication / mobilization activities especially during periodic immunization events, such as Child Health Days and National Immunization Days • Community-based VPD surveillance
Eastern Mediterranean Region		
Afghanistan	2011-2015	• Vaccine promotion to increase coverage • Provision of immunization and primary health care services • Community mobilization and awareness raising through Information Education Communication (IEC) • Community-based Maternal and Neonatal Tetanus (MNT) surveillance

Country	cMYP timeframe	Roles of civil society organizations
Pakistan	2011-2015	• Advocacy and communications to build community awareness and demand for immunization • Provision of immunization and health services in hard-to-reach areas
South-East Asia Region		
India	2013-2017	• Advocate for policy changes and greater transparency to hold governments and other healthcare stakeholders to account • Provision of immunization services • Community education and mobilization to increase acceptance of vaccines and immunization demand through the introduction of Accredited Social Health Activists (ASHA) as community health workers • Community-based VPD surveillance and reporting
Indonesia	2015-2019	• Provision of immunization services at administrative and community levels

V. COUNTRY-LEVEL EXAMPLES OF LEADERSHIP AND ACCOUNTABILITY STRATEGIES

This section includes examples provided by 22 country-level stakeholders from nine focus countries (excluding Pakistan) on leadership and accountability strategies, activities implemented by civil society and the results of these strategies. Country-level stakeholders were also asked to provide examples of strengthened CSO capacity in the areas of: i) communication and advocacy; ii) networking, collaboration and linkages (with government, donors, other organizations and stakeholders); iii) gender (e.g. gender equity, gender-sensitive approaches); and iv) community mobilization, participation and involvement at all levels. The examples below (Table 7) are drawn primarily from responses to the questionnaire.

Table CSO 3: Examples of Leadership Strategies by Civil Society at Country Level

Country	Leadership Examples
African Region	
Chad	The national civil society immunization and health systems platform in Chad, le Plateforme des Organisations de la Société Civile pour le Soutien à la Vaccination et à l'Immunisation au Tchad, (POSVIT), has taken a leadership role in advocacy, communications, education, and social and community mobilization. POSVIT members have carried out community dialogues (e.g. home visits by community volunteers, educational talks targeting small groups of women during their prenatal consultations); mass awareness campaigns (e.g. sermons in churches and mosques, radio programs); and advocacy targeting administrative authorities and traditional and religious leaders. As a result of these activities, rumors and prejudices about vaccines have been dispelled and cultural constraints removed, leading to greater community understanding of the benefits of vaccines and greater general acceptance of vaccination. Health center manager respondents reported that POSVIT has helped to increase immunization coverage. As evidence that the Ministry of Public Health and its decentralized structures (i.e. regional health delegations) understand the value of CSO contributions especially around demand creation, CSOs have been called upon to help during vaccination days.
DRC	CSOs carry out leadership activities in a number of areas: a) community sensitization on the benefits and importance of vaccination to help change social attitudes about immunization; b) community mobilization to increase demand for immunization and ultimately immunization coverage; c) outreach to unvaccinated or undervaccinated children and their mothers; and d) facilitating interaction between the community and immunization service providers; e) strengthening technical and managerial capacities of CSOs to improve quality of care and services for vulnerable groups in the community. CSOs participate in meetings of government decision-makers to develop key documents including standards and guidelines related to vaccination. CSOs participate in decision-making bodies and processes such as the Inter-Agency Coordination Committee, the National Steering Committee for Health Systems Strengthening, and mid-term and annual health program reviews. CSOs also participate in the planning and implementation of immunization interventions on the ground.

Country	Leadership Examples
African Region	
Ethiopia	CSOs lead in training health workers and Health Extension Workers (i.e. workers trained to deliver 16 interventions at the village level that are part of the government's Health Extension Package) on: a) immunization in practice; b) cold-chain management; c) immunization management for mid-level managers; and d) supportive supervision. These trainings also provide a forum for health workers and Health Extension Workers to share their experiences. Other CSOs, mainly faith-based NGOs, are supporting health facilities and provide immunization services directly to the community. CSOs also support routine immunization and campaigns in areas where there are no other partners supporting the national Expanded Program for Immunization (EPI). CSOs support government health offices in capacity building; delivery of vaccines and supplies; provision of immunization services; provision of technical and logistical support for strengthening routine immunization; and planning and implementation of supplementary immunization activities.
Kenya	CSOs have been involved in engaging members of Parliament to initiate a new law on immunization that more clearly defines the roles and responsibilities of the national vs country governments in immunization delivery in Kenya. As a result, the Parliamentary Health Committee drafted legislation clarifying the functions of the national vs county governments in the delivery of immunization services. CSOs have been at the forefront in enhancing the capacity of county health authorities to take charge of immunization services at the county level.
Nigeria	CSOs were instrumental in maintaining high-level political attention and commitment for the Polio Eradication Initiative (PEI). CSOs closely monitored the PEI 'commitment' dashboard to track release of counterpart funds and key indicators of political commitment, followed up on gaps highlighted by the dashboard through one-on-one engagement, organized roundtables at national and state levels to bring together key stakeholders to understand the new 'era' of polio eradication efforts in Nigeria and to create momentum towards polio-free certification. CSOs also proactively engaged national and state media to ensure editorial content reflected the new message framework and supported efforts to enhance political commitment. As a result, there was strong political support for the Polio Eradication Initiative (PEI), which was critical to Nigeria's success in achieving polio-free status.
Uganda	Using both routine data and their field findings, CSOs get involved in EPI decision-making processes at national, regional, district, health sub-district and sub-county levels, thus influencing country leadership in immunization planning, budgetary allocation and programming. As a result, the government immunization program is better informed by needs at the community level.
Eastern Mediterranean Region	
Afghanistan	As a country in crisis for many years, CSOs are at the frontline providing the majority of health services of which immunization is one of the core components. CSOs have been critical at providing immunization and health services to remote communities, refugees, border populations, and recruiting and training more female health workers. As a result of CSO activities, immunization coverage has increased.
South-East Asia Region	
India- Rajasthan	The Association for Rural Advancement through Voluntary Action and Local Involvement (ARAVALI) promotes innovations in development and serves as a link between the government and NGOs in the state of Rajasthan. In the mining district of Dholpur, the state chapter utilized the strength of Self Help Group (SHG) federations to increase immunization demand. With local NGO partners, the state chapter identified and trained Community Resource Persons among SHG federation members. Following the training, the women shared the information on the benefits of immunization with other SHG members and the information was disseminated throughout their communities. The SHG federations also started to monitor the status of immunization-related services in their SHG meeting agenda. In Rajasthan, immunization demand has increased among grassroots communities leading to higher immunization coverage.
Jharkhand	In Jharkhand, Village Health and Nutrition Day (VHND) are observed statewide as a focus day to provide a package of health services at community level where immunization is one of the most important activities. The Abhivyakti Foundation worked with the government Integrated Child Development Services (ICDS) workers, community health workers, local government Panchayati Raj Institution (PRI) leaders to develop a plan to strengthen VHNDs at community level and use them as an opportunity for mass sensitization and education on immunization. The plan also included interactive quizzes, games, shows and competitions to make the VHNDs more appealing. ICDS centers set up examination tables and screens for antenatal, postnatal and growth monitoring services in privacy. This significantly increased the turnout of pregnant and lactating mothers on VHNDs. The activities of Abhivyakti Foundation in Jharkhand around the VHNDs increased attendance of mothers and the number of children coming for immunizations three-fold. The model of VHNDs was replicated in two other districts, which now have regular VHND sessions with active involvement of local service providers to meet the increased demand from the communities.

Country	Leadership Examples
South-East Asia Region	
Indonesia	The Indonesian Pediatric Society (IPS) leads child health and immunization efforts in technical areas. The IPS Immunization Taskforce organizes regular vaccinology training for general practitioners, pediatricians and midwives to increase health professionals' skills and knowledge in immunization. IPS has published many recommendations, consensus documents and guidelines in order to help all its members give quality and equal care. These include a new recommendation for the immunization schedule, which has been updated every 2-3 years, guidelines for its members on addressing vaccine adverse events, and an immunization guideline book for child health professionals. IPS uses various media (e.g. Facebook, Twitter, website) to disseminate information and educate the public about child health and immunization issues. The Islamic Medical Association and Network of Indonesia (IMANI) takes the lead in highlighting the health interest in public policies, educating the public on the importance of immunization, its side effects vs preventable complications, herd immunity, etc., and empowering the public to support immunization program by building champions among local public figures. CSOs provide leadership by acting as agents of change in leading the community to address social barriers to immunization uptake. For example, in West Sumatra, immunizations are negatively viewed by some communities and so CSOs have worked with traditional and religious leaders to sensitize communities on their benefits. As a result of strategies used by CSOs, Universal Child Immunization (UCI) coverage has increased in West Sumatra province from 71.2% (2013) to 74.1% (2016) and no significant decrease in the number of children who are on track with their immunization schedule.

Table CSO 4: Examples of Accountability Strategies by Civil Society at Country Level

Country	Accountability Examples
African Region	
Chad	At the central level, POSVIT organized monthly meetings with the Directorate of Vaccination to account for its actions. These types of meetings are replicated at the regional level – POSVIT committees attend these consultations called Regional Action Committees chaired by the Governors. In addition, bi-annual meetings are held with POSVIT and all the technical directorates and departments of the Ministry of Public Health to take stock of CSO activities (in terms of successes and difficulties), and to build consensus for more efficiency in the field. Sessions provide an opportunity for POSVIT to make recommendations for improvement and to advocate for sufficient funding for health facilities. At the decentralized level, monthly meetings are held between members of POSVIT's regional committees and the heads of Regional Health Delegations. As a result, the population is more open and trusting of CSOs as a voice for their needs because they see the improvements. Health managers are able to make more informed decisions to address problems. Shortages of vaccine and consumables have been prevented. Monitoring of the responsiveness and quality of immunization services has improved.
DRC	CSOs hold the government accountable by engaging in advocacy with political and administrative decision makers to track the results of their commitments and to mobilize resources for immunization. CSOs also participate in monitoring and evaluation (M&E) of immunization policies and activities, and in government-led mid-term and annual reviews of immunization and health programs. As a result, certain bottlenecks in immunization delivery have been addressed.
Ethiopia	Several member CSOs of the Ethiopian Civil Society Health Forum (ESHF), the national civil society immunization and health systems platform, conducted joint planning with the government and partners and agreed on their roles and responsibilities in the implementation of the national immunization program. At the end of every year, review meetings are held during which the government, partners and implementing CSOs report on their activities. CSOs have established a sound partnership with the Federal Ministry of Health, which has resulted in Gavi funds to CSOs to support implementation of the national immunization program mainly in low coverage and hard-to-reach areas. CSOs have successfully advocated government health offices for more funding for immunization to continue EPI service delivery activities after the phase out of some CSO projects.

Country	Accountability Examples
African Region	
Kenya	Despite the fact that immunization services are free in public health facilities, immunization demand is low especially in hard-to-reach places. CSOs have been raising this with government officials and advocating for greater communication to alert the public of the policy. The government has organized more frequent immunization campaigns and called on CSOs to help get the word out and also participate in the campaigns. At the country level, CSOs have engaged county governments to address the issue of decline in immunization coverage, as well as addressing questions around stock out of vaccines. CSOs have also worked with the media to highlight some of the issues around immunization.
Nigeria	CSOs were instrumental in maintaining high-level political attention and commitment for the Polio Eradication Initiative (PEI). CSOs closely monitored the PEI 'commitment' dashboard to track release of counterpart funds and key indicators of political commitment, followed up on gaps highlighted by the dashboard through one-on-one engagement, organized roundtables at national and state levels to bring together key stakeholders to understand the new 'era' of polio eradication efforts in Nigeria and to create momentum towards polio-free certification, and proactively engaged national and state media to ensure editorial content reflected the new message framework and supported efforts to enhance political commitment. As a result, there was strong political support for the Polio Eradication Initiative (PEI), which was critical to Nigeria's success in achieving polio-free status. In addition, Routine Immunization has been scaled up and funding for immunization has increased. In addition, advocacy by CSOs propelled the government to develop an accountability framework for the PEI and Routine Immunization in Nigeria, which was considered a landmark achievement.
Uganda	Since 2013, health focused CSOs involved in immunization are organized under the Uganda Civil Society Immunization Platform (UCSIP), with coordination structures aligned alongside the Uganda National Expanded Program on Immunization (UNEPI) structures in the country, from national, to regional, district, health sub-district and sub-county levels. These structures allow CSOs and communities to participate in immunization program monitoring visits, and review meetings. Increasing CSO participation in immunization program monitoring and program review at national, regional, district, health sub-district and sub-county levels has fostered transparency around the Uganda National Expanded Program on Immunization (UNEPI) and a move towards accountability to the community and service users. Though there are still gaps, CSO participation in immunization accountability processes has taken root at different levels of management in the country. Overall, CSO involvement in EPI decision making processes, using both routine data and their field findings at national, regional, district, health sub-district and sub-county levels, has progressively nurtured community participation in the country leadership of immunization planning, budgetary allocation and programming.
Eastern Mediterranean Region	
Afghanistan	Development of micro-planning for EPI and National Immunization Days has involved many stakeholders including CSOs. CSOs have also joined regular reviews of implementation of immunization activities.
South-East Asia Region	
India- Rajasthan Delhi Haryana U.P Punjab	The Association for Rural Advancement through Voluntary Action and Local Involvement (ARAVALI) operates in the state of Rajasthan and developed a strategy to incorporate immunization into the agenda of different programs of NGOs working in the state. These programs include creating a Child Labor Free Zone, livelihood strengthening projects, and community institution building projects. For example, one NGO incorporated immunization education, awareness-raising and tracking as an activity under the Child Labor Free Zone initiative. This NGO is working with over 7000 stone worker families at the household level to track all children working in the Budhpura sandstone mining area. Due to efforts made by the NGO in partnership with local health officials, immunization coverage has increased from 30% to 65%. Government officials recognize the valuable work of ARAVALI in reaching marginalized communities with immunization and health services. ARAVALI is shedding light not only on the violations of Child Labor in mining areas, but also on the lack of immunization and basic health services for the mining families. The community-based monitoring system used by Abhivyakti Foundation like the tracking of Severe Acute Malnutrition (SAM) and Moderate Acute Malnutrition (MAM) children, using the My Village My Home Tool (for immunization status of children) and Community Score Card (for effectiveness of services in local areas) has helped to generate data and evidence which are being taken up at the block level with authorities. For example, the Community Score Card exercise in Goslidih village for Aanganwadi village health services highlighted that immunization services are poor due to lack of household visits. In meetings with authorities, service providers explained that there need to be more home visits by community-based Accredited Social Health Activist (ASHA/Sahiya) workers. As a result of community-based monitoring by the Abhivyakti Foundation, another ASHA was appointed in the Goslidih village to help cover the need for home visits for immunization outreach – immunization coverage increased.

Country	Accountability Examples
South-East Asia Region	
Indonesia	CSOs closely coordinate with national health authorities, and Provincial and District Health Offices. They hold regular meetings to report on activities and challenges, and share responsibility in monitoring for results and conducting evaluations. The Islamic Medical Association and Network of Indonesia (IMANI) encourages accountability by publicizing the National Immunization Program in all public and private health facilities and publishing a quarterly report of national immunization coverage and preventable diseases prevalence. At the provincial level in West Sumatra, a Memorandum of Understanding was signed between CSOs and the Provincial Health Office that requires CSOs to submit quarterly and annual reports to the PHO. CSOs also participate in the West Sumatra Communication Forum for Care Immunization (Forum Komunikasi Peduli Imunisasi).

Table CSO 5: Examples of Strengthened Capacity of Civil Society

	Communication & Advocacy
African Region	
Chad	Training sessions were organized by POSVIT with its members to increase knowledge of key concepts relating to vaccination (i.e. importance, types of vaccine preventable diseases, vaccination schedule for the mother and the child from 0 to 11 months); to strengthen skills in case management especially around those who are reluctant or refuse vaccinations; to improve communicate effectively information about vaccinations to communities; to show how create, implement and evaluate an advocacy strategy. Trainings were also organized for journalists on key messages around vaccination and health to be used in mass media campaigns to raise awareness and increase demand.
DRC	With support from Gavi, nearly 2925 community actors and mobilizers from 325 NGOs and CBOs working in 65 health zones were trained in communications and advocacy techniques; another 3726 community mobilizers in 50 health zones were also trained in communication for EPI targeting unvaccinated children and pregnant women.
Ethiopia	CSOs conduct advocacy and communication activities to mainstream immunization across different religions so that religious leaders will be involved in awareness-raising activities (e.g. educational talks to congregations at the end of church or mosque services). The Ethiopian Civil Society Health Forum (ECSHF) has also conducted a study on the contributions of CSOs in the national immunization program, which showcases their significant contributions in the delivery of immunization services in the country. ECSHF is using this study to make the case for continued partnership with and support by the government.
Kenya	There has been some capacity building for a number of CSOs on grassroots advocacy, which has resulted in various engagements with elected leaders. However, there is a huge gap to actually build capacity of lower level CSOs on communication and advocacy.
Nigeria	In the Polio Eradication Initiative (PEI), effective communication and advocacy improved the understanding and the commitments of all the stakeholders towards immunization, hence resolving non-compliance cases, provision of funds and mobilization of resources. The Civil Society Platform on Health (CSPH) had trained its state members on effective communication and advocacy in the Federal Capital Territory which led to the implementation of the activities around the Polio Eradication Initiative (PEI) and Routine Immunization. Health workers' interpersonal communications (IPC) skills have also improved, though more can still be done in this area because of the high attrition rate particularly in the rural areas.
Uganda	Through Gavi funding, over 25 CSOs from two out of 14 sub-regions of the country have been trained in advocacy and communication skills for strategic immunization advocacy and negotiations.

Communication & Advocacy	
South-East Asia Region	
India- Rajasthan Jharkhand	Through advocacy and communication activities by ARAVALI, a greater number of NGOs associated with ARAVALI in Rajasthan are now working in immunization and have integrated it into their existing programmes. NGOs understand the importance of timely and full immunization coverage for saving their future generations and reducing expenses on health. Earlier many NGOs did not consider human capital and health as an important element in livelihood programming. Now they are able to articulate the economic impact of immunizations. Community volunteers of Abhivyakti Foundation (AF) working in Pipratol village in Barwan panchayat of Deoghar district, Jharkhand state used a communication strategy targeting the elderly of the village and parents to motivate them to immunize their children. The village is very hard to reach and did not receive any immunization services for two decades. In that time, the community had become resistant to immunizing their children due to lack of information and knowledge of the benefits of immunization. AF volunteers used the immunization mark on the elderly as an entry point to have a conversation about immunizations and eventually won their support. However, the nearest immunization point was 1.5 km away so the village decided to ask the government health department to conduct a health outreach camp in the village. The first camp was organized in the village after two decades and was linked to the nearest Aanganwadi village health center for regular immunization services for their children.
Indonesia	The Islamic Medical Association and Network of Indonesia (IMANI) produced a book in 2014 on immunization called 'Bunga Rampai Kedokteran Islam: Kontroversi Imunisasi' (Anthology of Islamic Medicine: Immunization Controversy), which has become an effective education tool. The book is endorsed by the Ministry of Health and the Indonesian Pediatric Society. IMANI conducted a series of talks on immunization on roadshows throughout the country and is also actively educating the public via television, radio and social media.
Networking, Collaboration & Linkages	
African Region	
Chad	Before 2013, CSOs working on immunization were uncoordinated, but now over 100 CSOs are united around a national umbrella organization, POSVIT. Three members of POSVIT took part in an international training organized with the support of Gavi. This provided an opportunity for networking with other organizations working on immunization to share, learn and bring back lessons and experiences to POSVIT members.
DRC	With support from the Gavi CSO Constituency Country Platforms project, CSOs are grouped around a platform called "Coalition des OSC Mavimpi na Magwele" (COMAMA), which is a network of over 10 CSOs operating in four provinces of the country.
Ethiopia	Through the Ethiopian Civil Society Health Forum managed by the Consortium of Christian Relief and Development Associations (CCRDA), CSOs working on immunization meet regularly to share their experiences, get updates on immunization-related policy issues, and participate in immunization capacity-building trainings.
Kenya	CSOs have come together under the national civil society immunization and health systems platform hosted by the Health NGOs Network of Kenya (HENNET). At the sub-national level there are some good efforts by CSOs to self-organize, with one county in Kenya (Kajiado) having recently launched a health CSOs website. There is however still some work to be done to make immunization work a priority among CSOs at the community level.
Nigeria	The Association of Civil Society Organizations for Malaria, Immunization and Nutrition (ACOMIN) serves as the national civil society platform for immunization and health systems bringing together 800 CSOs across the country. Regular stakeholders meetings, dialogues, consultations and networking with civil society networks working on HIV/AIDS, TB and primary health care, have improved immunization processes and programs in Nigeria as all have come together around a common goal around quality and equitable health for all.
Uganda	Through the Uganda Civil Society Immunization Platform (UCSIP) established in 2013, over 290 CSOs (big and small) have been brought together for strategic collaboration, linkages and networking on immunization programming, and joint actions such as resource mobilization advocacy.
South-East Asia Region	
Indonesia	CSOs have a system of collaboration with the Provincial and District Health Offices (PHO/DHO) and are included as a member of the PHO/DHO Communication Forum. The IPS Immunization Taskforce collaborates with the local health officers to monitor vaccine adverse events and with the Ministry of Health on implementation of the Polio Eradication Program, as well as the measles and rubella eradication campaign. Overall, IPS collaborates with the government, other professional organizations, and NGOs to promote the Sustainable Development Goals (SDGs) and coordinates with local government to make complete immunization status a prerequisite for a child to be enrolled in a public school. This policy had been active in Jakarta and several other provinces in Indonesia.

Gender	
African Region	
Chad	Through the inclusion and promotion of several women's organizations as members in POSVIT, the broader POSVIT membership has been able to learn about gender aspects of immunization (e.g. gender-sensitive approaches, gender norms affecting immunization uptake and delivery).
South-East Asia Region	
Indonesia	The IPS Immunization Taskforce is led by a female pediatrician. There are growing numbers of IPS local branch that are led by female pediatricians with equal rights, responsibility, and authority as male pediatricians. Women run the majority of CSOs that support the national immunization program.
Community Mobilization, Participation & Involvement	
African Region	
Chad	CSOs are increasingly visible on the ground and equipped with accurate information and effective communication skills. They have the ability to organize community dialogues and educational talks to correct misperceptions and hesitancies about vaccines, secure the support of radio to disseminate messages, and find unimmunized and under-immunized children. POSVIT participates in joint assessments and in the development of the national EPI plan.
DRC	Community leaders have developed a program in health zones of local branches and community outreach units to sustain involvement of and ownership by communities in the fight against vaccine preventable diseases. In the program, administrative and political authorities and community leaders, such as village chiefs and religious leaders, are mobilized in leadership and accountability processes. The participation and involvement of community volunteers in educating households and finding unvaccinated or under-vaccinated children have increased immunization coverage.
Ethiopia	CSOs conduct community mobilization activities to improve demand for immunization and to increase community support for immunization service delivery. CSOs are represented and participate in national level taskforces and policy dialogues on immunization.
Nigeria	Traditional and religious leaders, and Ward Development Committees are now immunization-friendly as a result of community mobilization efforts of CSOs. Communities are also involved, for example, as Village Community Mobilizers (VCMs).
Eastern Mediterranean Region	
Afghanistan	CSOs involve religious leaders and community elders in community mobilization efforts.
South-East Asia Region	
Indonesia	CSOs are effective at mobilizing the community to participate in the EPI program due to their close relation with the community. The IPS Immunization Taskforce created the "FAQ forum" on immunization which is on the IPS website. People who want to know more about immunization can post their questions on the forum and a member of the Taskforce will answer them. This has encouraged community participation and involvement in building their knowledge of immunization. Community volunteers supporting the local health post (i.e. Posyandu) play important roles in educating and empowering the public. Members of the Islamic Medical Association and Network of Indonesia (IMANI) are encouraged to become known figures in their local area so that they can be positive influences and a source for immunization and health-related information.

VI. COUNTRY-LEVEL CHALLENGES

Questionnaire responses reveal a range of continuing challenges faced by civil society in carrying out activities at the country level. Although progress has been made as described in the Tables above, recurring issues such as insufficient funding for CSOs, and coordination and capacity weaknesses among CSOs, continue to hinder the scale up and reach of CSO activities to support immunization efforts. Responses by country are included below.

AFRICAN REGION

Chad –

- Existence of isolated CSOs who are not part of the national platform, POSVIT, therefore efforts between POSVIT members and these isolated CSOs are uncoordinated and less effective – need support to expand the platform across the entire country

to ensure collaboration across all CSOs working on immunization.
- Lack of funding and support from the Ministry of Public Health for CSOs to document their activities and feed CSO information and data into the national health information system – need to strengthen the existing collaboration between CSOs and the Ministry to develop data collection tools and a system to harmonize CSO data with the national system; need to build CSO skills in data collection and documentation; need better supervision, monitoring and evaluation of CSO activities.
- CSOs not well integrated in the health system despite existence of a national community health policy – need continued political commitment to implement the policy and support for CSOs to build capacity in new health systems areas.
- Lack of well-defined CSO activities in the national immunization plan with funding to implement – need clearer identification and description of CSO activities in the national plan with accompanying funding.

DRC –

- Weak mobilization of financial resources to support the activities of CSOs.
- Weak technical and managerial capacity in project management and financial resources management.
- Difficulties in reaching children and unvaccinated pregnant women with services in hard-to-reach areas, and sustaining health interventions.
- Weak motivation of CSOs working on the ground.
- Low quality of information generated by CSOs.

Ethiopia –

- Weak capacity and coordination among CSOs.
- Limited enabling environment for civil society.
- Lack of funding for CSOs.
- Lack of strong media serving in an accountability role.

SOUTH-EAST ASIA REGION

India –

- Lack of knowledge about the introduction of new vaccines.
- Lack of understanding and capacity to monitor issues related to the vaccine cold chain and logistics.

Kenya –

- Need support and funding for capacity-building of CSOs especially at the community level to:
- realize the importance of immunization work
- develop and implement community-based immunization programs
- improve skills in immunization advocacy around policy formulation
- improve and expand community education and engagement for increased community demand.
- Lack of community-based monitoring

Nigeria –

- Weak capacity of CSOs in the areas of proposal writing, M&E, project and financial management, training for community-based organizations on advocacy, communications and social mobilization, operational research to evaluate impacts and outcomes of CSO activities.
- Lack of adequate funding of the CSOs.
- Lack of accountability tools especially around budget tracking and monitoring.

Uganda –

- Fragile acceptance of CSOs as a valuable contributor and partner in decision-making processes; some still view CSOs with suspicion and mistrust and are more comfortable having CSO activities continue to focus on social mobilization and community sensitization.
- Weak skills of CSOs in advocacy and negotiating.

EASTERN MEDITERRANEAN REGION

Afghanistan –

- Lack of training of more vaccinators and cold-chain staff.
- Lack of effective and regular supervision.
- Insecurity which affects outreach, mobile and supplementary activities.
- Lack of documentation, manuals and tools on how to build capacity of grassroots in immunization education – need to develop a capacity-building manual in order to standardize the process.
- Insufficient number of Community Resource Persons on immunization – need to reach out to more

CBOs and use their presence to build a network of Community Resource Person in each district.
- Low capacity of CSOs to conduct resource mobilization.
- Limited coordination at the state level between the government health system and CSOs.

Indonesia –

- Language barrier – there is an urgent need to translate policies and recommendations into lay terms in order to make it understandable for the common people.
- Weak capacity of some CSOs in organizing and community empowerment for Routine Immunization.
- Limited funding.
- Ability to penetrate certain faith-based groups who strongly oppose immunization and actively influence others.
- Lack of data from the government to inform programming.
- Supply constraints and shortages.
- Low education level of the public and very low government subsidy for immunization (only for 8 types of vaccines).
- Insufficient human resources to carry out the national strategy on immunization across a country made up of thousands of islands.

VII. PERSPECTIVES FROM CURRENT AND FORMER SAGE MEMBERS

A number of SAGE members responded to a short questionnaire to understand their perspectives of the contributions by civil society at the global, regional and national levels. Questions were grouped around four areas: 1) access to information on civil society immunization activities; 2) civil society as a partner in regional and national immunization plans; 3) strategies used by CSOs in ensuring leadership and accountability; and 4) civil society capacity in leadership and accountability.

Access to CSO information:

There was agreement that at the global level, information on CSOs is fairly easy to access through online sources such as the Gavi website and websites of CSOs, from CSO representatives on the Gavi Board and working groups, and at international conferences. At the country level, information can be accessed using a more proactive approach – through country visits, knowing who the CSOs are and reaching out to them, and through country offices of technical and donor partners.

Civil society as a partner:

At the regional level, it was noted that Regional Vaccine Action Plans (RVAPs) acknowledge that CSOs are working in countries, but lack specificity of what they are actually doing. At the country level (e.g. Ghana, Nigeria), civil society were part of the plans, but it is unclear as to how active they are and how much of a role they have in changing, shaping, influencing and challenging. On the other hand, one response noted that CSOs seem to be "brought in" to play assigned roles by the government, but in fact have minimal direct input into more content-focused discussions.

Strategies used by CSOs:

Regarding global-level leadership, CSO representatives on SAGE and the Gavi Programme and Policy Committee (PPC) have been helpful. Leadership of many of the major international NGOs comes to the biannual SAGE meetings where they interact with other SAGE members. Relations have been established for some to the extent that one response explained that some NGO leaders have reached out to individual SAGE members when they want to know what SAGE is likely to recommend on a given topic or when they have suggestions or concerns about one or more vaccine programs.

At the country level, one response described that while CSOs are helpful in disseminating simple public health messages (e.g. increase immunization coverage), they lack a more medium- and long-term understanding of the issues and the ability to insert themselves or participate in negotiations – i.e. who will pay; should immunization be part of the national health package; how much will it cost; who is responsible for different things at different stages; etc. The respondent was concerned that perhaps CSOs are used more tokenistically for campaigns, new agendas and their roll out, and that there is still a lack of trust of CSOs because CSOs cannot be controlled and sometimes veer off government or donor messages and/or oppose campaigns altogether – sometimes among certain faith-based organizations.

One example given of CSO accountability efforts is the work of Médecins Sans Frontières (MSF) and its

campaign for lower vaccine prices. MSF leadership has been vigorous in demanding that all global partners work to help decrease the price of pneumococcal conjugate vaccines to make them more affordable and accessible.

Civil society capacity:

In terms of strengthening civil society capacity to contribute to GVAP, RVAPs and national immunization plan implementation, responses varied. One response emphasized the value of having CSO representatives on SAGE, Regional Immunization Technical Advisory Groups (RITAGs) and National Immunization Technical Advisory Groups (NITAGs), and the need to find opportunities at various venues such as conferences and meetings to encourage civil society engagement – perhaps using examples from strong civil society engagement at HIV conferences. Other responses discussed the need for governments and donors to be clearer and more direct on their expectations of CSOs and to encourage CSOs to be active and visible when things are going well and not just when there is an outbreak, disease upsurge or a vaccine shortage. Also mentioned was the need to support CSOs to develop or adjust their implementation plans based on the latest data and in line with best practices in the field as well as globally (i.e. SAGE) recommendations, all within the cultural and community context in which they are working.

VIII. A LOOK BACK: CIVIL SOCIETY RECOMMENDATIONS FROM 2014 AND 2015

In 2014, the Gavi CSO Constituency and Steering Committee independent submission included the following recommendations. Civil society proposed that the first four recommendations should be tracked and monitored annually as part of the GVAP monitoring process.

2014 recommendations

1. *National and regional immunization plans, programmes and strategies should clearly articulate civil society's role and expected contributions to their implementation and monitoring*
2. *Memorandums of understanding (MOU) and signed agreements between governments or development partners and CSOs should be formalized and increased to enable CSOs to expand their reach and contribution to immunization plans and programmes*
3. *Immunization Coordinating Committees (ICCs) as well as technical and non-technical working groups at national and sub-national levels (where they exist) should include CSOs working in immunization so that they can share their experiences (e.g. routine immunization, demand generation, etc.) and propose solutions to addressing barriers to increasing vaccine coverage*
4. *WHO and UNICEF country representatives and offices should organize roundtables with CSOs at national and sub-national levels to increase overall awareness and understanding of the GVAP and civil society's role in its achievement*
5. WHO should develop clear information on the timeline and processes to develop regional and country level GVAPs, and communicate this information widely across stakeholders, including CSOs; information should include the contact details for specific persons responsible for overseeing these efforts
6. WHO should include during its regional Expanded Programme on Immunization (EPI) meetings a forum for countries to exchange experiences and lessons on regional and country level GVAP development as well as on successes, challenges, and innovative approaches to addressing barriers to immunization scale up; CSO leadership from Gavi-supported CSO country platforms should be invited to the annual regional and global EPI review meetings
7. GVAP Secretariat should convene a sub-working group within the GVAP Monitoring & Evaluation/Accountability working group to develop CSO or community-level indicators for each SO to be integrated in the GVAP M&E/ Accountability framework
8. GVAP Secretariat should task the GVAP M&E/ Accountability working group with developing CSO-friendly tools and processes to allow CSO contributions to the GVAP to be assessed and verified as part of a systematic and standardized process for reporting by all stakeholders to the GVAP
9. CSOs should be supported to carry out annual GVAP reporting at country, regional and global levels

2015 recommendations

In 2015, CSOs submitted additional recommendations to improve and increase their involvement at the country, regional and global levels to support the achievement of the GVAP.

1. To improve the involvement of CSOs at country level in the development and implementation of national immunization plans and programs, governments and in-country development partners should:
    a. Consult and include CSOs in developing outcome-based plans for national immunization and in evaluating progress towards reaching national immunization targets
    b. Include CSOs in National Immunization Technical Advisory Groups (NITAGs) to enable them to provide input on technical issues from the community perspective
    c. Increase funding and support (e.g. stipends, equipment, supplies, materials, supervision) for CSO-led immunization activities and capacity building, including training more community mobilizers and documenting approaches to increase demand and coverage
    d. Involve CSOs in technical trainings, especially on national program data collection processes and how to use data collection tools; develop with CSOs a mechanism for regular data collection and reporting
    e. Coordinate CSO activities within districts and regions to ensure that they are complementary to the national program and inclusive of all geographic areas; include CSOs in the planning of activities
    f. Establish task forces at various administrative levels that are responsible for addressing problems in vaccine delivery; include CSOs in the process to establish them and in developing guidelines on member responsibilities
    g. Involve CSOs in national and sub-national planning and projections for vaccines and materials with the aim of preventing stockouts and resolving problems with the vaccine supply chain
2. To improve the involvement of CSOs in regional and global processes related to GVAP implementation, governments and development partners should:
    a. Support regional institutions and CSO coalitions/platforms/networks to organize annual meetings to review RVAP and GVAP progress
    b. Facilitate the establishment of regional CSO platforms/coalitions for immunization advocacy and information sharing
    c. Develop and/or improve the regularity of information sharing with CSOs on RVAP and GVAP progress at regional and country levels

2016 recommendations

In 2015, civil society put forward two recommendations that were not implemented in 2015. For 2016, civil society maintains the same two recommendations. A third recommendation has been added in this 2016 independent submission. Finally, civil society urges SAGE to include a discussion on next steps to implement the 2016 recommendations at its upcoming meeting.

1. A meeting should be organized with the Gavi CSO Steering Committee and the SAGE GVAP working group to discuss how recommendations from 2014 and 2015 can be supported, implemented and monitored as appropriate and relevant at the country, regional and global levels.
2. Guidance should be made available to country-level immunisation and Health Systems Strengthening (HSS) staff regarding how to work with CSOs to strengthen immunisation and health programmes, with a focus on engaging local CSOs. As this guidance does not currently exist, the Gavi CSO Steering Committee would welcome an opportunity to collaborate with WHO, the SAGE GVAP working group and the GVAP Secretariat to produce it.
3. Provide support to, and work with, in-country CSOs to help them regularly collect data that they analyze and report on in order to clearly communicate their contributions to immunization- and health-systems strengthening. Small grants should be provided for CSO trainings on data collection, analysis, monitoring and reporting.

V

Independent submissions

AMERICAN RED CROSS

Submitted by Mary Agocs, July 2016

In 2015 the American Red Cross as part of the Measles & Rubella Initiative (MRI) contributed towards Goals 2, 3, and 5 of the Global Vaccine Action Plan (GVAP), activities focused on Strategic Objective 2 Demand for Immunization. Working through the Red Cross Movement formal partnerships with Red Cross national societies were established to train and mobilize volunteers to support measles and rubella vaccination campaigns within targeted areas. Volunteers conducted social mobilization activities providing information to communities and encouraging caregivers to bring eligible children to vaccination posts, thereby increasing demand within supported areas.

Social mobilization campaigns coincided with measles/measles and rubella Supplemental Immunization Activities (SIA) or Periodic Intensification of Routine Immunization (PIRI) campaigns in six countries Burundi, Liberia, Madagascar, Mali, Nepal, and Timor-Leste. In general the activities conducted by the volunteers focused on house to house visits within intervention areas. Volunteers were mobilized within their own communities to provide a built-in level of trust that enables them to better engage community members and increase demand through education and encouragement. Table 10 below provides an overview of the activities conducted in each of the supported countries.

Table IS 1: Activities conducted by the American Red Cross in 2015

National Society Supported by American Red Cross	Supplementary Immunization Intervention*	Number of Subnational Areas Targeted	Households Visited	Number of Volunteers Recruited	Targeted Population
Burundi Red Cross Society	M	2	80,000	400	32,000
Liberia Red Cross Society	M	6	433,511	2,850	368,484
Madagascar Red Cross Society	M	1	105,600	704	59 851
Mali Red Cross Society	M	6	443,584	1507	1,067,930
Nepal Red Cross Society	MR	14	NA	435	596,757
Timor-Leste Red Cross Society	MR	13	NA	265	501,832
Total		**42**	**1,062,695**	**6,161**	**2,567,003**

*M = measles vaccine; MR = combined measles rubella vaccine

Through informal comparison of data from Red Cross supported versus unsupported geographic areas in a country, an average increase of up to 10% in coverage rates has been observed in Red Cross supported areas. Additionally convenience sample interviews of caregivers at vaccination posts found that information provided by Red Cross volunteers one of the most frequently cited sources of information about the vaccination campaigns. American Red Cross has begun discussions with the U.S. Centers for Disease Control and Prevention as well as the International Federation of Red Cross Red Crescent Societies to launch a joint initiative to better quantify these results. At this time, the anecdotal information tends to support the positive impact that Red Cross volunteers have in increasing the demand for vaccines within communities.

CENTERS FOR DISEASE CONTROL AND PREVENTION OF THE UNITED STATES OF AMERICA

Submission by Rebecca Martin, July 2016

CDC's global immunization activities focus on supporting global and regional immunization partnerships, and national immunization programs, that provide capacity and coordination needed to maximize the health impact of vaccines. These investments contribute to the goals of the Decade of Vaccines and the Global Vaccine Action Plan (GVAP).

Goal 1—Achieving a Polio-Free World

- CDC is the U.S. lead scientific agency[82] in the global effort to eradicate polio. CDC is working to support GPEI efforts to interrupt poliovirus transmission in the two remaining polio endemic countries – Afghanistan and Pakistan; maintain a polio-free Africa; and to prevent, detect, and respond to poliovirus importations in polio-free countries are critical to achieve polio eradication.
- CDC's Global Reference Lab for polio: plays a significant role formulating the standards for laboratory containment of poliovirus stocks and samples worldwide; and provides quality assurance, diagnostic confirmation, and genomic sequencing of samples obtained worldwide.
- CDC is leading GPEI efforts to document and transition the knowledge, lessons learned, assets and infrastructure accumulated by the initiative to address other health goals, while sustaining polio functions still needed after polio eradication is achieved.

Goal 2—Meet Global and Regional Elimination Targets

- Measles and Rubella: CDC is the U.S. lead scientific agency[83] for the Measles and Rubella Initiative. CDC's programmatic support for measles is also provided through the Global Health Security Agenda's Immunization package and measles vaccination coverage is the performance measure for immunization program improvement.
- CDC's Global Measles Reference Laboratory serves as the leading worldwide reference laboratory for measles and rubella; provides specimen confirmation and testing was well as training for country and regional labs, conducts essential measles and rubella research, and supports expansion of environmental surveillance capabilities in the field; and provides public health laboratories access to molecular testing and global molecular proficiency testing
- CDC works with WHO regions to monitor measles incidence and risk through developing and analyzing high quality surveillance data and risk estimates, estimating burden of disease and death, and verifying elimination. CDC also helps partners monitor rubella and congenital rubella syndrome disease burden through seroprevalence surveys.

Goal 3—Meet Vaccination Coverage Targets at Every Level

- CDC helped develop the Global Routine Immunization Strategies and Practices companion document to the GVAP which highlights routine immunization service delivery as the foundation for sustained decreases in morbidity and mortality from VPDs across the lifecycle of all individuals.
- CDC supports country efforts to increase vaccination coverage through routine immunization services by developing and advocating for the scale up of interventions to: 1) address community- and health sector-based barriers to vaccine access and utilization; 2) minimize missed opportunities for vaccination; and 3) provide catch-up vaccination (e.g. school-entry record checks and follow-up vaccination).
- CDC develops and supports implementation of strategies to link planning, delivery, and vaccination monitoring of vaccination with other related health interventions administered across the life span (e.g. Second Year of Life project piloted in Ghana).
- CDC provides expertise and consultation to develop immunization information systems (IIS) which are able to collect, analyze, and report high-quality, immunization-related data to support management of immunization programs. These interventions include appropriate technologies to track and improve vaccine delivery across the life course, and approaches to improve target population estimates.

[82] http://www.cdc.gov/polio/why/
[83] http://www.measlesrubellainitiative.org/learn/about-us

Goal 4—Develop and Introduce New, Improved Vaccines & Technologies

- CDC works to increase the development, introduction, and use of new and underused vaccines to prevent diseases of global and regional public health importance. Recent vaccine introductions CDC has supported include: *Haemophilus influenza* type b, rotavirus, PCV, meningococcus A, human papillomavirus (HPV), influenza, typhoid, cholera, Japanese encephalitis and inactivated polio vaccines.
- CDC scientists are actively involved in the development of disease burden studies and clinical trials of new vaccines for malaria, dengue, Ebola, and Zika virus.
- CDC supports efforts to use vaccine introduction to strengthen other disease prevention and control initiatives includes linking rotavirus and pneumococcal conjugate vaccine introductions with implementing the Global Action Plan for Prevention of Pneumonia and Diarrhea, HPV vaccine with cervical cancer prevention, and malaria vaccine with other malaria control and elimination strategies.
- CDC laboratories serve as global special reference laboratories supporting global and regional VPD surveillance networks used to assess VPD burden and impact new vaccine introduction.
- CDC works to strengthen immunization policy bodies, which play important roles in reviewing technical, operational, and programmatic evidence for new vaccine introduction, and in developing immunization goals, policies and guidelines.

The Network for Education and Support in Immunisation (NESI)

Submitted by Carine Dochez, July 2016

The Network for Education and Support in Immunisation (NESI), based at the University of Antwerp in Belgium, is an international multidisciplinary network with the mission to strengthen immunisation programmes in low- and middle-income countries. Through partnerships with WHO, academic institutions, Ministries of Health and other interested parties, NESI focuses on capacity building, education and training, and institutional strengthening, in order to fulfil its mission.

Human resources play a crucial role in the delivery of quality immunisation services and maintaining public trust through effective communication with individuals and communities. NESI's pre- and in-service educational programmes are tailored to the needs of the immunisation programme in the respective partner countries, with country ownership as guiding principle.

Due to its links with universities and other health training institutions, which are vital to achieving sustainable capacity and competence building in the field of vaccinology, NESI is unique in its attention on pre-service training, particularly on the development of curricula and training for nurses, medical doctors, pharmacists, public health specialists and other related health professionals.

The high-level in-service vaccinology courses, other interactive courses and workshops (mid-Level management training and Experience Exchange workshops), enable NITAG members, policy-makers, EPI managers and staff to make evidence-based recommendations and decisions on vaccines and immunisation, and to contribute to efficient management of immunisation programmes.

Table 11 below summarizes NESI's key activities during 2015, contributing to two of the six Strategic Objectives of the Global Vaccine Action Plan. Our major achievement was the roll-out of a two-year project "Strengthening country adolescent immunisation programmes and health systems in the African Region using HPV vaccine as a case study", providing countries in Eastern and Southern Africa with a forum to exchange best practices and challenges, in order to strengthen their national capacity for introduction of the HPV vaccine and other adolescent health interventions.

Table IS 2: Summary of NESI-reported activities in support of GVAP SOs

SO1: All countries commit to immunisation as a priority	**Strengthen national capacity to formulate evidence-based policies.** • Two regional forums with peer-to-peer exchange of information, best practices and tools organised on: "Implementing HPV vaccination in Africa: opportunities for strengthening adolescent health" with participation of Eastern and Southern African countries, in collaboration with the South African Vaccination and Immunisation Centre (SAVIC)/Sefako Makgatho Health Sciences University, South African Medical Research Council (SA-MRC) and with support from WHO and the African Region (Pretoria, South Africa, March 2015 and Johannesburg, South Africa, October 2015).
SO4: Strong immunisation systems are an integral part of a well-functioning health system	**Strengthen capacity of managers and frontline workers.** In-service training: • Co-organised and co-facilitated vaccinology courses: – Berlin, Germany (January 2015), as partner of the Institute of Tropical Medicine and International Health. – Mbour, Senegal (September 2015), as partner of the African Region. • Contributed to the finalisation of an integrated EPI/IMCI interactive resource, as partner of the African Region. Pre-service training: • Contributed to the finalisation of EPI prototype curricula, as partner of the African Region. • Country support given to Indonesia, Kenya and Morocco to strengthen EPI training at medical faculties and nursing schools.

PATH

Submitted by Nicole Fallat, July 2016

Driving GVAP progress through innovation

A roundup of much of PATH's work in 2015 and early 2016 in support of key GVAP goals and objectives.

PATH is the leader in global health innovation. An international non-profit organization, we save lives and improve health, especially among women and children. We accelerate innovation across five platforms—vaccines, drugs, diagnostics, devices, and system and service innovations—that harness our entrepreneurial insight, scientific and public health expertise, and passion for health equity. By mobilizing partners around the world, we take innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. Together, we deliver measurable results that disrupt the cycle of poor health. Learn more at www.path.org.

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Country commitment (OBJECTIVE 1)

- To bolster national policymakers' capacity to make evidence-based immunization decisions, PATH provides technical assistance, facilitates peer learning, and helps strengthen advocacy capacity. Recent work includes:
- Assisting the governments of more than 20 low-resource countries in Africa and Asia in the planning, implementation, and evaluation of HPV vaccine delivery.
- Continuing to cultivate an African-led, member-owned, peer-to-peer learning network to inform national and global decision-making around immunization data.
- Convening African officials and global leaders at the first Ministerial Conference on Immunization in Africa to build political will for improving immunization supply chains.
- Facilitating—through targeted advocacy with parliamentarians—the Democratic Republic of the Congo (DRC) government's release of US$2 million to co-finance the procurement of Gavi-supported vaccines.

Demand (OBJECTIVE 2)

To build demand for vaccines, PATH develops evidence on the efficacy, impact, safety, and cost-effectiveness of vaccines and disseminates findings through advocacy outreach and training. Recent work includes:

- Collaborating with groups in pastoral Ethiopia such as the Ministry of Health, Afar Regional Health Bureau, and Regional Islamic Affairs Office to revitalize social mobilization committees—helping generate greater vaccine demand and immunization coverage.
- Conducting studies to identify ways to improve or enhance the performance of globally available rotavirus vaccines in low-resource settings.

Equity (OBJECTIVE 3)

To help ensure vaccines reach every child in even the most remote regions, PATH works with countries to test and scale innovative technologies, tools, strategies, and policies that improve coverage and health equity. Recent work includes:

- Partnering to provide more than 235 million Africans with MenAfriVac®—a low-cost meningitis A vaccine developed by PATH, WHO, and Serum Institute of India, Pvt. Ltd. (SIIPL). The vaccine has virtually eliminated the disease where introduced. Initial national routine immunization introductions began in 2016.

Stronger immunization systems (OBJECTIVE 4)

PATH works alongside countries to build, identify, test, scale, and advocate for innovative solutions that strengthen immunization systems as part of an integrated health system. Recent work includes:

- Partnering with the governments of Tanzania and Zambia to develop and refine interventions to improve immunization data collection, quality, and use—including launching an electronic immunization registry.

- Collaborating with global, national, and regional institutions to strengthen and expand disease surveillance systems and the use of vaccine safety monitoring tools and practices to generate more accurate vaccine impact and safety data.

Supply (OBJECTIVE 5)

PATH helps predict, measure, and ensure a sustainable supply of safe and effective vaccines in partnership with manufacturers and procurement agencies. Recent work includes:

- Partnering with a Chinese manufacturer to support and enable endemic countries to introduce a Japanese encephalitis vaccine—the first WHO prequalified Chinese vaccine—at an affordable price. To date, more than 232 million doses have been delivered.

Research and Development (OBJECTIVE 6)

PATH is a leader in the research and development of innovative vaccines as well as formulation, packaging, and delivery devices, tool, and strategies that increase the safety, effectiveness, and reach of immunization. Recent milestones include:

- Presenting the Phase 3 results of PATH and GlaxoSmithKline's RTS,S malaria vaccine candidate to European regulators, who issued a positive opinion, which informed the WHO recommendation on pilot implementations in Africa.
- Advancing research into whether an alternative-dose formulation of RTS,S could improve protection against malaria.
- Supporting SIIPL in the development of a low-cost rotavirus vaccine, as well as another Indian-manufactured rotavirus vaccine, ROTAVAC®, which the Indian government introduced into routine immunization in 2016.
- Continuing clinical evaluation of non-replicating rotavirus vaccine candidates, which may offer a promising approach for improving rotavirus vaccination protection.
- Supporting SIIPL to complete a Phase 1/2 trial in The Gambia of its low-cost pneumococcal conjugate vaccine candidate, which is poised to enter Phase 3 in 2017.
- Building the evidence base and policy pathways for controlled temperature chain (CTC) delivery of more temperature-stable vaccines, including MenAfriVac, which has now reached an additional 4 million people through use of a CTC.
- Continuing to support the WHO with equipment prequalification through the field testing of new cold-chain equipment and temperature indicators, and conducting studies in the PATH laboratory to inform WHO prequalification protocols.
- Working with the WHO to lead a Delivery Technologies working group that guides the development of new primary container and delivery technologies.
- Collaborating with a range of partners to advance several novel platform delivery technologies (e.g. microarray patches, novel primary containers, and barcodes, among others).
- Developing a vaccine technology prioritization and health systems cost analysis methodology that can serve as a tool for global stakeholders.

USAID

Submitted by Endale Beyene, July 2016

Support for Routine Immunization (Supports GVAP Goal 3; Strategic objectives 1-4)

USAID technical inputs into immunization programs help countries improve quality, equity and coverage metrics while strengthening the systems to extend equitable access to life-saving vaccines in a timely, reliable, and sustainable manner. Our technical contributions to immunization system improvements protect and optimize the investments to Gavi for vaccine procurement, since a newly-introduced vaccine can achieve its promised impact only if the vaccination services are strong. To this end, USAID supports the development of sound immunization policy, strategies, and guidelines so routine immunization programs are well-planned and managed.

Last year, USAID and its implementing partners supported countries through participation in national immunization planning, external immunization reviews and evaluations, national ICC meetings and other important activities. USAID also supported countries in immunization systems strengthening activities which included human resource capacity, cold chain and logistics, data quality and use and demand creation as well as the implementation of innovative approaches and tools such as the reaching every district (RED) to expand equitable access to vaccination.

Ending Preventable Child and Maternal Deaths (EPCMD) within a generation is a top priority of the U.S. Agency for International Development. Immunization stands as a central component of USAID's strategy for EPCMD. USAID has refocused resources on 25 priority countries, primarily in sub-Saharan Africa and South Asia, that account for 70% of maternal and child deaths and half of the global unmet need for family planning services.[84] USAID's support to routine immunization contributes to goal 3 and strategic objectives 1-4 of the global vaccine action plan.

Engagement in Global Polio Eradication

USAID has been a key player in polio eradication activities since the beginning of the initiative. Last year, USAID and its implementing partners provided financial and technical support targeted to the remaining polio endemic and outbreak countries, and in several high risk countries, which are prone for importation. USAID's main implementing partners are WHO, UNICEF, and the CORE Group Polio Project. The activities we have supported include surveillance, supplementary immunization activities and communications and social mobilizations. USAID actively participated in global and regional polio advisory group meetings, surveillance reviews and outbreak response assessments. This financial ($59 million) and technical support of USAID is in line with the endgame plan and contributes to Goal 1 and strategic objectives 1 and 2 of the global vaccine action plan.

Engagement in New Vaccine Introduction and Vaccine development

Since 2001, USAID has contributed over $1.6 billion to Gavi, the Vaccine Alliance. Through its annual contribution ($235 million in FY16) to Gavi, USAID supports the accelerated introduction of new and underutilized vaccines in Gavi-eligible countries. USAID also engages in Gavi governance bodies as a member of the Gavi Board and the Board's Program and Policy and Audit and Finance Committees. At country level, USAID and its partners provide technical support for the introduction of the new vaccines in to the routine immunization system. Over the years, USAID's flagship reproductive, maternal, newborn, and child health Projects and bilateral Mission projects have played an important role in the smooth introduction of new vaccines in several countries. USAID has also supported a number of post introduction evaluations and assessments.

USAID also supports vaccine research and development. USAID and its partners demonstrate continued commitment to improve the prevention and treatment of HIV and AIDS while enhancing preparation for future epidemics and sustainable development. USAID's investments aim to enhance the larger African research environment by enabling/encouraging talented scientists on the continent to contribute – and eventually lead – novel HIV vaccine design and testing in low- and lower-middle-income countries hardest hit by the HIV pandemic. USAID's Malaria Vaccine Development Program provides financial support for development of a malaria vaccine that could enhance malaria control efforts. This work focuses on three stages of the parasite life cycle including before and during liver stages and during the blood stage. USAID funding for HIV vaccine research and development focuses on candidate products that address the specific challenges faced by the low- and lower-middle-income countries hardest hit by the HIV pandemic. These USAID programs contribute to Goal 4 and strategic objectives 3, 4 and 6 of the global vaccine action plan.

[84] The 24 EPCMD countries include Afghanistan, Bangladesh, Burma, Congo DR, Ghana, Ethiopia, Haiti, India, Indonesia, Kenya, Liberia, Mali, Malawi, Madagascar, Mozambique, Nepal, Nigeria, Pakistan, Rwanda, South Sudan, Senegal, Tanzania, Uganda, Yemen and Zambia

JSI

Submitted by Sarah Melendez, 29 July 2016

Working with partners, JSI strengthens routine immunization (RI) systems, supports introduction of new vaccines, contributes to the achievement of disease control targets, and informs regional and global policies and strategies. In 2015, JSI supported the achievement of the objectives of the Global Vaccine Action Plan through a wide range of activities and programs described below:

STRATEGIC OBJECTIVE 1: COUNTRY COMMITMENT

- In 2016, JSI partnered with WHO, UNICEF and leadership across Africa to design and implement the first Ministerial Conference on Immunization in Africa to increase country ownership and financial commitment to immunization. We also proposed, jointly hosted, and technically supported, a CSO side event which highlighted the importance of engaging civil society, looking beyond NGOs to community leaders and traditional institutions.

STRATEGIC OBJECTIVE 3: EQUITY

- JSI technically supported countries to identify and reach underserved populations to improve equitable coverage as part of the Reaching Every District (RED) approach in all 16 countries mentioned under Objective 4 and supported countries to learn how to transition from RED to Reaching Every Child.
- Over the past decade, JSI provided technical support for 30 new nationwide vaccine introductions in 15 countries, including vaccines against polio (IPV), measles (2nd dose), rubella, cervical cancer (HPV), pneumonia (PCV), rotavirus (RVV), and cholera (OCV). In 2015, JSI supported introductions of IPV (Kenya, Ethiopia, South Sudan, Uganda, Niger, Nigeria, Tanzania), measles second dose (Malawi, Zimbabwe), rotavirus (India, Niger, Madagascar, Liberia, Kenya), HPV (Niger, Liberia, Madagascar, Zimbabwe), two dose MR (Tanzania, Zimbabwe), and PCV (Niger). JSI also supported post introduction evaluations in many countries.

STRATEGIC OBJECTIVE 4: STRONG IMMUNIZATION SYSTEMS

- JSI provided technical support to strengthen RI systems as an integral part of the broader health system and/or introduce new vaccines in Uganda, Ethiopia, Tanzania, Kenya, Nigeria, Madagascar, Malawi, Zimbabwe, Mozambique, South Sudan, Niger, Liberia, Guinea, India, Pakistan, and Haiti.
- JSI documented experience with the introduction of an integrated vaccination and child health visit in the second year of life in Zambia and Senegal and drafted a related field guide for WHO.
- JSI launched projects on Dose per Container Partnership and on Coordination and Implementation of Child Health Record Redesigns (Home Based Records), and we co-authored WHO's Practical Guide for the Design, Use, and Promotion of Home-Based Records.

STRATEGIC OBJECTIVE 5: SUSTAINABLE ACCESS TO PREDICTABLE FUNDING, QUALITY SUPPLY AND INNOVATIVE TECHNOLOGIES.

- JSI Technical Advisors in Madagascar played a key role in the development of the 2014 vaccine finance law amendment to expand the law to include sustainable financing for the purchase of additional equipment and to increase strategies such as national routine vaccination days and community dialogues.

STRATEGIC OBJECTIVE 6: RESEARCH AND INNOVATION

- JSI developed and technically supported the MOH in Tanzania on a Vaccine Information Management System. Support was also provided to the Pakistan MOH to develop and implement a Vaccine Logistics Management Information System.
- JSI studied the feasibility and accessibility of using both 1- and 10-dose vials of Pentavalent vaccine side-by-side within health facilities in Kenya.

JSI is dedicated to improving and promoting public health in the United States and across the globe. JSI works across a full range of public and community health areas, strengthening health systems to improve services—and ultimately, people's health.

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Vaccine manufacturers

No contribution.


BILL & MELINDA
GATES foundation

Gavi
The Vaccine Alliance

unicef

World Health
Organization