GLOBAL VACCINE ACTION PLAN

MONITORING, EVALUATION & ACCOUNTABILITY

SECRETARIAT ANNUAL REPORT 2018

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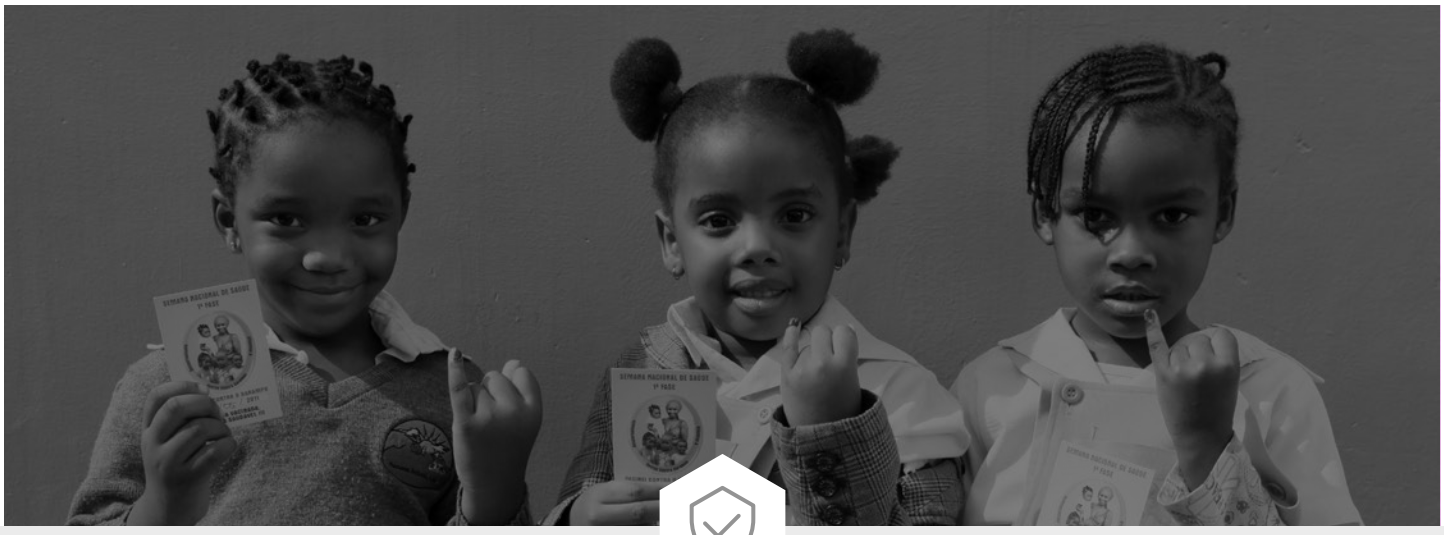

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INDEPENDENT SUBMISSIONS

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Technical input

Ananda Amarasinghe, Yagob Al Mazrou, Jon Andrus, Sébastien Antoni, Blanche-Philomene Anya, Maria Aranguren Garcia, Narendra Arora, Sunil Bahl, Madhava Ram Balakrishnan, Ashley Birkett, Christopher Beisel, Logan Brenzel, Robb Butler, Cara Carrubba, Cristina Cassetti, Tania Cernuschi, Mark Challberg, Diana Chang Blanc, Irtaza Chaudhri, Thomas Cherian, Adam Cohen, Carine Cruz Payan, Alya Dabbagh, Hemanthi Dassanayake, Siddhartha Datta, Peter Dull, Laure Dumolard, Katrin Eichelberg, Susan Elden, Antonietta Filia, Adam Finn, Andrew Ford, Martin Friede, Marta Gacic-Dobo, Brigitte Giersing, Isaac Gobina, Ajay Goel, Tracey Goodman, Jennifer Gordon, Ulla Griffiths, Xin-Xing Gu, Stephen Guichard, Lee Hall, Louise Henaff, Joachim Hombach, Ahmadreza Hosseinpoor, Xiao Xian Huang, Angela Hwang, Sudhir Joshi, Ana Lea Kahn, David Kaslow, Robert Kezaala, Alireza Khadem Broojerdi, Sudhir Khanal, Sonnie Kim, Rajen Koshy, Alenka Kraigher, Katrina Kretsinger, Sarah Lane, Diane Le Corvec, Jayantha Liyanage, Kristina Lu, Noni MacDonald, Yvette Madrid, Stefano Malvolti, Nikhil Mandalia, Carsten Mantel, Amani Mahmoud Mustafa, Rebecca Martin, Lisa Menning, Annie Mo, Richard Mihigo, Randy Mungwira, Robin Nandy, Laura Nic Lochlainn, Emily Nickels, Huda Oleru, Sirima Pattamadilok, Claudio Politi, Diane Post, Azar Abid Raza, Helen Rees, Magdalena Robert, Carmen Rodriguez Hernandez, Sigrun Roesel, Oliver Rosenbauer, Cuauhtemoc Ruiz Matus, David Salisbury, Deb Schweikert, Dena Seabrook, Fatima Serhan, Christine Sizemore, Silvija Staprans, Christoph Steffen, Claudia Steulet, Yoshihiro Takashima, Nadia Teleb, Hapsatou Toure, Johan Vekemans, Emily Wootton, Steve Whitehead, Ole Wichmann, Huang Xiao Xian, Ke Xu, Ahmadu Yakubu, Darin Zehrung, Patrick Zuber, Flint Zulu

SAGE, Decade of Vaccines working group

Oleru Huda Abason, Jon Kim Andrus, Narendra Kumar Arora, Yagob Yousef Al-Mazrou, Susan Elden, Noni MacDonald, Marie-Yvette Madrid, Amani Abdelmoniem Mahmoud Mustafa, Rebecca Martin, Helen Rees, David Salisbury, Qinjian Zhao

Decade of Vaccines partner agencies

Magdalena Robert (Bill & Melinda Gates Foundation), Hope Johnson (Gavi, the Vaccine Alliance), Lee Hall and Andrew Ford (National Institute of Allergy and Infectious Diseases), Robin Nandy (UNICEF), Diana Chang Blanc, Joachim Hombach and Martin Friede (WHO)

Decade of Vaccines Secretariat

Christoph Steffen, Ofelia Cazacu

Design and web production

Ofelia Cazacu, Hayatee Hasan, Louise Henaff, Christoph Steffen, Sarah Buscail and Anthony Leclercq (Paprika)

Editorial assistance

Kai Lashley (Further Consulting)

Abbreviations

AEFI	adverse events following immunization
AFP	acute flaccid paralysis
ASEAN	Association of Southeast Asian Nations
BCG	Bacille Calmette–Guérin (vaccine)
BFS	blow-fill-seal
BNabs	broadly neutralizing anti-Env antibodies
CCI	Composite Coverage Index
CDC	United States Centers for Disease Control and Prevention
CHIM	controlled human infection model
CHMI	controlled human malaria infection
CI	confidence interval
CMIU	cell-mediated immunity
CMV	cytomegalovirus
cMYP	comprehensive multi-year plan
CPI	(United States) Consumer Price Index
CRS	congenital rubella syndrome
CSO	civil society organization
CTC	controlled temperature chain
cVDPV	circulating vaccine-derived poliovirus
DHS	Demographic and Health Survey
DoV	Decade of Vaccines
DSJI	disposable syringe jet injector
DTP	diphtheria–tetanus–pertussis (vaccine)
EPI	Expanded Programme on Immunization
fIPV	fractional dose IPV
GACVS	Global Advisory Committee on Vaccine Safety
GAPIII	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
Gavi	Gavi, the Vaccine Alliance
GHED	Global Health Expenditure Database
GISN	Global IB-VPD Surveillance Network
GNI	gross national income
GPEI	Global Polio Eradication Initiative
GRSN	Global Rotavirus Surveillance Network
GTFCC	Global Task Force on Cholera Control
GVAP	Global Vaccine Action Plan
GVIRF	Global Vaccine and Immunization Research Forum
HepB	hepatitis B
HepB-BD	hepatitis B birth dose
Hib	*Haemophilus influenzae* type b
HIC	high-income countries
HPV	human papillomavirus
IB-VPD	invasive bacterial vaccine-preventable disease
ID adapters	intradermal adapters
IPAC	Immunization Practices Advisory Committee
IPV	inactivated polio vaccine
IVB	Immunization, Vaccines and Biologicals Department (WHO)
JRF	(WHO-UNICEF) Joint Reporting Form (on Immunization)
M&E/A	monitoring and evaluation/accountability
mAbs	monoclonal antibodies
MAP	microarray patch
MCV	measles-containing vaccine
MenAfriVac	Serogroup A meningococcal conjugate vaccine
MHC	major histocompatibility complex
MIC	middle-income country
MICS	Multiple Indicator Cluster Surveys
MIM	Multilateral Initiative Malaria
MMR	measles–mumps–rubella (vaccine)
MNT	maternal and neonatal tetanus
MNTE	maternal and neonatal tetanus elimination
MOV	missed opportunities for vaccination
MR	measles–rubella (vaccine)
MSF	Médecins Sans Frontières
Mtb	*Mycobacterium tuberculosis*
NGO	nongovernmental organization

NIAID	National Institute of Allergy and Infectious Diseases
NITAG	National Immunization Technical Advisory Group
NRA	national regulatory authority
NVC	(Measles) National Verification Committee
OCV	oral cholera vaccine
OPV	oral polio vaccine
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCV	pneumococcal conjugate vaccine
POD	prevention of disease
POI	prevention of infection
polio	poliomyelitis
POR	prevention of recurrence
PQS	performance, quality and safety
PrEP	pre-exposure prophylaxis
R&D	research and development
RCV	rubella-containing vaccine
RSV	respiratory syncytial virus
RTAG	Regional Technical Advisory Group
RVC	(Measles) Regional Verification Commission
SAGE	Strategic Advisory Group of Experts (on immunization)
SAR	Special Administrative Region
SDG	Sustainable Development Goal
SHA	System of Health Accounts
SIA	supplementary immunization activity
SIVAC	Supporting Independent Immunization and Vaccine Advisory Committees
SO	(GVAP) Strategic Objective
TB	tuberculosis
TdaP	Tetanus, diphtheria and pertussis
TT	tetanus toxoid
TTCV	tetanus toxoid-containing vaccines
UHC	universal health coverage
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS (UNAIDS)
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
V3P	Vaccine Product, Price and Procurement (project)
VAEIMS	Vaccine Adverse Events Information Management System
VPD	vaccine-preventable disease
VVM-TI	Vaccine vial monitor with threshold indicator
WG	working group
WHO	World Health Organization
WPV	wild poliovirus
WUENIC	WHO-UNICEF estimates of national immunization coverage
YF	yellow fever

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. The need for this annual reporting mechanism has been re-emphasized in resolution WHA70.14 at the Seventieth World Health Assembly in May 2017.

Updates to the GVAP Secretariat report, 2018

This report includes a few new features from the 2017 edition, as outlined below.

1. The report focuses primarily on the new data gathered for the past year. The reader will find detailed elements on background and methodology in the 2017 GVAP Secretariat report.
2. Progress on the GVAP research and development indicators is reported on this year, in line with biennial reporting requirements.

Table 1: The GVAP monitoring and evaluation/accountability framework: goals, strategic objectives and indicators to evaluate progress

Goal/strategic objective	Indicators
GOALS	
Achieve a world free of poliomyelitis	G1.1 Interrupt wild poliovirus transmission globally
	G1.2 Certification of poliomyelitis eradication
Meet global and regional elimination targets	G2.1 Maternal and neonatal tetanus elimination
	G2.2 Measles elimination
	G2.3 Rubella/Congenital rubella syndrome (CRS) elimination
Meet vaccination coverage targets in every region, country and community	G3.1 By 2015, reach 90% national coverage and 80% in every district or equivalent administrative unit with three doses of diphtheria–tetanus–pertussis-containing vaccines
	G3.2 By 2020, reach 90% national coverage and 80% in every district or equivalent administrative unit for all vaccines in national programmes, unless otherwise recommended

[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
Develop and introduce new and improved vaccines and technologies	G4.1 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
	G4.2 Licensure and launch of at least one platform delivery technology **Note:** this indicator is included in the "research and development" section
	G4.3 Number of low-income and middle-income countries[3] that have introduced one or more new or under-utilized vaccines **Note:** this indicator is included in the "immunization coverage" section
Exceed the Millennium Development Goal 4 target for reducing child mortality and integration indicators	G5.1 Reduce under-five mortality rate **Note:** this indicator has not been reported on this year
	G5.2 Integration of health care interventions and immunization activities
STRATEGIC OBJECTIVES (SOs)	
Ensuring country ownership of immunization	SO1.1 Increasing domestic expenditures for immunization per person targeted **Note:** this indicator is included in the "sustainable financing and supply for immunization" section
	SO1.2 Presence of an independent technical advisory group that meets the defined criteria
Demand for immunization	SO2.1 Percentage of countries that have assessed the level of hesitancy in vaccination at a national or subnational level
	SO2.2 Reasons for vaccine hesitancy
	SO2.3 Percentage of countries that include in their immunization programme actions to promote or sustain public demand for vaccines and vaccination services
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 **Note:** this indicator is included in the narrative of the "immunization coverage" section, Goal G3.1
	SO3.2 Reduction in coverage gaps between wealth quintiles and other appropriate equity indicator(s) **Note:** this indicator is included in the "immunization coverage" section, Goal G3.1
Strong immunization systems are an integral part of a well-functioning health system	SO4.1 Dropout rates between first dose (DTP1) and third dose (DPT3) of diphtheria–tetanus–pertussis-containing vaccines **Note:** this indicator is included in the "immunization coverage" section, Goal G3.1
	SO4.2 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, Goal G3.1
	SO4.3 Immunization coverage data assessed as high quality by WHO and UNICEF **Note:** *This indicator is no longer monitored*
	SO4.4 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

[3] World Bank country classification by income level: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

Goal/strategic objective	Indicators
Stock-out and access to sustained supply of vaccines of assured quality	SO5.1 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
	SO5.2 Number of countries reporting a national-level stock-out of at least one vaccine for at least one month **Note:** this indicator is included in the "sustainable financing and supply for immunization" section
Country, regional and global research and development innovations maximize the benefits of immunization **Note:** All indicators in Strategic Objective 6, except SO6.4 and SO6.5, are part of the "research and development" section	SO6.1 Progress towards development of HIV, TB and malaria vaccines
	SO6.2 Progress towards a universal influenza vaccine (protecting against drift and shift variants)
	SO6.3 Progress towards institutional and technical capacity to carry out vaccine clinical trials **Note:** no report is available this year for this indicator
	SO6.4 Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain (CTC) at temperatures above the traditional 2–8°C range **Note:** this indicator is included in the "sustainable financing and supply for immunization" section
	SO6.5 Number of vaccine delivery technologies (devices and equipment) that have received WHO pre-qualification against the 2010 baseline

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MONITORING RESULTS: GOALS, STRATEGIC OBJECTIVES AND INDICATORS

1. DISEASE ELIMINATION

GOAL 1: ACHIEVE A WORLD FREE OF POLIOMYELITIS

Indicators G1.1 and G1.2

G1.1: Interrupt 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 1.1.

Box 1.1: Descriptions of indicators, results, data sources and highlights

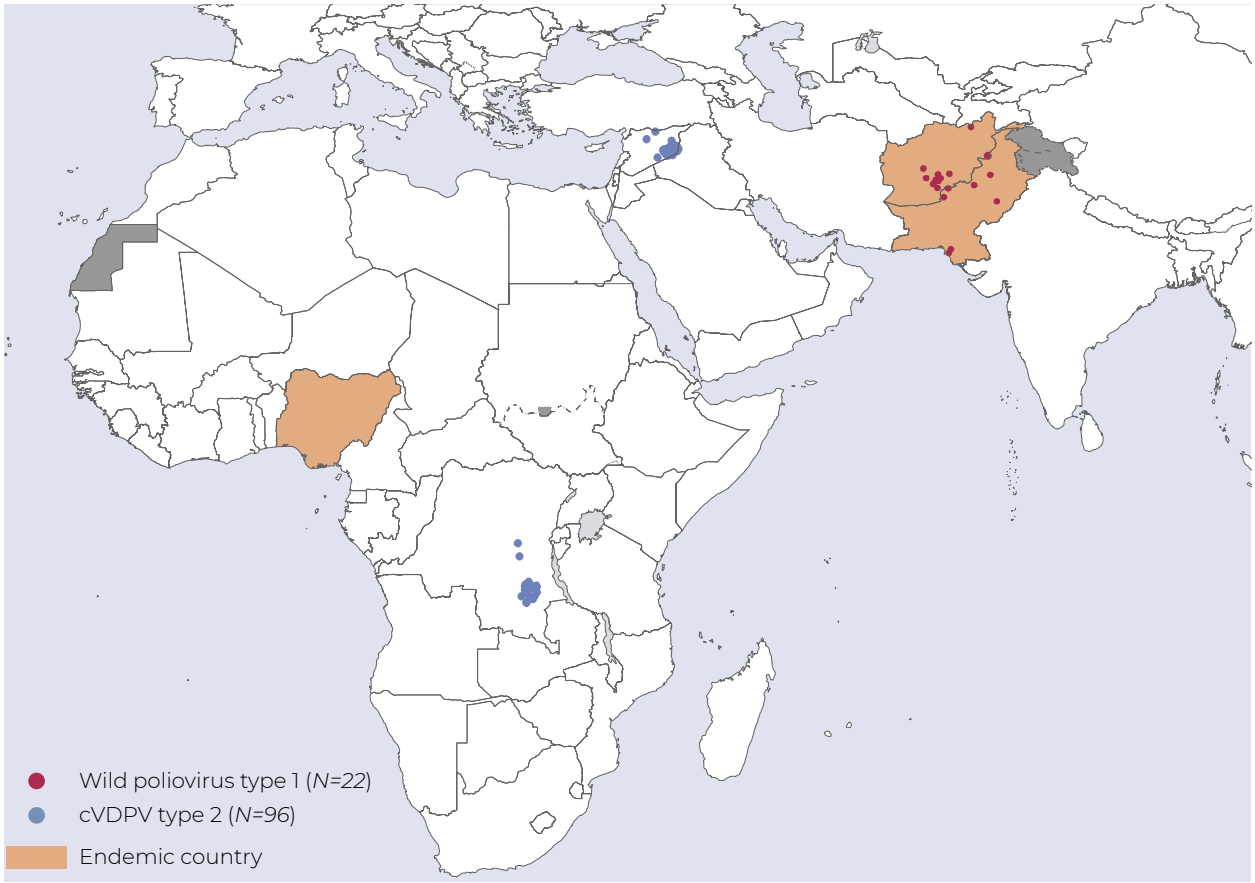
1. For context, see the GPEI status reports available at: http://www.polioeradication.org/Resourcelibrary/Strategyandwork/Annualreports.aspx
2. To review the latest report of the Independent Monitoring Board (IMB) of the GPEI, please visit: http://polioeradication.org/tools-and-library/policy-reports/imb-resources/reports/
3. The Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment (GAPIII-CCS). Geneva: World Health Organization; 2017 (http://polioeradication.org/wp-content/uploads/2017/02/CCS_2016EN.pdf, accessed 30 April 2018).
4. To consult the draft strategic action plan on polio transition: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_9-en.pdf
5. The Secretariat report to the World Health Assembly, March 2018: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_26-en.pdf is the basis for this GVAP polio section
6. Polio Post-Certification Strategy: http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/transition-planning/polio-post-certification-strategy/

A) Status of the GVAP poliovirus indicators, 2017

1) Interruption of wild poliovirus transmission

Twenty-two cases of paralytic poliomyelitis (polio) due to wild poliovirus (WPV) with onset of paralysis were reported globally in 2017, compared to 37 for 2016. All the cases were reported from Pakistan and Afghanistan and were caused by wild poliovirus type 1 (Fig. 1.1).

Fig. 1.1: Global wild poliovirus and circulating vaccinederived poliovirus (cVDPV[a]) cases[b, c] in 2017



[a] cVDPV is associated with ≥ 2 acute flaccid paralysis (AFP) cases or non-household contacts. VDPV2 cases with ≥ 6 (≥ 10 for type 1) nucleotides different from Sabin in VP1 are reported here.
[b] Excludes viruses detected from environmental surveillance.
[c] Two cVDPV type 2 isolated from sewage in Banadir province in Somalia in 2017 are not included on this map.

Endemic countries – Afghanistan, Pakistan and Nigeria

Afghanistan and Pakistan

In Afghanistan 14 cases were reported in 2017 compared to 13 in 2016. In Pakistan, 8 cases were reported in 2017, compared to 20 in 2016. Of particular concern are the border areas between the two countries and also Karachi (Pakistan), given the ongoing detection of positive environmental samples and since the confirmation of a case of paralytic poliomyelitis due to wild poliovirus in August 2017.

Nigeria

No new case of wild poliovirus type 1 was confirmed in Nigeria in 2017. However, due to continuing surveillance gaps in high-risk and inaccessible areas, undetected and continued circulation of this strain cannot be ruled out. A regional outbreak response across the Lake Chad subregion continues to be implemented.

2) Vaccine-derived poliovirus type 2 outbreaks

In 2017 two countries were affected by outbreaks of circulating vaccine-derived poliovirus (type 2): the Syrian Arab Republic and the Democratic Republic of the Congo, with 74 cases and 22 cases reported, respectively. The monitoring of and response to circulating vaccine-derived poliovirus type 2 transmission continues to be a global strategic priority, following the globally-coordinated withdrawal of the type 2 component of oral polio vaccine in April 2016.

Additionally, in October and November 2017, vaccine-derived poliovirus type 2 (VDPV2) was isolated from environmental samples collected in Mogadishu, Somalia, and this isolated virus was subsequently classified as "circulating" in early 2018, after detection of additional environmental positive samples in early 2018. The same virus was detected in March 2018 from an environmental sample in Nairobi, Kenya, which led to a regional response across the Horn of Africa.

A circulating VDPV2 outbreak in 2018 continued to expand geographically in the Democratic Republic of the Congo while a new strain was identified, meaning the country is now affected by three separate cVDPV2 outbreaks. In Nigeria, two cVDPV2 strains were confirmed in the first half of 2018. In Papua New Guinea a cVDPV type 1 was confirmed in June 2018. Inadequate routine immunization continues to be a major risk factor of emergence of cVDPVs. A further risk factor in (re)emergence is subnational surveillance gaps – the more rapidly a strain is detected, the more rapidly a response can be mounted. High-quality outbreak response is needed to successfully stop cVDPVs.

Conclusion

Endemic transmission of WPV1 is continuing, as evidenced both by detection of AFP cases in core reservoir areas and – more widely – by the continued detection of WPV1-positive environmental samples. All efforts must be made to maximize the impact of national emergency action plans in these remaining reservoir areas, if WPV1 transmission is to be successfully interrupted in the short term.

Concurrently, inadequate routine immunization levels coupled with subnational surveillance gaps in high-risk countries continue to be the main risk factors for the emergence or continuing circulation of cVDPVs. Efforts must be strengthened to address both risk factors. These efforts, however, are complicated by the fact that OPV is causing cVDPVs but is the only option to stop WPV; until WPV eradication has been completed OPV use cannot be stopped. WPV eradication has therefore become a "dual emergency": to eradicate WPV for its own sake and prevent global re-emergence of such strains, but also to eradicate WPV as urgently as possible, for the sake of rapidly being able to stop OPV use, and thereby prevent future cVDPV outbreaks.

Additional information on WPV and cVDPV outbreaks is available at: http://polioeradication.org/polio-today/polio-now/ and https://extranet.who.int/polis/public/CaseCount.aspx.

Update on WPV and cVDPV cases in 2018 (as of 22 August 2018)

Globally 14 cases of WPV type 1 were reported: 11 in Afghanistan and 3 in Pakistan. Additionally, 25 cases of cVDPV were reported: 11 in the Democratic Republic of Congo, 4 in Nigeria, 6 in Somalia and 4 in Papua New Guinea.

B) Update on the global polio situation, 2017-2018

Inactivated poliovirus vaccine introduction

To prepare for the switch to bivalent oral polio vaccine, all countries have committed themselves to introduce at least one dose of inactivated poliovirus vaccine (IPV) into their routine immunization programmes. Global constraints that emerged owing to technical difficulties encountered by IPV manufacturers in scaling up production resulted in a total of 35 countries experiencing delays in IPV supply. Manufacturers project increases in supply; coupled with the fact that countries are increasingly adopting the dose-sparing approach using intradermal fractional IPV instead of full dose intramuscular IPV, all countries that have experienced delays should receive the vaccine by mid-2018. During the period of shortage, the available supply was prioritized for routine immunization in countries at highest risk of outbreaks of vaccine-derived poliovirus type 2.

Containment

As of May 2018, 174 countries and territories reported that they no longer hold wild or vaccine-derived poliovirus type 2, 30 reported that they intend to retain type 2 polioviruses in 99 poliovirus-essential facilities, and two were completing their reports. Of the 30 countries planning to retain type 2 polioviruses, 18 have made significant progress with the establishment of national authorities for containment and are preparing to certify their designated poliovirus-essential facilities as per the containment requirements described in 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) (Box 1.1).

The World Health Assembly adopted in May 2018 a resolution seeking international consensus on containment urging Member States to reduce to an absolute minimum the number of facilities designated for the retention of polioviruses and to take the appropriate measures in those facilities to meet containment requirements.

The importance of effective poliovirus containment is perhaps best illustrated by recalling that the last infection due to smallpox virus – the only human pathogen to have been thus far eradicated globally – occurred as a result of an accidental laboratory containment failure. In a limited number of facilities, poliovirus will continue to be retained to serve critical national and international functions such as the production of polio vaccine or research. It is crucial that this poliovirus material is appropriately contained under strict biosafety and biosecurity handling and storage conditions, to ensure that the virus is not released into the environment, either accidentally or intentionally, to again cause outbreaks of the disease in susceptible populations. Safe containment is a cornerstone strategy to sustaining eradication.

Successful and sustained eradication carries significant humanitarian and economic benefits: with no child ever again suffering polio paralysis, and upwards of US$ 50 billion saved, those funds can be used to address other public health needs. Failure to sustain eradication would have significant consequences, however, with global resurgence of the disease, and as many as 200 000 new cases every single year, all over the world, within a period of ten years. That is why full implementation of resolution WHA71.16 on containment of polioviruses is so important. As the day nears where wild poliovirus transmission is interrupted, plans for the future must be made to secure this success. Poliovirus containment is a critical component of the risk assessment developed for certification of the eradication of poliomyelitis. All partners, agencies, Member States, laboratories and vaccine manufacturers have a responsibility to invest in containment. Full implementation of GAPIII and resolution WHA71.16 will ensure that the humanitarian and economic benefits of the global eradication of polio will be sustained for all future generations to come.

Polio transition planning

The World Health Organization (WHO) and Member States that are currently funded by the Global Polio Eradication Initiative (GPEI) face significant financial, human resources and programmatic risks as a result of the scaling down of the GPEI budget and its eventual closure. Member States therefore requested the WHO Director-General to develop a strategic action plan on polio transition that will mitigate these risks, as well as strengthen country health systems. Delegates considered WHO's 5-year strategic action plan on polio transition. The strategy responds to Member States' requests and has three key objectives: i) sustaining a polio-free world after eradication of polio virus; ii) strengthening immunization systems, including surveillance for vaccine-preventable diseases (VPDs); and iii) strengthening emergency preparedness, detection and response capacity in countries to ensure full implementation of the International Health Regulations (IHR 2005).

The strategic action plan outlines how essential polio functions like surveillance, laboratory networks and some core infrastructure of the Post Certification Strategy will be needed in the long term to sustain a polio-free world, and can be integrated into the Expanded Programme on Immunization (EPI) or Health Emergencies Programme, or integrated into national health systems. The plan provides detailed costing for the integration of essential polio functions into WHO's thirteenth general programme of work 2019–2023[1], and some financing options.

The three polio-endemic countries (Afghanistan, Pakistan, Nigeria) and a few high-risk countries battling VDPV outbreaks have been excluded from transition planning until transmission of the virus has been stopped. All other GPEI-funded countries are expected to plan for polio transition. However, transition must be planned and implemented with extreme caution, to not endanger the progress achieved in eradicating polio. Robust capacity must be maintained through certification and beyond, particularly in the fields of immunization and surveillance, to achieve eradication (of both WPVs and cVDPVs through OPV cessation) and subsequently to sustain eradication. Continued support by both domestic contributions and contributions from the international development community through certification and beyond will be needed to secure a lasting polio-free world.

GOAL 2: MEET GLOBAL AND REGIONAL ELIMINATION TARGETS: ACHIEVE MATERNAL AND NEONATAL TETANUS ELIMINATION (MNTE)

Indicator G2.1

A) Status of the MNTE GVAP indicator, 2017

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[2]; the neonatal tetanus indicator acts as proxy for maternal tetanus. To monitor sustainability of elimination, the routine Expanded Programme on Immunization (EPI) and 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.
DATA SOURCES	• WHO-UNICEF Joint Reporting Forms (JRFs). • Country health management information system (HMIS) 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 validation surveys.
TARGET	• All 40 countries that had to achieve MNTE in 2010 have achieved the goal by 2015.

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 1.2.

[1] http://www.who.int/about/what-we-do/gpw-thirteen-consultation/en/
[2] Please refer to GVAP Secretariat Report 2013 for more information: http://www.who.int/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf

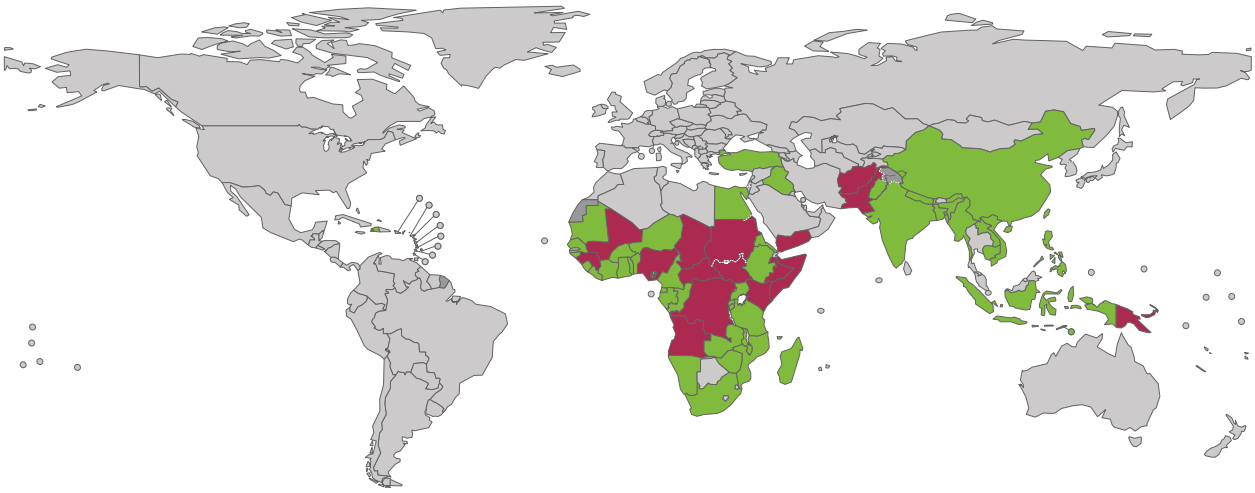
Box 1.2: Descriptions of indicators, results, data sources and highlights

For more information, please consult:
http://www.who.int/immunization/diseases/MNTE_initiative/en/

The total number of countries that have achieved MNT elimination (MNTE) since 2010 is 25 (of the 40 required to meet the GVAP milestone for 2015). As of December 2017, a total of 44[3] of the 59 priority Member States (75%) had achieved MNTE (see Fig. 1.2).

In 2017, three additional countries (Ethiopia, Haiti and the Philippines) and five south-eastern states[4] of Nigeria (referred to as the "south-east zone") achieved MNTE.

Fig. 1.2: Member States[a] with validated elimination of neonatal tetanus (as of December 2017)



Not eliminated
Eliminated since 2000
Eliminated prior to 2000

[a] This includes the south-east zone of Nigeria and the Punjab province of Pakistan.
Source: WHO-UNICEF database, 8 January 2018.

In 2017, tetanus toxoid (TT) vaccination campaigns targeting women of reproductive age (15–49 years) were conducted in six Member States[5], reaching an additional 4 million women in 2017. The total number of countries that have implemented TT supplementary immunization activities (SIAs) from 1999 to 2017 remains 53, however.

Targeted campaigns for women of reproductive age in high-risk areas with tetanus toxoid-containing vaccines (TTCV) have protected[6] over 153 million women globally. However, 53 million women of reproductive age still remain to be reached through SIAs in the remaining 15 priority countries that have not yet attained MNTE. Timely availability of resources including funds has been dictating the phase of work in terms of reaching more women of reproductive age with protective doses of TTCV during SIAs, and this will be critical to the implementation of countries' action plans.

B) Update on MNTE activities, 2017–2018

In 2017 Ethiopia, Haiti and the Philippines were validated for maternal and neonatal tetanus elimination and Chad and Kenya completed implementation of planned vaccination activities. Validation surveys are planned for Chad and the southern region of Mali in 2018. Pre-validation assessments of Pakistan (Sindh province) and the Democratic Republic of the Congo are also expected in 2018.

There remain 14 priority countries yet to achieve MNTE – Kenya conducted and passed its validation survey in 2018. Two of these countries have partially eliminated MNT: Pakistan (Punjab province) and Nigeria (south-east region). All the remaining 14 countries are eligible for support from Gavi, the Vaccine Alliance; some of them face challenges of access and security (e.g. the Central African Republic and Yemen) and competing health priorities such

[3] Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, China, Comoros, Congo, Côte d'Ivoire, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Guinea Bissau, Haiti, India, Indonesia, Iraq, Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Mauritania, Mozambique, Myanmar, Namibia, Nepal, Niger, Philippines, Rwanda, Senegal, Sierra Leone, South Africa, Timor-Leste, Turkey, Togo, Uganda, United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.
[4] Abia, Anambra, Ebonyi, Enugu and Imo states.
[5] Chad, Kenya, Nigeria, Pakistan, Philippines and Sudan.
[6] With at least two doses of vaccine.

as poliovirus circulation (Afghanistan, Pakistan, Somalia). South Sudan is currently scheduling a last round of immunization for three states in the north of the country. Annex 1.1 shows the status of MNT elimination efforts by country.

Further work at the international level includes the drafting of a guide for EPI programmes on sustaining MNTE, which highlights the critical activities that countries need to undertake to sustain elimination status; this will be finalized by quarter 3 2018. Additionally, a TT Uniject business case was submitted to Gavi's Policy and Programme Committee to request financial assistance to support the production and availability of this critical pre-filled device. The business case was aimed at markedly increasing access to the tetanus toxoid vaccine, particularly in very remote parts of selected countries, where currently access is seriously compromised as a result of insecurity, active conflicts and lack of human resources. Gavi's Policy and Programme Committee did not approve the business case, unfortunately (according to a January 2018 communication). Without Gavi financing, it seems unlikely that this very important initiative will materialize.

The first phase of the MNTE investment case, which focuses on the 14 remaining countries yet to attain elimination, has been completed. This phase highlights the resources needed and will also be used for resource mobilization. The United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA) and WHO have all significantly contributed to building this case.

Annex 1.1: Status of MNT elimination in countries

Country category and definition	List of countries in this category	Progress
Countries likely to attain MNTE in 2018	Angola, Chad, Democratic Republic of the Congo, Kenya and Mali	Kenya was validated as having attained MNTE in March 2018. Chad and southern Mali have completed pre-validation assessments, and validation surveys are planned by end of 2018. Angola and the Democratic Republic of the Congo are planning corrective actions in some areas, to prepare for assessments following delays due to emergencies related to a yellow fever outbreak in 2017, and Ebola virus disease outbreak in 2018, respectively.
Countries likely to attain MNTE in 2019	Papua New Guinea, Guinea, South Sudan, Sudan	Implementation efforts in Papua New Guinea and Sudan are lagging; implementation is on hold in Papua New Guinea due to emergencies (recent earthquakes) and due to some logistical issues in Sudan. South Sudan is affected by conflict; however, the country is on course to attain MNTE, with completion of a third round of SIAs in 2018. Guinea reviewed the MNTE risk status of districts and is planning further implementation of SIAs in September 2018.
Countries likely to achieve MNTE in 2020 or after	Afghanistan, Central African Republic, Somalia, Mali, Nigeria, Pakistan, Yemen	Afghanistan, Central African Republic and Somalia: Implementation of MNTE activities has stalled due to a mix of low commitment, competing priorities and insecurity; further advocacy and technical assistance is required. It is in these countries that TT Uniject devices would be instrumental in vaccinating populations in remote locations. It is foreseeable that MNTE will only be achieved after 2020. Mali is planning TT SIAs in the northern part of the country following a risk assessment; a pre-validation assessment for the south is completed and a validation survey expected by end 2018. The south-east zone of Nigeria was validated for MNTE in 2017 and the south-west zone of the country is conducting corrective SIAs following the recommendations from the pre-validation assessment – for possible validation in late 2018. Nigeria's south-south zone has reviewed the MNT risk status and will commence implementation of TT SIAs in September 2018. The remaining three northern zones will carry out an MNT risk review early in 2019 to prepare for implementation of MNTE activities in a phased manner to meet the goal by 2020. Pakistan has embarked on a province-by-province approach. Punjab province achieved MNTE in 2016. Sindh province has completed TT SIAs and is preparing for a pre-validation assessment in July 2018. Further MNTE activities are planned in another two at-risk provinces with larger populations (Balochistan and Khyber Pakhtunkhwa). Yemen has resumed implementation of TT SIAs in a phased approach with the aim of achieving MNTE by 2020. The country has completed the first round in 46 districts and is planning the second round for October 2018, delayed due to cholera and diphtheria outbreaks in 2017 and ongoing conflict in the country.

GOAL 2: MEET GLOBAL AND REGIONAL ELIMINATION TARGETS: ACHIEVE MEASLES ELIMINATION

Indicator G2.2

DEFINITION OF INDICATOR	Framework for verification of measles elimination[7] 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.
DATA SOURCES	• WHO-UNICEF 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 2017.
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 2013 GVAP Secretariat report[8]. • Regional verification commission reports are only available from four regions: European Region, Region of the Americas, South-East Asia Region and the Western Pacific Region.
MILESTONES	• Measles elimination goals by WHO region:[9] – Region of the Americas: last endemic case in 2002 and verified as having eliminated measles in 2016 – Western Pacific Region: elimination by 2012 – European Region: elimination by 2015 – Eastern Mediterranean Region: elimination by 2020 – African Region: elimination by 2020 – South-East Asia Region: elimination by 2020.

[7] Framework for verifying elimination of measles and rubella. Wkly Epidemiol Rec. 2014; 88(9):89–99.
[8] Global Vaccine Action Plan. Monitoring, evaluation & accountability: Secretariat annual report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1, accessed 21 August 2018).
[9] Global measles and rubella strategic plan: 2012–2020. Geneva: World Health Organization; 2012 (http://reliefweb.int/sites/reliefweb.int/files/resources/Measles_Rubella_StrategicPlan_2012_2020.pdf, accessed 21 August 2018).

GOAL 2: MEET GLOBAL AND REGIONAL ELIMINATION TARGETS: ACHIEVE RUBELLA AND CONGENITAL RUBELLA SYNDROME ELIMINATION

Indicator G2.3

DEFINITION OF INDICATOR	• Rubella and congenital rubella syndrome (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 CRS cases excrete 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.
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 2013 report of the GVAP Secretariat[10]. • Coverage estimates for the first dose of rubella-containing vaccine are based on WHO and UNICEF estimates of coverage of measles-containing vaccine.
COMMENTS ON DATA QUALITY	• None
MILESTONES	• Region of the Americas: Rubella eliminated in 2009 and the International Expert Committee for Measles and Rubella Elimination verified the region free of rubella and CRS in April 2015. • European Region: Rubella elimination by 2015. • Western Pacific Region: Rubella elimination pledged but no target date set. • South-East Asia Region: Rubella control by 2020. • African Region: No target. • Eastern Mediterranean Region: No target.

A) Status of GVAP measles indicators, 2017

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 1.3.

Box 1.3: Descriptions of indicators, results, data sources and highlights

For further detail see:

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/Measles_Rubella/progress_2000_2016.pdf

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles/en/

[10] Global Vaccine Action Plan. Monitoring, evaluation & accountability: Secretariat annual report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf, accessed 21 August 2018).

All six WHO regions have committed to measles elimination by or before 2020. The sixty-third World Health Assembly in 2010 endorsed three global measles targets for 2015 as milestones towards global eradication of measles;[11] progress in meeting them, however, has been slow.

Measles elimination status, incidence and mortality

To date, all six WHO regions have established regional verifications commissions (RVCs). However, the African and the Eastern Mediterranean Regions, which established their RVCs in 2017, have not yet started verifying the elimination status within countries. Among the four regions verifying countries, 80 Member States (41%) and two areas have been verified as having eliminated measles (Table 1.1) – four additional Member States since 2016.

Table 1.1: Progress towards measles and rubella elimination in 2017

		Established NVCs that submitted annual status reports	Member States that were verified in 2017 free of endemic		Member States that have interrupted[c] in 2017		Member States still endemic in 2017 with	
			measles	rubella	measles	rubella	measles	rubella
WHO region	**No. Member States**	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
African	47	0	0	0	0	0	47 (100%)	47 (100%)
Americas	35	35 (100%)	35 (100%)	35 (100%)	NA	NA	0	0
Eastern Mediterranean	21	0[a]	0	0	0	0	21 (100%)	21 (100%)
European	53	53 (100%)	37 (70%)	37 (70%)	6 (11%)	5 (9%)	10 (19%)	11 (21%)
South-East Asia	11	11 (100%)	2 (18%)	0	0	0	9 (82%)	11 (100%)
Western Pacific	27	27 (100%)	6 (22%)[b]	2 (7%)	0	0	21 (78%)	25 (7%)
Global	194	–	80 (41%)	74 (38%)	6 (3.1%)	5 (2.6%)	108 (55.6%)	115 (59.3%)

[a] Region established RVC in 2017 but review of NVC reports has not yet taken place.
[b] Two areas in the Western Pacific Region, Hong Kong Special Administrative Region (China) and Macao Special Administrative Region (China), have been verified as having eliminated measles.
[c] Member State interrupted measles or rubella transmission for > 12 months but < 36 months.
Note: all percentages in the table are based on the total number of Member States in the region.

From 2010 to 2016 global reported measles incidence has decreased by 62% from 50 cases per million population in 2010 to 19 in 2016; in 2017, however, this has increased to 25 cases per million population in 2017. The increase in 2017 was seen in four of six WHO regions, increasing the overall global figure (Table 1.2 and Fig. 1.3).

Incidence in the South-East Asia Region did not change in 2017 and there was a significant decline (81%) in incidence in the Western Pacific Region. The increase in incidence was most significant in the Eastern Mediterranean (82% increase) and European Regions (82%), followed by the African Region (46%). Following a record low number of measles cases in the European Region in 2016 (4363), cases resurged in 2017: 24 293 cases and 35 deaths. This is related to declines in overall routine immunization coverage, consistently low coverage among some marginalized groups or interruptions in vaccine supply. The increase in reported cases in the Eastern Mediterranean Region is largely due to the acute and protracted emergency situation affecting several countries in the region.

[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 5 cases per million population and maintain that level; 3) reduce measles mortality by 95% or more in comparison with 2000 estimates.

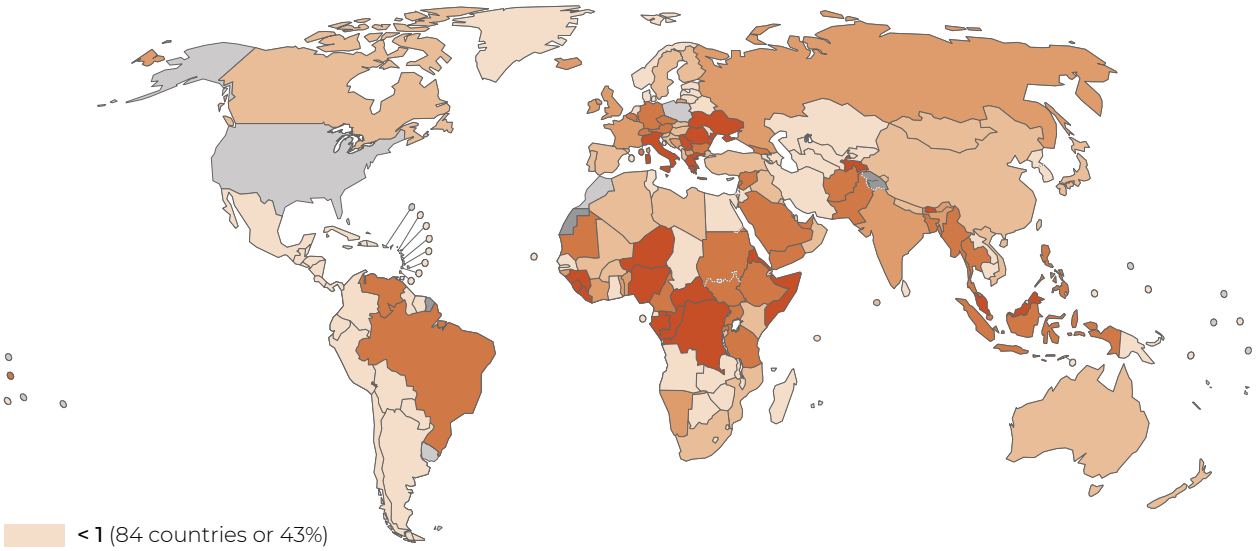
Of particular concern is the situation in the Regions of the Americas: the region had been verified as having eliminated measles in 2016 (Table 1.1), but a measles outbreak has been ongoing in the Bolivarian Republic of Venezuela since June 2017 with more than 1000 reported cases. Population movement due to the recent political and socioeconomic situation in the Bolivarian Republic of Venezuela led to measles cases in Colombia, Brazil and Ecuador (Fig. 1.3). Due to the outbreak resulting in an uninterrupted chain of measles virus transmission for more than 12 months, the Bolivarian Republic of Venezuela lost its measles elimination status in June 2018, as has the region as a whole. However, the remaining 34 Member States in the region continue to sustain their measles elimination status in 2018.

Table 1.2: Number of measles cases and incidence by WHO region, in 2016–2017 and baseline 2010

WHO region	WHO-UNICEF estimates for MCV1 national coverage (%)			WHO-UNICEF estimates for MCV2 national coverage (%)			Measles incidence per million population[a]			Percentage of Member States with incidence < 5 per million population		
	2017	2016	2010	2017	2016	2010	2017	2016	2010	2017	2016	2010
African	70	70	73	25	23	5	69	37	232	53	51	30
Americas	92	92	93	74	80	43	2	0.02	0.3	97	100	100
Eastern Mediterranean	81	81	77	67	67	52	57	10	17	55	50	40
European	95	93	93	90	88	80	28	5	34	56	84	71
South-East Asia	87	87	83	77	75	16	14	14	30	45	27	36
Western Pacific	97	96	96	94	93	87	6	31	27	80	68	68
All	**85**	**85**	**84**	**67**	**66**	**39**	**25**	**19**	**50**	**60**	**69**	**60**

[a] Excludes Brazil, Cook Islands, Fiji, Marshall Islands (the), Morocco, Nauru, Niue, Poland, Tuvalu, United States of America (the), Uruguay and Vanuatu, which did not report measles case data in the 2017 JRF.
Source: JRF data, as of 28 June 2018.

Fig. 1.3: Reported measles incidence rates[a] per country, 2017



< 1 (84 countries or 43%)
1 to < 5 (33 countries or 17%)
5 to < 10 (15 countries or 8%)
10 to < 50 (31 countries or 16%)
≥ 50 (19 countries or 10%)
Not available/no data reported to WHO headquarters (12 countries or 6%)
Not applicable

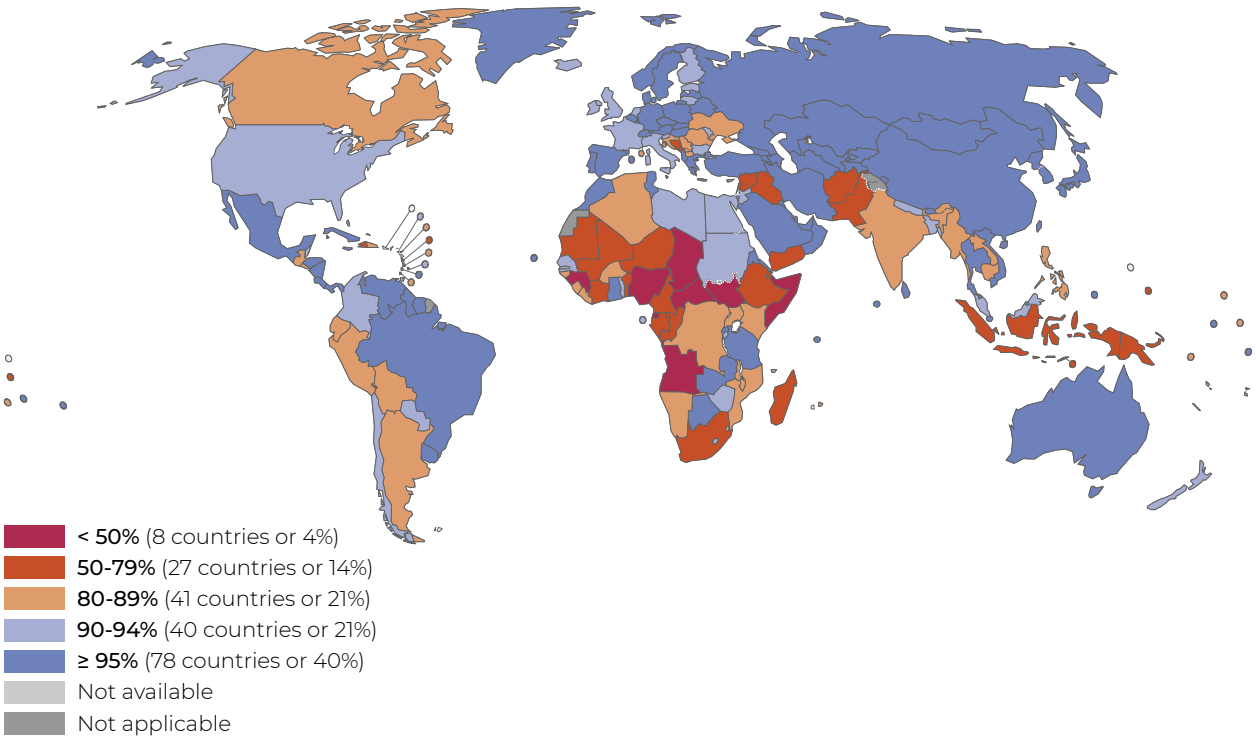
[a] Per million population
Source: JRF data, as of 28 June 2018.

Between 2000 and 2016[12], estimated measles deaths decreased by 84% (from 550 100 [95% CI = 374 000–896 500] in 2000 to 89 780 [95% CI = 45 700–269 600] in 2016). Progress since 2010, however, has been too slow and the target of 95% mortality reduction was not achieved.

Coverage of measles-containing vaccine

Between 2010 and 2017, global routine measles vaccine coverage (measles-containing vaccine first dose, MCV1) stagnated at around 85% – well below the 2015 target of ≥ 90%.[13] Three of the six WHO regions have sustained measles-containing vaccine (MCV1) coverage above 90% (Region of the Americas, European and Western Pacific Regions), two regions achieved coverage between 80 and 90% (Eastern Mediterranean and South-East Asia Regions) and one region failed to reach 80% coverage (African Region); see Fig. 1.4. Global MCV2 coverage has been steadily increasing and reached 67% in 2017. This increase is largely due to the growing number of countries that have introduced MCV2: to date, 167 countries (86%) have introduced MCV2 into their routine Immunization programme and five additional countries are planning introductions in 2018. The majority of countries yet to introduce MCV2 are in the African Region (Fig. 1.5).

Fig. 1.4: Immunization coverage of infants with routine first dose of measles-containing vaccines (MCV1), by country, 2017

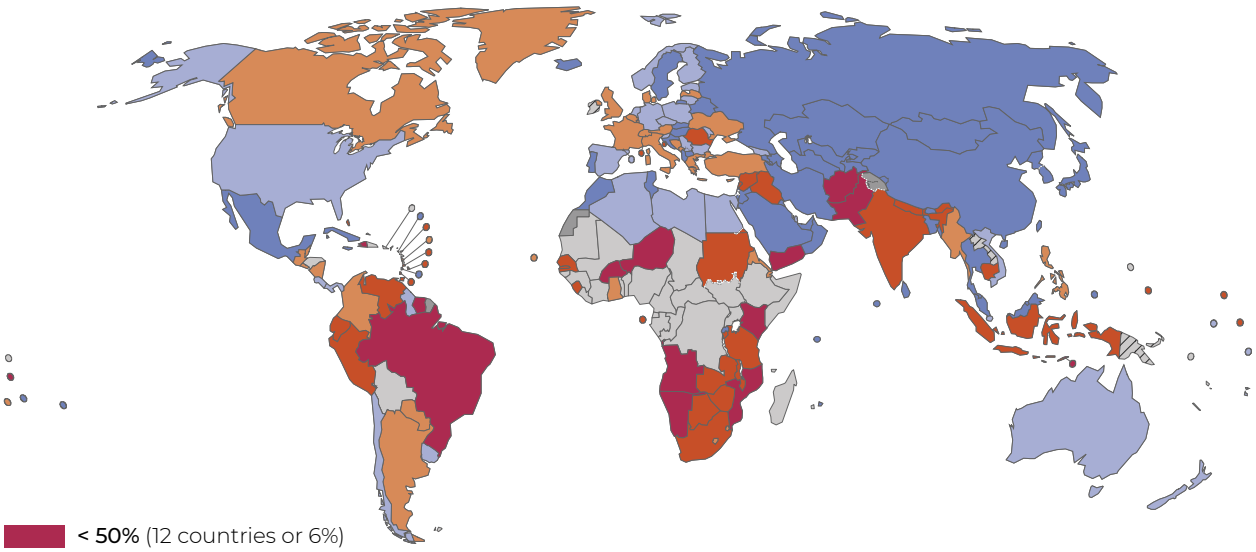


Source: WHO-UNICEF coverage estimates 2017 revision, July 2018.

[12] The mortality estimates for 2017 were not available at the time of writing this report.

[13] 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 age groups born since the introduction of measles vaccine.

Fig. 1.5: Immunization coverage of infants with routine second dose of measles-containing vaccines (MCV2), by country, 2017



Source: WHO-UNICEF coverage estimates 2017 revision, July 2018.

Many countries regularly supplement routine efforts through the use of SIAs. In 2017, 67 preventive SIAs vaccinated more than 195 million children in 49 Member States, with 16 of those (23%) providing one or more additional child health interventions during the SIA (such as Vitamin A, deworming, and oral polio vaccination). Coverage was reported as ≥ 95% in only 33 (48%) of the 67 preventive SIAs conducted in 2017 (based on doses administered). However, among the five countries conducting post-SIA coverage surveys and reporting the outcome to WHO in 2017, one estimated coverage at ≥ 95%. While SIAs have contributed to decreasing disease incidence among (low income) countries conducting them regularly, SIAs are labour intensive and costly, and every effort should be made to strengthen routine immunization systems so that SIAs can eventually be ceased.

Conclusion

In summary, some improvement has been observed in 2017, in MCV2 coverage levels, in the number of RVCs established, and in the number of Member States verified as having eliminated measles. However, global measles incidence has increased over 2016 and only one region (Region of the Americas) met the global 2015 target of fewer than 5 cases per million population. The global coverage with MCV1 has remained stagnant and given the gaps in coverage and population immunity, major outbreaks continue to occur in all of the six WHO regions. Given this, the global and regional measles targets for 2015 continue to be missed. Moreover, one region lost its hard-earned measles elimination status.

As a highly infectious disease, measles elimination requires both very high and homogeneous population immunity and a high-quality surveillance system. There is an urgent need for sustained efforts to raise and maintain high levels of immunization coverage even in areas where elimination-level control has previously been attained. Every opportunity to address system bottlenecks and to increase routine immunization coverage should be seized. Surveillance is the other critical element to managing the vaccination programme and verifying countries' elimination status. However, resources are currently inadequate and are at risk of being further reduced due to dwindling polio resources, which have been instrumental in supporting measles and rubella and other VPD surveillance systems.

As part of resolution WHA70.14, Member States have requested the WHO Director-General to report to the Seventy-third World Health Assembly (in 2020) on the epidemiological aspects and feasibility of, and potential resource requirements for, measles and rubella eradication. Regardless of the outcome of that report on a more ambitious global goal, key stakeholders, donors and national governments need to increase their efforts and support to reach and sustain the global and regional measles elimination goals.

B) Status of GVAP rubella indicators, 2017

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 1.4.

Box 1.4: Descriptions of indicators, results, data sources and highlights

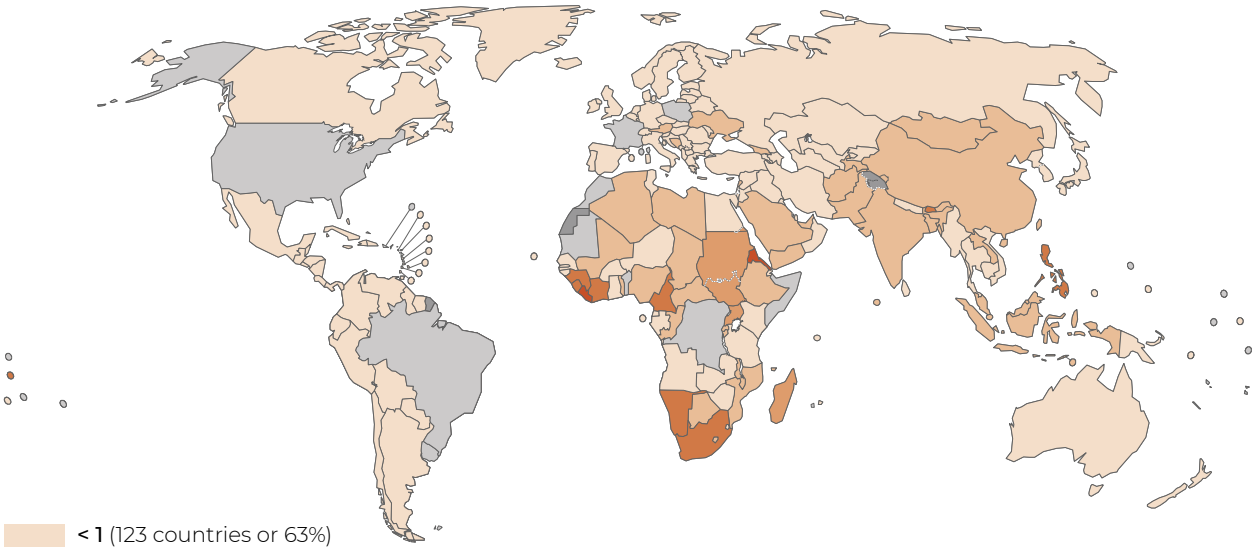
For further detail see:

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/rubella/en/

There has been no change since 2016 in the establishment of regional rubella elimination targets: only the Region of the Americas, European and Western Pacific Regions have set targets, though the Western Pacific Region has not yet set a target date. The Region of the Americas has been verified as having eliminated rubella and Congenital Rubella Syndrome (CRS) in 2015 and has sustained elimination status. Globally, 74 Member States (38%) have been verified as having eliminated rubella (Table 1.1) – four more Member States than in 2016.

In 2017, the global incidence of rubella was estimated at 2.4 per million population (reported by 176 (91%) Member States) compared to 3.4 per million population (reported by 169 (87%) Member States) in 2016, showing an apparently significant decline. However, rubella surveillance is weak in many countries and the reported incidence is likely not an accurate reflection of the control status in all countries. Rubella incidence has dramatically increased in the African Region despite increasing vaccine coverage; this is likely not an increase in cases per se, but rather due to improved rubella surveillance systems (Fig. 1.6 and Table 1.3).

Fig. 1.6: Reported rubella incidence rates[a] by country, 2017



< 1 (123 countries or 63%)
1 to < 5 (38 countries or 20%)
5 to < 10 (4 countries or 2%)
10 to < 50 (9 countries or 5%)
≥ 50 (2 countries or 1%)
Not available/no data reported to WHO headquarters (18 countries or 9%)
Not applicable

[a] Per million population
Source: JRF, as of 28 June 2018

As of 28 June 2018, 162 (84%) Member States had introduced RCV, with eight additional Member States planning introductions in 2018. Twenty-four Member States have yet to introduce the vaccine. Average coverage globally has steadily increased from 35% in 2010 to 47% in 2016 and 52% in 2017; coverage, however, varies from 21% in the South-East Asia Region to 97% in the Western Pacific Region[14] (Table 1.3 and Fig. 1.7).

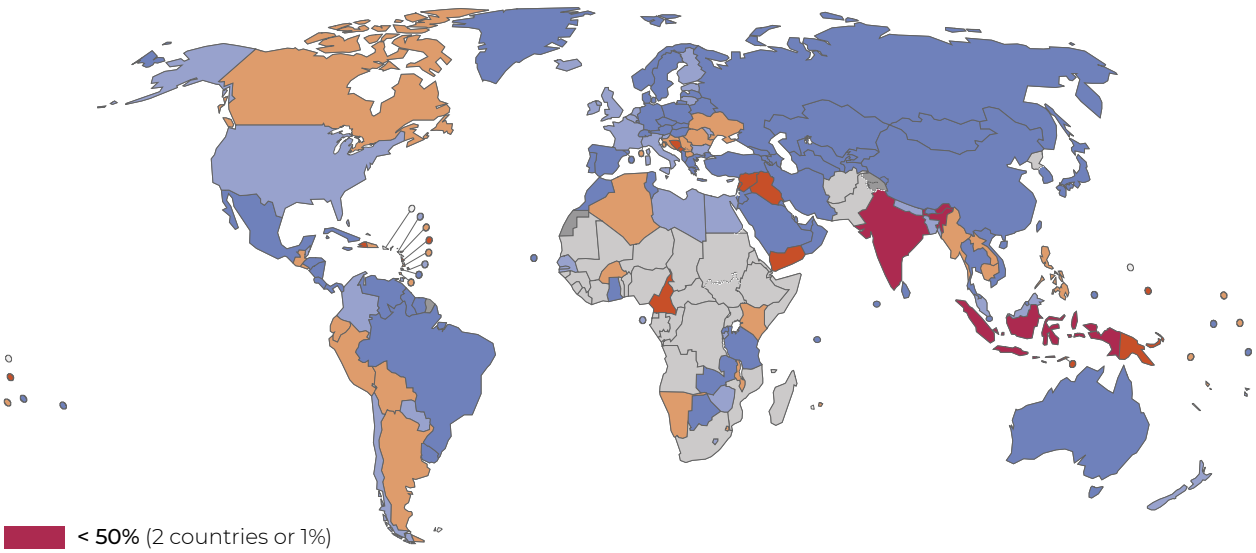
[14] Calculation of coverage takes into account all birth cohorts regardless of the introduction status of RCV.

Table 1.3: Rubella incidence and rubella-containing vaccine coverage by WHO region, 2015–2017 and baseline 2010

WHO region	Rubella incidence per million population				RCV1 coverage (%)[a]			
	2017	2016	2010	% change 2010–2017	2017	2016	2010	% change 2010–2017
African	77	4	3	51	26	13	0	100
Americas	0	0.002	0.02	0	92	92	93	-1
Eastern Mediterranean	1	3	2	-50	46	46	38	17
European	0.5	2	12	-96	95	93	93	2
South-East Asia	2	5	8	-75	21	15	3	86
Western Pacific	2	3	25	-92	97	96	61	37
Total	**2**	**3**	**11**	**-82**	**52**	**47**	**35**	**33**

[a] Coverage estimates for the first dose of rubella-containing vaccine are based on WHO and UNICEF estimates of coverage of measles-containing vaccine.
Source: JRF data, as of 28 June 2018.

Fig. 1.7: Immunization coverage of infants with routine first dose of rubella-containing vaccinea by country, 2017



< 50% (2 countries or 1%)
50-79% (13 countries or 7%)
80-89% (34 countries or 18%)
90-94% (36 countries or 19%)
≥ 95% (77 countries or 40%)
Not available or rubella vaccine not introduced (32 countries or 17%)
Not applicable

[a] Coverage estimates for the first dose of rubella-containing vaccine are based on WHO and UNICEF estimates of coverage of measles-containing vaccine.
Source: WHO-UNICEF coverage estimates 2017 revision, July 2018.

As all WHO regions have measles elimination goals, it would represent a missed opportunity not to include rubella elimination as a disease target for countries that meet the rubella vaccine introduction criteria. Hence, there is a need to advocate for resources and build support for the three remaining regions to adopt elimination goals. This includes ensuring that all Member States can achieve and maintain the minimum coverage (≥ 80%) through routine services and/or SIAs required for introduction of RCV.

Financial support from Gavi together with the leadership, coordination and technical expertise from the Measles & Rubella Initiative, 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. 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 the remaining five WHO regions by 2020.

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2. IMMUNIZATION COVERAGE

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 (DPT3) 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 working group (WG)**

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 2.1.

Box 2.1: Descriptions of indicators, results, data sources and highlights

Main background documentation

For discussion about data availability and quality see the 2017 GVAP Secretariat report.

Slides with additional global coverage infographics include:

- Summary presentation of key indicators towards global immunization goals
- Progress and Challenges with Achieving Universal Immunization Coverage
- Global vaccine introduction status
- Vaccines coverage scorecards by WHO region and Member State

Additional information

- Global and regional immunization profile
- WHO-UNICEF vaccine coverage estimates by country
- Maps of Diphtheria-tetanus-pertussis (DTP3) immunization coverage over time
- Subnational immunization coverage data

Important note: **The entire time series** of WHO UNICEF estimates of national immunization coverage (WUENIC) are updated annually, based on the availability of new data that might affect the coverage estimates over a period of time, for example new coverage surveys results, updates sent by Member States or data submitted late in the previous year. Thus, the coverage estimates for 2016 in this report for certain countries may not be the same as those reported in the previous GVAP report. For consistency, coverage data may only be compared across time or countries within the same time series and not between different GVAP Secretariat reports. For more information see the first GVAP Secretariat report and WUENIC methodology description.

GOAL 3: MEET VACCINATION COVERAGE TARGETS IN EVERY REGION, COUNTRY AND COMMUNITY

Indicator G3.1 (also includes indicators SO3.1, SO4.1, SO4.2): DTP3 coverage of 90% nationally and 80% in every district by 2020

TARGET	DTP3 coverage of 90% nationally and 80% in every district by 2020 in all Member States.
DEFINITION OF INDICATOR	National coverage data based on WHO-UNICEF estimates of national immunization coverage (WUENIC). For district-level coverage, the data are considered valid only if the WUENIC estimates and administrative data from the WHO-UNICEF Joint Reporting Forms (JRFs) are the same or if the WUENIC estimates are ≥ 90%.
DATA SOURCES	• WUENIC estimates. • Administrative data from JRFs (to compare with WUENIC estimates as a check of validity).

A) Status of THE GVAP coverage indicators, 2017

In total 123 Member States (63%) achieved a national diphtheria–tetanus–pertussis-containing vaccine (DTP3) coverage rate of 90% or above in 2017, and 113 of them sustained this coverage rate for three or more years. District data were available for 82% of countries, and valid in 62% of countries. Overall only 26% of the countries had national DTP3 coverage above ≥ 90% and valid district data above 80% in all districts (Table 2.1).

Table 2.1: Summary of national coverage and district-level coverage data for DTP3, 2017[a]

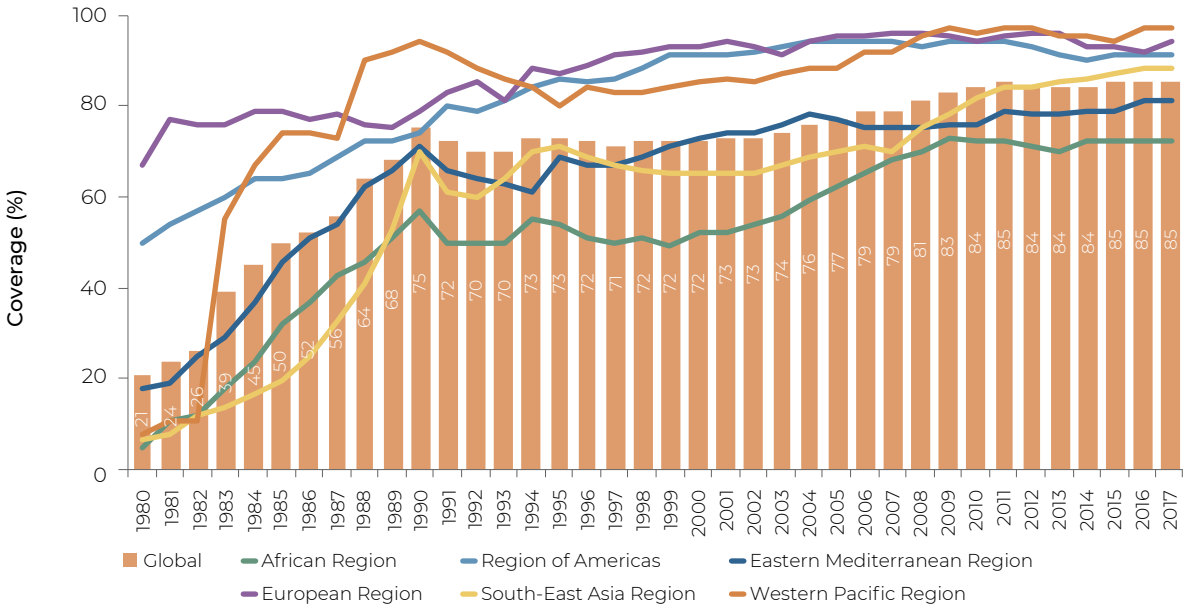
National DTP3 coverage	No. of countries (%) with valid district data and DTP3 coverage ≥ 80% in all districts	No. of countries (%) with valid district data, but not achieving 80% in all districts	No. of countries (%) with invalid/not reported district data	Total
≥ 90%	50 (26%)	46 (24%)	27 (14%)	123 (63%)
< 90%	0 (0%)	24 (12%)	47 (24%)	71 (37%)
Total	50 (26%)	70 (36%)	74 (38%)	194 (100%)

[a] The primary source for the aggregated district data is the district table of sheet 6 of the Joint Reporting Form. However, whenever data were missing in that sheet, and available from the annual subnational coverage data collection mechanism, data were used from that second source.

1) National-level DTP3 coverage

Globally in 2017 the average coverage with three doses of DTP-containing vaccine (DTP3) remained at 85%, with no significant change during the past year. The coverage pattern across World Health Organization (WHO) regions was also comparable to last year (Fig. 2.1). Only the European Region observed a 2-point increase to 94% due mainly to Ukraine moving from 19 to 50% coverage.

Fig. 2.1: Global and regional average coverage rate (%) with DTP3, 1980–2017



Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.

Six countries[1] which in 2016 had national DTP3 coverage rates below the 90%-threshold reached or exceeded the threshold in 2017. Conversely, 11 countries[2] which in 2016 had national DTP3 coverage rates above the threshold dropped below the 90%-threshold in 2017. There was a significant increase in DTP3 coverage (over 10 points) as compared to 2016 in the following two countries: Kazakhstan and Ukraine.

There are eight countries that had less than 50% DTP3 coverage in 2015 throughout 2017: the Central African Republic, Chad, Equatorial Guinea, Guinea, Nigeria, Somalia, South Sudan and the Syrian Arab Republic.

The number of children un- or under-vaccinated with DTP decreased between 2010 and 2017 by over 1.7 million – to 19.9 million in 2017 (49% in the African Region, 21% in the South-East Asia Region and 16% in the Eastern Mediterranean Region. The countries with the highest number of children un- or under-vaccinated with DTP remain Nigeria, India, Pakistan, Indonesia and Ethiopia; together these five countries represent half of the 19.9 million un- or under-vaccinated worldwide.

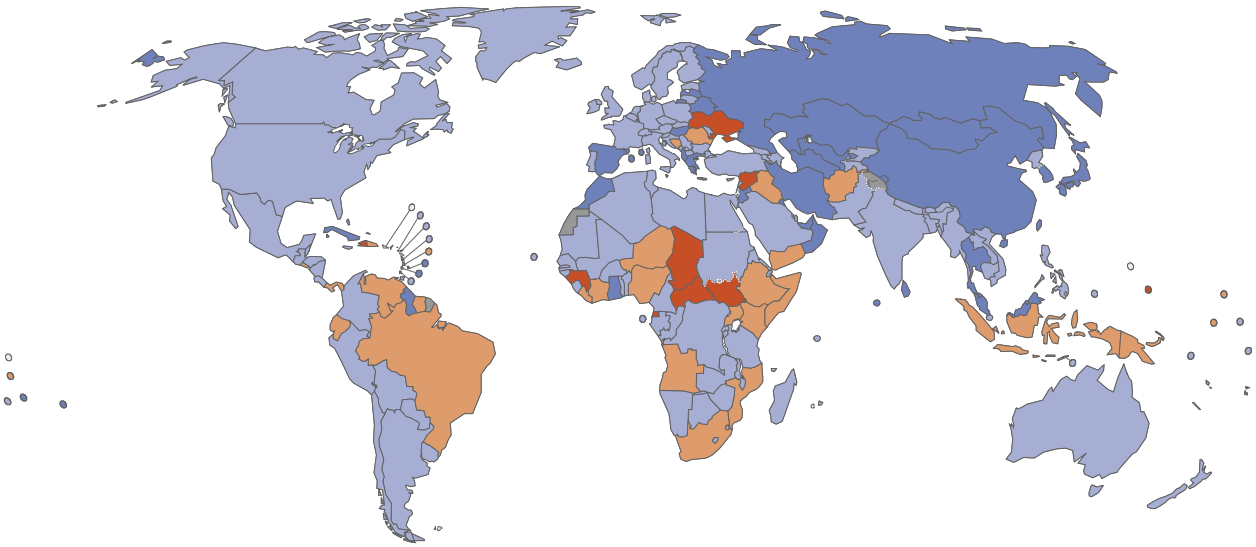
DTP1–DTP3 drop-out rates

Drop-out rates of countries where DTP3 coverage was below 90% have been analysed. Globally the patterns of countries with drop-out issues are unchanged from last year.

[1] Austria, Kazakhstan, Kiribati, Nepal, Sierra Leone and Togo
[2] Argentina, Belize, El Salvador, Finland, Iceland, Myanmar, Nauru, Saint Lucia, Suriname, Trinidad and Tobago and Zimbabwe

Eight countries[3] had DTP3 coverage below 50% (thus drop out measurement is irrelevant with regard to increasing overall coverage). Among the 63 countries with DTP3 coverage between 50 and 89%, 31 countries[4] experienced a drop-out rate of 10 points or more in 2017. Among those, three countries had a drop-out rate ≥ 20 points (Fig. 2.2), Haiti, Micronesia (Federated States of) and Ukraine.

Fig. 2.2: DTP1–DTP3 drop-out rates in 2017



≥ 20% (9 Member States or 5%)
10–19% (29 Member States or 15%)
1–9% (119 Member States or 61%)
0% (37 Member States or 19%)
Not applicable

Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.

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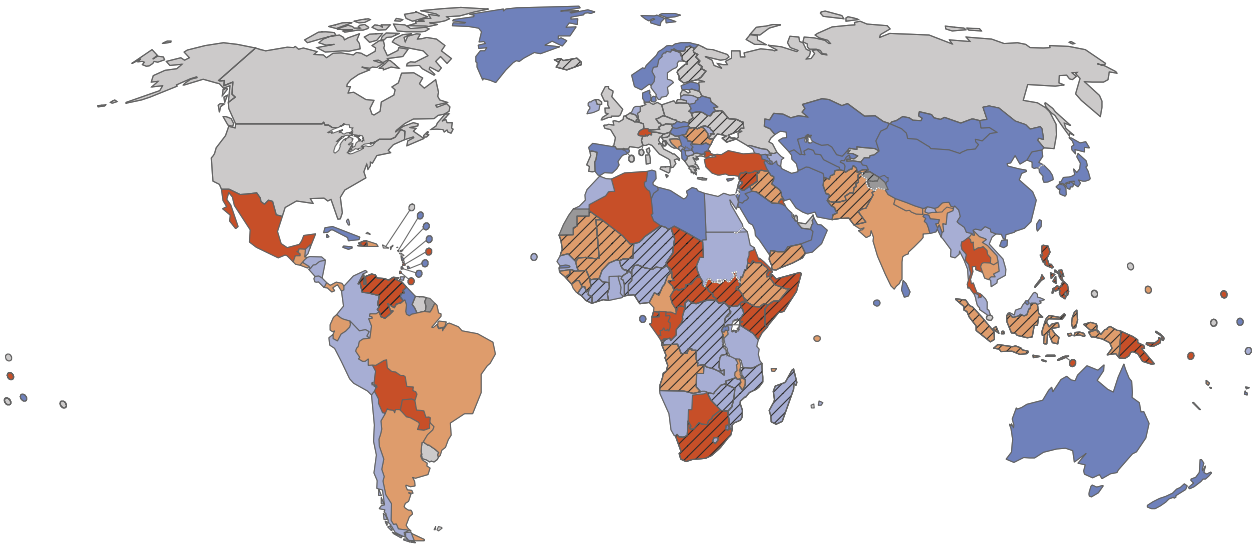
[3] Central African Republic, Chad, Equatorial Guinea, Guinea, Nigeria, Somalia, South Sudan and Syrian Arab Republic

[4] These countries are: Afghanistan, Angola, Bosnia & Herzegovina, Brazil, Côte d'Ivoire, Dominican Republic, Ecuador, El salvador, Ethiopia, Haiti, Indonesia, Iraq, Kenya, Liberia, Mali, Marshall Islands, Micronesia (Federated States of), Mozambique, Nauru, Niger, Panama, Papua New Guinea, Romania, Saint Lucia, Samoa, South Africa, Suriname, Uganda, Ukraine, Venezuela (Bolivarian Republic of) and Yemen

2) District-level DTP3 coverage

Among the 120 (62%) countries with valid district-level data, only 50 (26%) had achieved 90% national coverage and coverage of ≥ 80% in every district meeting the indicator G3.2 target (Fig. 2.3).

Fig. 2.3: Member States by the percentage of districts with DTP3 coverage ≥ 80% and valid data, 2017



< 50% (31 Member States (16%), 16 of which have administrative coverage DTP3 data considered not valid)
50–79% (32 Member States (16%), 13 of which have administrative coverage DTP3 data considered not valid)
80–99% (47 Member States (24%), 11 of which have administrative coverage DTP3 data considered not valid)
All districts (50 Member States (26%), 0 of which have administrative coverage DTP3 data considered not valid)
WHO-UNICEF (WUENIC) estimate is < 90% or differs from country administrative coverage reported on the JFR and therefore **district data are not considered valid** (46 Member States or 24%)
Not available (34 Member States (18%), 6 of which have administrative coverage DTP3 data considered not valid)
Not applicable

Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.

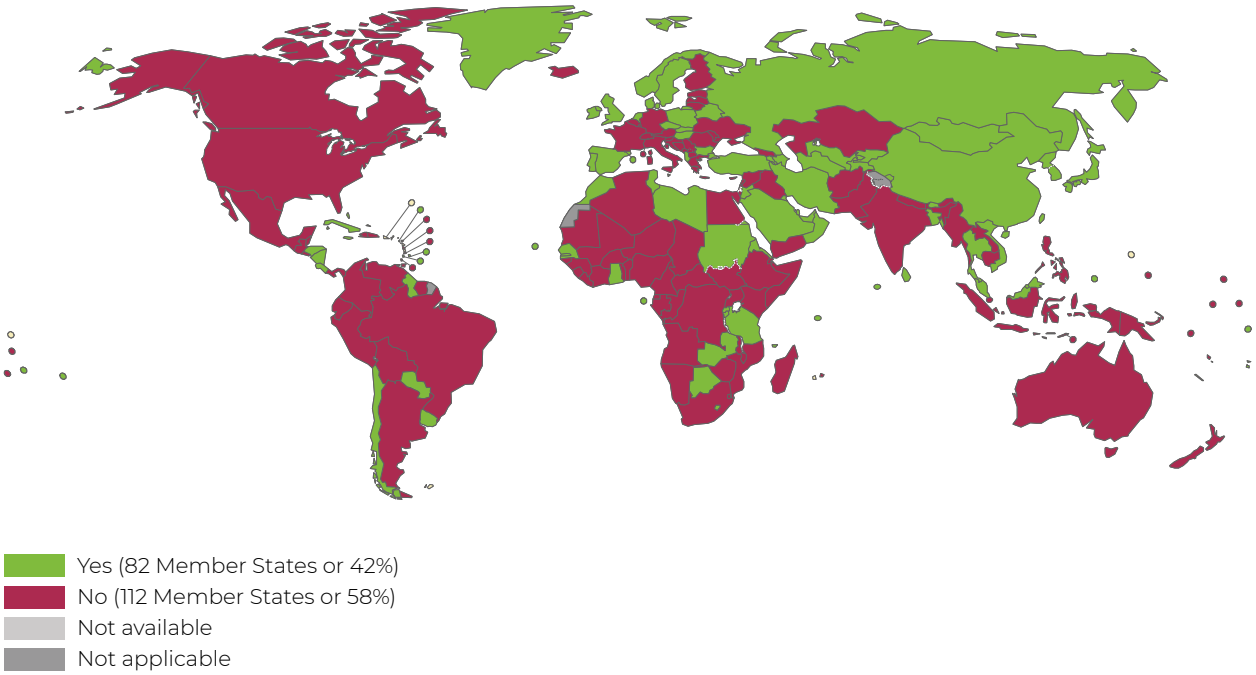
Indicator G3.2: 90% coverage nationally of all vaccines in national schedule and 80% in every district by 2020

TARGET	90% coverage nationally of all vaccines in national schedule and 80% in every district by 2020 in all Member States.
DEFINITION OF INDICATOR	• Indicator includes the following vaccines: • Three doses of DTP, poliovirus and the first dose of MCV for all Member States • BCG for Member States where included in the schedule (i.e. not limited to high-risk populations) • Three doses of HepB, Hib, 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 full year before the JRF reporting year (e.g. coverage reported for the full calendar year 2016 for a vaccine introduced nationwide in 2015) and in countries that have reported these data. DTP3 district-level coverage data are used as a proxy for all vaccine district-level coverage data.
DATA SOURCES	• WHO-UNICEF estimates of national immunization coverage (WUENIC). • Administrative data from WHO-UNICEF Joint Reporting Forms (JRFs).

A) Status of the GVAP coverage indicators, 2017

Countries achieving in 2017 national coverage of ≥ 90% for all vaccines in their immunization schedule are shown in Fig. 2.4. In 2017, 82 Member States (42%) reached this target for all vaccines while the remaining 112 (58%) did not.

Fig. 2.4: Member States that have achieved national coverage of ≥ 90% for all vaccines included in the national infant immunization schedule in 2017[a]

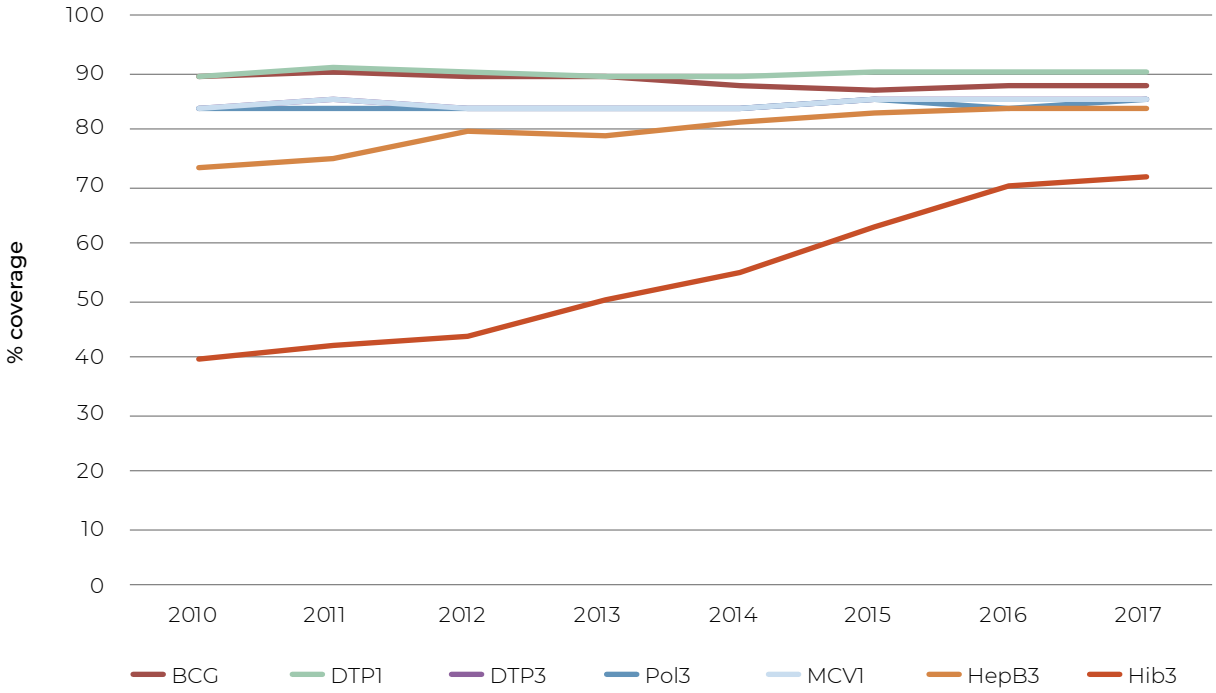


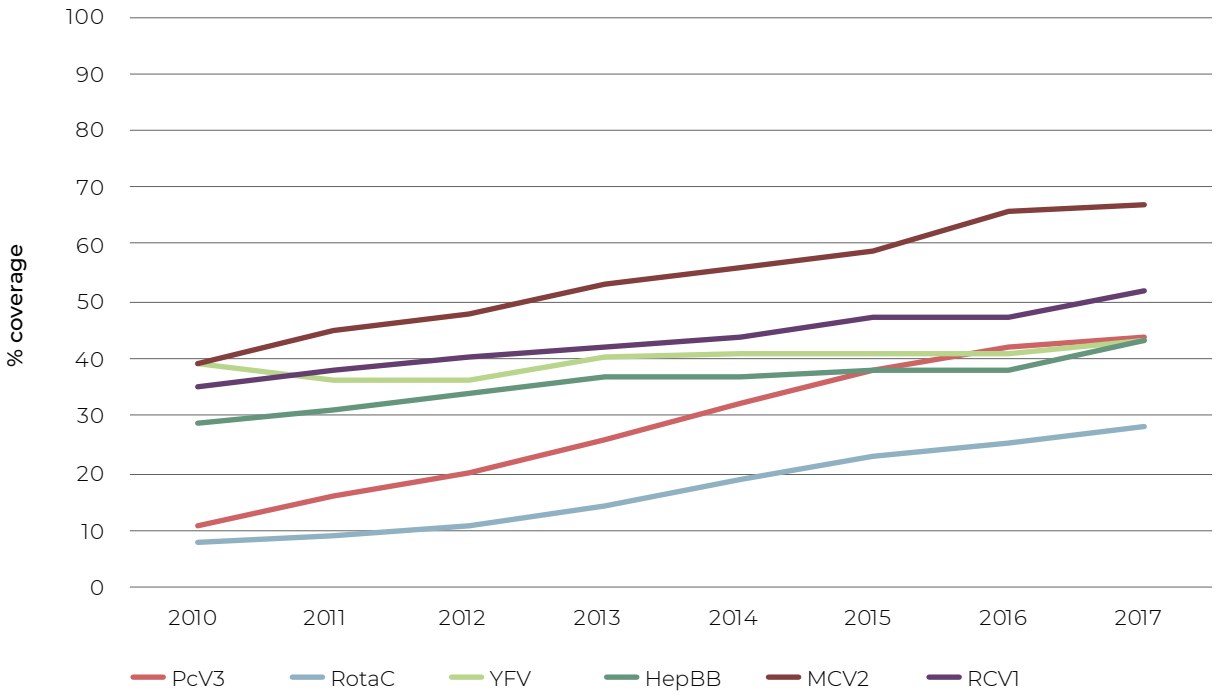
[a] Basket of vaccines for this indicator includes infant vaccines that are universally introduced, not infant vaccines used for risk groups and/or infant vaccines introduced in some parts of the country only.

Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.

The global coverage of individual vaccines varies from one vaccine to another. While global coverage for bacille Calmette–Guérin (BCG) vaccine, DTP3, hepatitis B (HepB) (third dose), poliovirus and measles-containing vaccine first dose (MCV1) are all above 80%, global coverage for HepB birth dose (Fig. 2.5a), rubella-containing vaccines (RCV1), MCV2 and new vaccines like rotavirus, pneumococcal conjugate vaccine (PCV) (Fig. 2.5b) and *Haemophilus influenzae* type b (Hib) remains low (Fig. 2.5a). Many countries are yet to introduce these vaccines in their national programmes.

Fig. 2.5a and 2.5b: Global coverage estimates of vaccines[a], 1980–2017





[a] BCG, DTP1, DTP3, MCV1 & MCV2, HepB (birth and 3rd doses), Hib (3rd dose), poliovirus 3rd dose (either OPV or IPV), PCV3, RCV1, rotavirus vaccine (last dose) and yellow fever vaccine (YFV).
Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.

1) District-level coverage for all vaccines in the national programme

Thirty-nine countries (20%) reached 90% coverage for all vaccines in the national programme and 80% coverage in every district for DTP3 (Table 2.2) in 2017. This figure has remained stable for the past three years, with 39 and 41 countries in 2016 and 2015 achieving this target, respectively.

Table 2.2: Number of countries (%) meeting the GVAP target for national level coverage for all vaccines in the national schedule, and district-level coverage for DTP3, 2017

National coverage of all vaccines	No. of countries where district DTP3 data valid and ≥ 80% in all districts	No. of countries where district DTP3 data valid, but not achieving 80% in all districts	No. of countries where district DTP3 data not valid or not reported	Total
≥ 90%	39 (20%)	30 (15%)	13 (7%)	82 (42%)
< 90%	11 (6%)	40 (21%)	61 (31%)	112 (58%)
Total	50 (26%)	70 (36%)	74 (38%)	194 (100%)

B) Global Immunization update, 2017

Immunization is a building block of strong primary health care and universal health coverage—it provides a point of contact for health care at the beginning of life and offers every child the chance of a healthy life from the start. According to the most recent WHO and United Nations Children's Fund (UNICEF) immunization estimates about 123 million infants worldwide, 9 in 10, received at least one dose of DTP3 in 2017, protecting them from infectious diseases that can cause serious illness, disability or can be fatal.

Since 2015, the percentage of children who received a full course of three doses of DTP3 during routine immunization continues to be sustained at 85% (116.2 million infants). Although global immunization coverage with DTP3 remains at 85%, it is important to highlight that an additional 4.6 million infants have been vaccinated globally in 2017 compared to 2010, due to global population growth. Similarly, although DTP3 coverage in the African Region has remained at 72% since 2010, due to population growth, this means that approximately 3.2 million more infants were vaccinated in 2017 than in 2010.

1) More concerted efforts needed to reach universal immunization coverage

If universal immunization coverage is to be realized, an estimated 20 million additional children need

to be vaccinated with DTP3; 45 million additional children need to be vaccinated with a second dose of MCV and 76 million more children need to be vaccinated with 3 doses of PCV.

Additional investments must be secured to ensure the long-term sustainability of national immunization programmes, especially as funding for polio activities decreases, and countries away from the support they receive from Gavi, the Vaccine Alliance.

Countries need to continue strengthening their health systems as they add new vaccines to their national immunization programmes. It is also crucial that countries ensure all children have access to vaccination and fully complete their vaccination series with all recommended vaccines.

Achieving high and equitable coverage requires targeted actions at subnational levels and ensuring access to vaccination for vulnerable populations. WHO and UNICEF continue to increase efforts to support countries in improving the quality and use of the coverage data at subnational levels to take actions to achieve high and equitable immunization coverage.

WHO and UNICEF continue to collect disaggregated data on immunization coverage at the subnational level. Of the 194 reporting countries, 141 reported on subnational coverage, covering nearly 24 000 districts and roughly two thirds of the global infant population. These data will help shed more light on geographical disparities in access to vaccines.

2) Celebrating the 20th anniversary of the Joint Reporting Form

WHO and UNICEF thank all countries for their strong commitment to the JRF process over the past two decades. The JRF is a comprehensive set of questions that requires focal points to invest a substantial amount of their time every year to report reliable immunization data that informs policies and strategies. More than 190 countries consistently do this year after year.

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

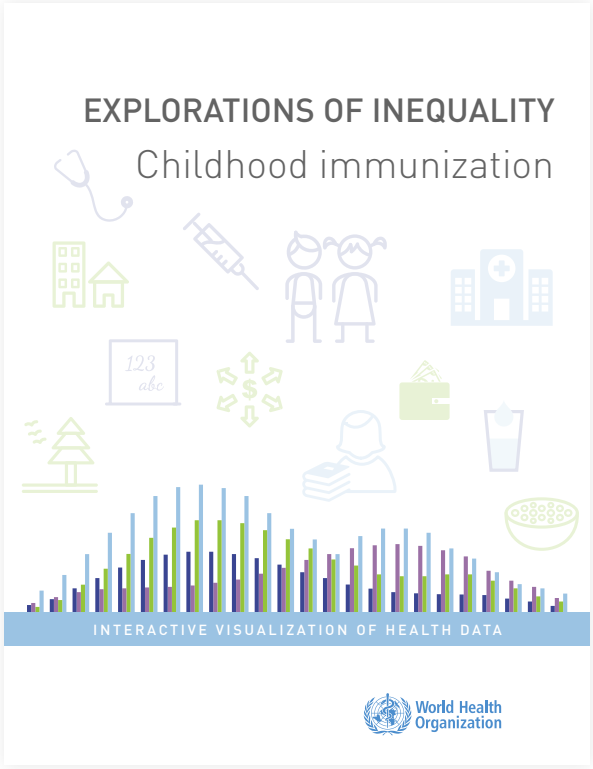
TARGETS	• Increasing trend in equity in immunization coverage. • Proportion of Member States with < 20% difference in DTP3 coverage between the lowest and highest wealth quintile: • 60% by 2015 • 75% by 2020.
DEFINITION OF INDICATOR	• DTP3 immunization coverage among 1-year-olds distributed by wealth quintiles for the period 2008–2015. • Determination of wealth index as defined in DHS and MICS. • Data are to be measured at least twice (by special study or survey), with an early and late measure.
DATA SOURCES	WHO Health Equity Monitor Database,[5] which contains data on more than 30 reproductive maternal, neonatal and child health indicators disaggregated by economic status, education, place of residence (rural vs urban) and subnational region as well as age and sex (where applicable). The Health Equity Assessment Toolkit (HEAT), a software application, facilitates the assessment of health inequalities within countries using the WHO Health Equity Monitor Database[6].

A) Status of the GVAP equity indicator, 2017

Equity data by wealth quintiles are generated from different types of surveys including Multiple Indicator Cluster Survey (MICS) reports, Demographic and Health Survey (DHS) reports. Those surveys are highly resource intensive and are not carried out every year in all countries. After reviewing the new available data related to immunization coverage disaggregated by wealth quintiles it was considered that there was insufficient data to conduct a new analysis this year. Please refer to 2017 GVAP Secretariat report for more information on this indicator.

[5] The database can be found at: http://apps.who.int/gho/data/node.main.HE-1540?lang=en.
[6] The tool can be found at: http://www.who.int/gho/health_equity/assessment_toolkit/en/index1.html.

B) Explorations of inequality: childhood immunization



WHO released a new publication[7] in July 2018 describing how a child's likelihood of being vaccinated is affected by socioeconomic, demographic and geographic factors. The report is based on international household health surveys conducted in 10 Gavi priority countries[8]. Interactive visuals and tables accompany the report, enabling further exploration of the data.

The report includes different types of analyses, including descriptive analyses of disaggregated data, summary measures as well as multiple regression analyses.

The report shows that despite the uniqueness of each country context, some commonalities were seen.

- Overall inequalities by child's sex tended to be minimal or non-existent while inequality by subnational region appeared substantial.
- All 10 priority countries showed a positive association between mother's education level and childhood immunization coverage.
- Household economic status was a strong indicator of inequality in most countries.
- In countries that reported low national immunization coverage such as Chad, Ethiopia and Nigeria the odds of immunization tended to be significantly higher in more advantaged socioeconomic subgroups.
- Countries with higher national immunization coverage such as India, Indonesia, Kenya and Uganda more often demonstrated an exclusion pattern among marginalized groups (coverage considerably lower in the most disadvantaged subgroup) but also lower urban–rural inequality.

Moreover the report shows that children who experience multiple forms of disadvantage are less likely to be vaccinated than children who experience a single type of disadvantage. For example, a child who lives in an underserved region may be at an increased risk of remaining unvaccinated if the child also belongs to a poor household. Conversely, children who belong to multiple subgroups that hold advantages are more likely to be covered. In many countries, children who are first born and whose mothers are highly educated have a compounded advantage (see Box 2.2).

While all 10 countries featured in the report experience a different situation with regard to childhood immunization coverage (largely related to the political situation, existing policies, living conditions, culture, etc.) the findings can nevertheless be used to inform equity-oriented policies, programmes and practices to promote universal childhood immunization coverage.

The report also highlights that childhood immunization coverage is linked to factors beyond the health system. Hence, solutions to ameliorate low immunization coverage may lie in coordinated efforts across sectors to reduce barriers to childhood immunization and identify and act on missed opportunities for immunization.

Lastly the report underscored the fact that regular monitoring and evaluation of childhood immunization (including inequalities, drivers and determinants) are instrumental to systematically track the impact of policies and programmes, and to identify bottlenecks in programme delivery and implementation.

[7] Explorations of inequality: childhood immunization. Geneva: World Health Organization; 2018.
[8] Afghanistan, Chad, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Nigeria, Pakistan and Uganda

Box 2.2: Compounded vulnerability and advantage

Children who experience multiple forms of disadvantage are less likely to be vaccinated than children who experience a single type of disadvantage. For example, a child who lives in an underserved region may be at an increased risk of remaining unvaccinated if the child also belongs to a poor household. Conversely, children who belong to multiple subgroups that hold advantages are more likely to be covered. In many countries, children who are 1st born and whose mothers are highly educated have compounded advantage. Certain living conditions and characteristics compound to exacerbate vulnerability or advantage.

For instance:

- **In Afghanistan** in 2015, a child of a teenaged mother with no education had one third the chance of being vaccinated as a child of a mother 20–49 years of age with secondary education or higher; if the child of the uneducated, teenaged mother belonged to the poorest 20%, this chance dropped to one ninth (compared to a child of a highly educated mother aged 20–49 years in the richest 20%).
- **In Chad** in 2014–2015, a child of a mother aged 20–34 years with secondary education or higher and belonging to the richest 20% had up to 7.2 times higher chance of receiving DTP3 immunization compared with a child of a teenaged mother with no education, from the poorest 20% household.
- **In Ethiopia** in 2016, the chance of receiving the third dose of DTP vaccine was 6.7 times higher for a child whose mother was 20–49 years of age and primary school educated, and who lived in a male-headed household, compared with a child of a teenaged mother with no education in a female-headed household.
- **In India** in 2015–2016, children with highly educated mothers aged 20–49 years who belonged to the richest 20% of the population had a 5.3 times higher chance of being vaccinated, compared with children born to teenaged mothers with no education, in the poorest 20% of the population.
- **In Indonesia** in 2012, a child who was part of a household in the richest 20%, and whose mother was aged 35–49 years, had a 6.4 times greater chance of being vaccinated compared to a child living in a household of the poorest 20%, and whose mother was a teenager.
- **In Kenya** in 2014, children had a higher chance of being vaccinated if they belong to the richest 40% of households and their mother had at least primary school education: compared to those in the poorest 20% and whose mother had no education, their chances were 6.3 times higher.
- **In Nigeria** in 2013, children of mothers aged 20–34 years who were highly educated, living in a rich household in the South South region were among the most advantaged in terms of childhood immunization: their chance of being vaccinated was 300 times higher than children with teenaged mothers with no education, living in poor households in the North West region.
- **In Pakistan** in 2012–2013, a child of a mother aged 20–34 years with higher than secondary education and from the richest 20% of the population had a 28 times higher chance of being vaccinated, compared with a child of a teenaged mother with no education and from the poorest 20% of the population.

Note: the above examples do not necessarily represent the most advantaged or disadvantaged subgroups; there may be other combinations of compounded vulnerability and advantage.

Source: Excerpted from Explorations of inequality: childhood immunization. Geneva: World Health Organization; 2018. p 63

GOAL 4: DEVELOP AND INTRODUCE NEW AND IMPROVED VACCINES AND TECHNOLOGIES

Indicator G4.3: Number of low-income and middle-income countries that have introduced one or more new and under-utilized vaccines

TARGET	• 2015: At least 90 low- and middle-income Member States. • 2020: All low- and middle-income Member States. • This year, the GVAP classifications of Gavi-eligible and non-Gavi-eligible middle-income countries have been used, representing 138 countries. The data from high-income countries are not included as they are not applicable to the indicator.
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 under-utilized vaccines are all vaccines that were not previously included in the national immunization schedule. • Introduction of a single dose of IPV as part of the polio eradication end-game strategy is not considered as an inclusion criterion for this indicator.
DATA SOURCES	• WHO-UNICEF Joint Reporting Forms (JRFs).
DATA AVAILABILITY AND QUALITY	• The limitations of JRF and WUENIC coverage data were discussed in the annex 1 of the GVAP Secretariat report 2013.[9]

Note: Since the indicator reviews sustained use (full calendar year) of vaccine, reporting on this indicator reviews data on vaccines introduced at latest by the end of December 2016. Hence, a vaccine introduced in 2016 will have completed its first full calendar year over the current 2017 reporting period.

A) Status of the new and underutilized vaccines introduction indicator, 2017

In the first seven years of the Decade of Vaccines – January 2010 to December 2016 – 113 of the 138 low- and middle-income countries added at least one new and under-utilized vaccine to their national immunization programme and sustained vaccine use for at least 12 months, i.e. until December 2016 (Table 2.3). These vaccines include: Hib-containing vaccine, pneumococcal conjugate vaccine (PCV), rotavirus vaccine, human papillomavirus vaccine (HPV), rubella and Japanese encephalitis. These 113 countries represent more than 70% of the world's population living in low- and middle-income countries. This is an increase of five countries since the previous report.

Table 2.3: Number of low- and middle-income Member States that introduced a new and under-utilized vaccine January 2010–December 2016 and sustained its use for at least 12 months, by vaccine and Gavi eligibility

Country classification	Total no. of countries by country classification	Member States having introduced at least one vaccine	Vaccine					
			Hib	Pneumo-coccal conjugate	Rota-virus	HPV	Rubella	JE
Countries eligible for Gavi support[a]	73	67 (92%)	14	53	37	4	17	4
Middle-income countries, no Gavi support	65	46 (71%)	14	24	14	19	7	0
Total	138	113 (82%)	28	77	51	23	24	4

JE, Japanese encephalitis.
[a] Includes countries eligible for Gavi support for new vaccines in 2015, but excludes countries transitioning out of Gavi support that year.

[9] For more information about the JRF and WUENIC coverage data, please refer to the GVAP Secretariat report 2013, Annex 1: http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf#page=145

Of the 113 low- and middle-income countries that introduced at least one vaccine from 2010 to 2016, 65 of them were countries that were not Gavi eligible, hence did not receive Gavi support. A total of 207 vaccine introductions took place in these 113 low- and middle-income countries during the first seven years of the Decade of Vaccines. Table 2.4 shows the breakdown by WHO region and by vaccine.

An increase in new and under-utilized vaccine introductions during recent years was seen with pneumococcal vaccines, which 57% of low- and middle-income countries introduced. Additionally, 37% of low- and middle-income countries introduced rotavirus vaccines between 2010 and 2016. During the same period, 24 low- and middle-income countries introduced and sustained rubella vaccine for at least twelve months after introduction, and 23 introduced and sustained the use of HPV through 2016 (only three of which – Lesotho, Rwanda and Uganda – are supported by Gavi). It is expected that the number of low- and middle-income countries introducing HPV will increase due to the Gavi policy supporting routine HPV introduction evidenced by Gavi's recent approvals of application requests.

Table 2.4: Number of low- or middle-income countries that have added one or more new and under-utilized vaccines[a] to their national immunization schedule 2010–2016, by vaccine and WHO Region

WHO region	No. of low- or middle- income countries having introduced at least one vaccine/total Member States in region (2016)	Vaccine					
		Hib	Pneumococcal conjugate	Rotavirus	HPV	Rubella	JE
African	43/47	5	36	30	5	11	N/A
Americas	19/35	1	14	6	10	0	N/A
Eastern Mediterranean	14/21	5	8	7	1	2	N/A
European	14/53	5	10	5	3	0	N/A
South-East Asia	10/11	7	3	0	0	4	1
Western Pacific	13/27	4	7	3	4	7	3
Total	113/194	27	78	51	23	24	4

[a] Excluding IPV.

Of the vaccines added in 2016 to national immunization schedules, 5 were for rubella, 4 for HPV and 3 for PCV and rotavirus each; and 9 of these 15 introductions were in non-Gavi-eligible countries. The HPV introductions were mainly seen in the European Region, however in the future it is expected that introductions in other regions will increase. Four of the five rubella introductions occurred in the African Region.

It is important to note that 21 of the low- or middle-income countries having introduced at least 1 vaccine had already introduced Hib vaccine before 2010 (the baseline date), and two of them had previously introduced PCV as well.

There are 25 low- or middle-income countries that had not introduced any new/under-utilized vaccine between 2010 and 2016, however three of these countries are part of the 30 countries that have introduced a vaccine between 2017 and 2018, which will be available in the 2019 GVAP Secretariat report.

To see maps of vaccine introductions globally by vaccine as per the latest available information, see: http://www.who.int/entity/immunization/monitoring_surveillance/VaccineIntroStatus.pptx

3. REDUCTION IN UNDER-FIVE MORTALITY AND INTEGRATION INDICATORS

GOAL 5: EXCEED THE MILLENNIUM DEVELOPMENT GOAL 4 TARGET FOR REDUCING CHILD MORTALITY

Indicator G5.1: Reduce under-five mortality rate

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

The 2017 mortality data were not available at the time of the report. This indicator will be reported on again in the 2019 GVAP report. For 2016 under-five mortality data please refer to 2017 GVAP Secretariat report.

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

DEFINITION OF INDICATOR	**Indicators proposed by the DoV Secretariat:** a) Composite Coverage Index (CCI), which is a weighted average of eight preventive and curative interventions for "Countdown countries"[1], and b) Comparative coverage by country 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), stratified by countries with CCI < 60, CCI 60–70, CCI > 70.
TARGET	No target set.
DATA SOURCES	Countdown 2030 Master Databases[2], recent WHO-UNICEF estimates of national immunization coverage (WUENIC) for DPT3, MCV1 and BCG and Demographic Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS).

[1] http://countdown2030.org/country-and-regional-networks/country-profiles
[2] http://countdown2030.org

A) Update on GVAP Integration indicator, 2017

In 2016, the GVAP Secretariat report presented a revised integration indicator, the Composite Coverage Index (CCI)[3]. The objective of this revised indicator was to measure country efforts in reducing the number of missed opportunities for any preventive interventions to reduce mother and child mortality and to also highlight opportunities for integration.

The CCI is calculated using Countdown to 2030 data, and previous reports used data from Countdown to 2015 for maternal, newborn and child survival rates in countries. In 2015, a final report of the Countdown to 2015 was published, which detailed the monitoring of 75 Countdown countries over a 10-year period. In 2017, the first Countdown report in the context of the 2030 agenda for sustainable development and the *Every Woman Every Child Global Strategy for Women's, Children's and Adolescent's Health* (2016–2030) was published. Countdown to 2030 now includes 81 countries and aims to build off the strengths of Countdown to 2015 in assessing progress towards universal health coverage for women, children and adolescents.

Here an update of the CCI and its component interventions for Countdown to 2030 are presented to measure potential missed opportunities between immunization and other health services.

1) Data availability and quality

For background information on the indicator and the methodology please consult the 2017 GVAP Secretariat report. For the 2018 GVAP Secretariat report, CCI data are derived from the Countdown 2030 Master Databases[28] updated with 2016 WHO-UNICEF estimates of national immunization coverage (WUENIC) for DPT3, MCV1 and BCG[4] and more recent data from Demographic Health Surveys (DHS)[5] or Multiple Indicator Cluster Surveys (MICS)[6]. Of the 75 Countdown to 2015 countries reported on in 2017, 68 remain as Countdown to 2030 priority countries and 54 of them had data from 2010 onwards and are included in the analysis[7]. A further 13 new priority countries were added to Countdown to 2030[8]; of these, 11 had data available from 2010 onwards. Therefore, 65 countries were included in the 2018 analysis compared to 59 in 2017.

Also compared were the CCIs of the 10 countries[9] presented in the 2017 GVAP Secretariat report, which this year had a second round of data available. The CCI results are stratified by countries with CCI < 60 (weak health systems), CCI 60–70 (less-weak health systems), CCI > 70 (stronger health systems).

2) Results

The available data from 65 Countdown to 2030 countries were used to calculate the median and stratified CCI and its four stages of component interventions, as shown in Table 3.2. Across all countries, both *immunization* and *maternal and newborn care* continue to have the highest median coverage. In Figs. 3.1–3.3 detailed data by country are stratified by CCI < 60, CCI 60–70 and CCI >70. Of the 11 new priority Countdown to 2030 countries with available data, all but one had a CCI > 70%. Coverage of *immunization* and *maternal and newborn care* was greater than *family planning* and *case management of sick children* in 85% of countries (n=17) with a CCI of 60–70% and 76% of countries with CCI > 70%.

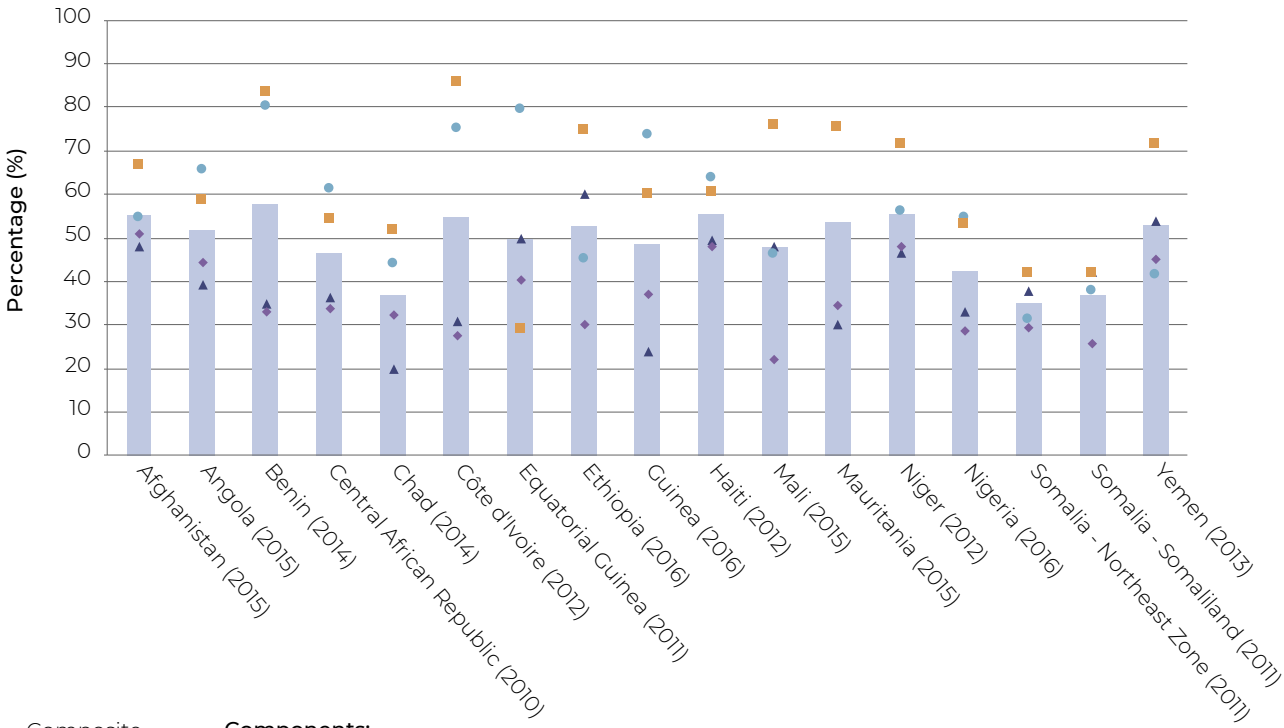
Table 3.2: Median coverage of the four Composite Coverage Index (CCI) components in 65 Countdown to 2030 countries[a] with a CCI < 60%, 60–70%, and > 70%

Component intervention 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	55%	39%	41%	76%
Maternal and newborn care	79%	56%	78%	89%
Immunization	86%	60%	87%	92%
Case management of sick children	51%	34%	50%	62%

[a] Countdown to 2030 countries with available data since 2010.
Source: Countdown 2030 Master Databases, WUENIC, DHS and MICS data.

[3] Boerma J, Bryce J, Kinfu Y, Axelson J, Victora C. Mind the gap: equity and trends in coverage of maternal, newborn, and child health services in 54 Countdown countries. Lancet. 2008; 371(9620):1259–67.
[4] http://www.who.int/immunization/monitoring_surveillance/routine/coverage
[5] http://dhsprogram.com/Publications/Publications-by-Country.cfm
[6] http://mics.unicef.org/surveys
[7] However, only 12 of these had a revised DHS/MICS survey available since the 2017 GVAP Secretariat Report.
[8] Algeria, Bhutan, Dominican Republic, Guyana, Honduras, Jamaica, Namibia, Nicaragua, Panama, Paraguay, Suriname, Timor-Leste and Venezuela (Bolivarian Republic of)
[9] Burundi, Congo, Ethiopia, Guinea, Mali, Mauritania, Nepal, Nigeria, Senegal and Uganda

Fig. 3.1: Composite Coverage Index (CCI) and coverage for four CCI components in 17 Countdown to 2030 countries[a] with a CCI < 60% (year of data collection indicated for each country)

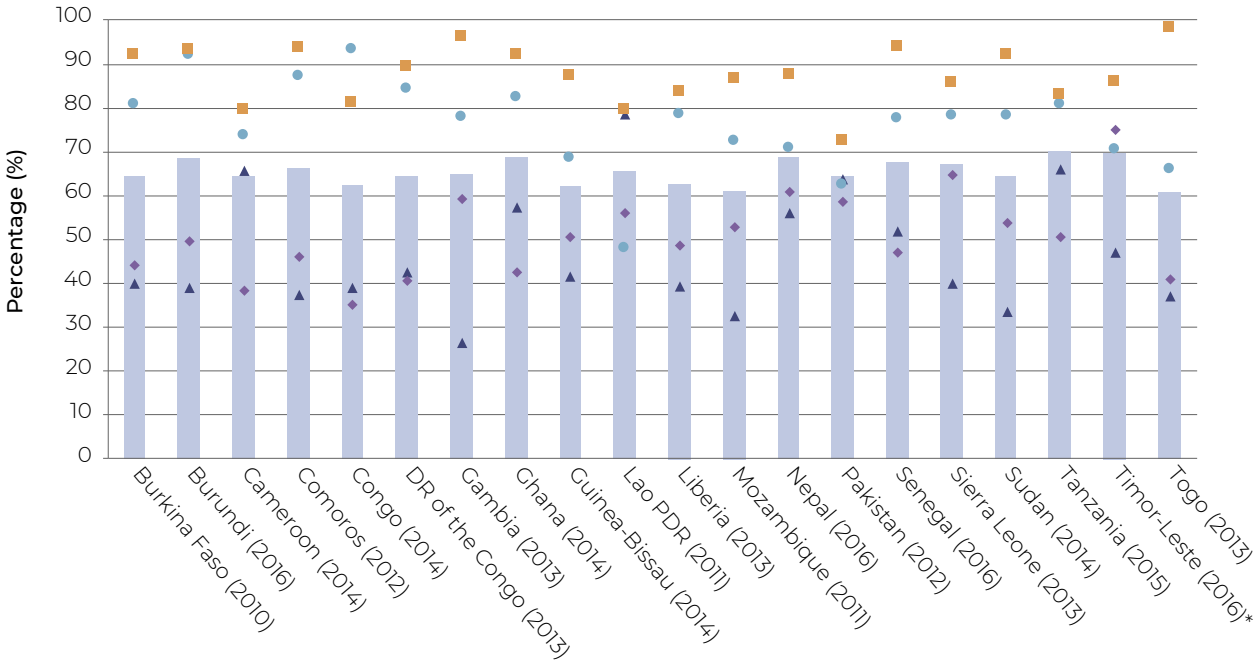


Composite Coverage Index (CCI)

Components:
- Family planning needs satisfied
- Maternal and newborn care (skilled birth attendant antenatal care with skilled provider)
- Immunization (DTP3, measles, BCG)
- Case management of sick children (ORS for children with diarrhoea, care seeking for pneumonia)

[a] Countdown to 2030 countries with available data since 2010.
Source: Countdown 2030 Master Databases, WUENIC, DHS and MICS data.

Fig. 3.2: Composite Coverage Index (CCI) and coverage for four CCI components in 20 Countdown to 2030 countries[a] with a CCI 60–70% (year of data collection indicated for each country)



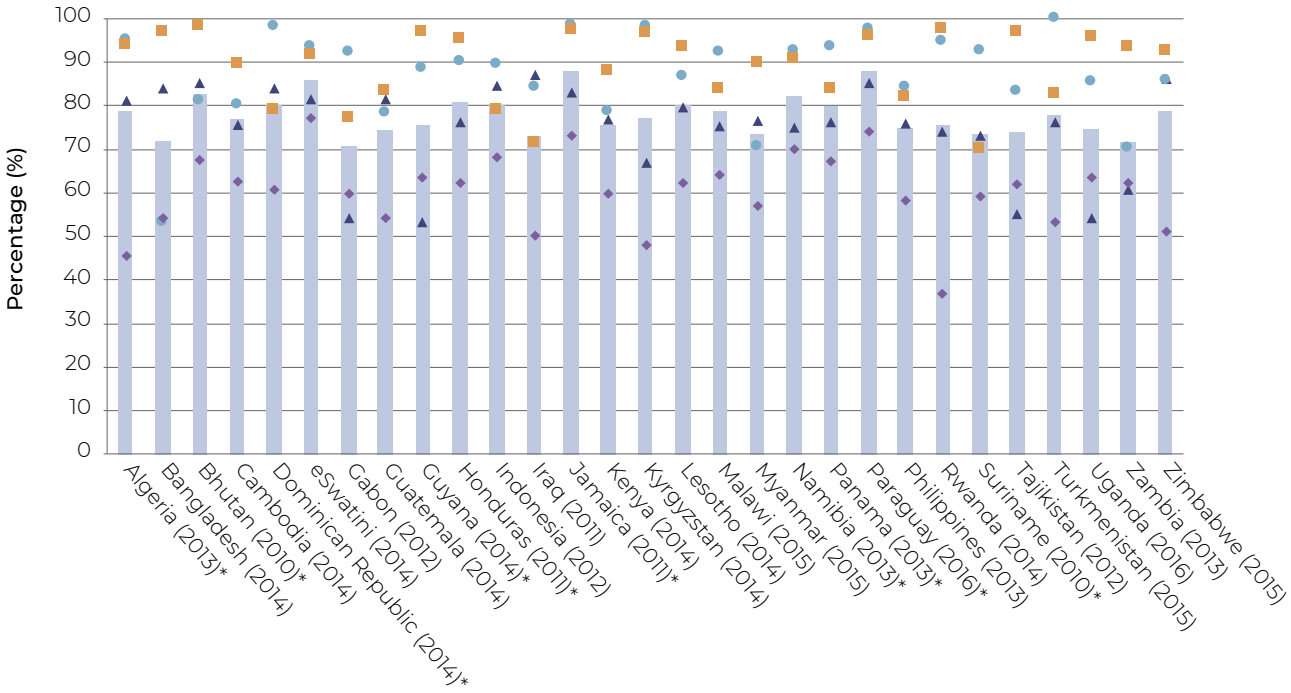
Composite Coverage Index (CCI)

Components:
- Family planning needs satisfied
- Maternal and newborn care (skilled birth attendant antenatal care with skilled provider)
- Immunization (DTP3, measles, BCG)
- Case management of sick children (ORS for children with diarrhoea, care seeking for pneumonia)

[a] Countdown to 2030 countries with available data since 2010.

* New Countdown to 2030 priority country.
Source: Countdown 2030 Master Databases, WUENIC, DHS and MICS data.

Fig. 3.3: Composite Coverage Index (CCI) and coverage for four CCI components in 29 Countdown to 2030 countries[a] with a CCI > 70% (year of data collection indicated for each country)



Composite Coverage Index (CCI)

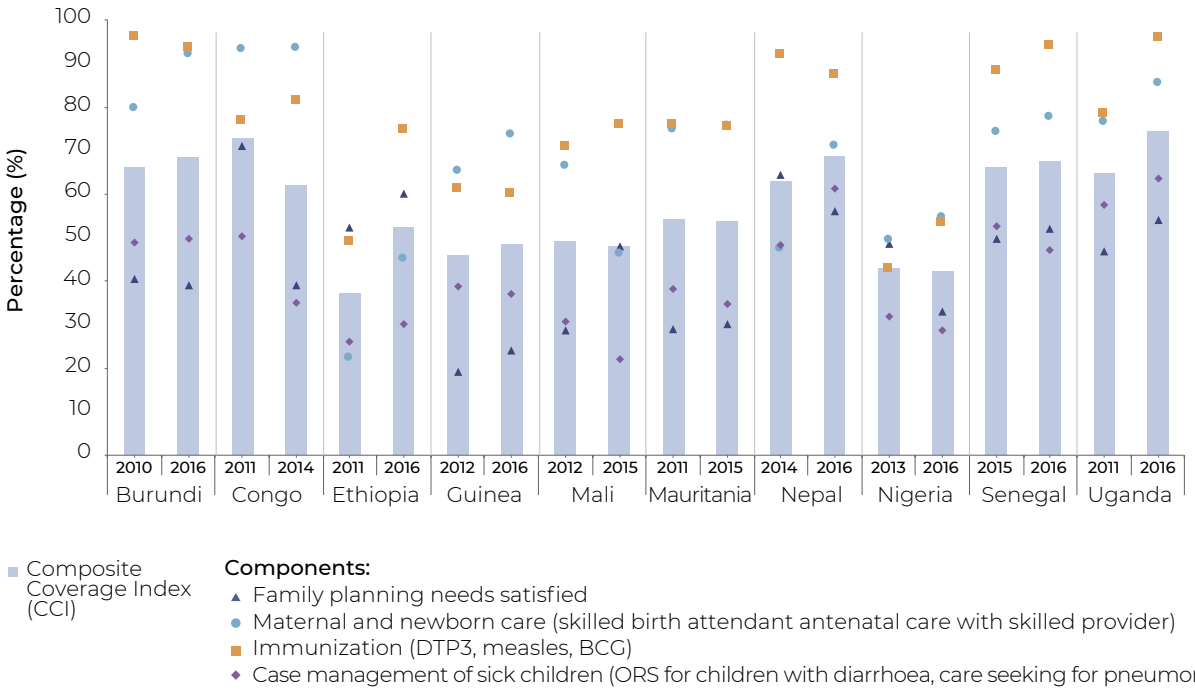
Components:
- Family planning needs satisfied
- Maternal and newborn care (skilled birth attendant antenatal care with skilled provider)
- Immunization (DTP3, measles, BCG)
- Case management of sick children (ORS for children with diarrhoea, care seeking for pneumonia)

[a] Countdown to 2030 countries with available data since 2010.
* New Countdown to 2030 priority country.
Source: Countdown 2030 Master Databases, WUENIC, DHS and MICS data.

In Fig. 3.4, 10 countries with data presented in the 2017 GVAP Secretariat report and with a second round of household survey data are compared. In the time period between surveys, the CCI and the four stages of continuum of care components have slightly improved or remained unchanged in the majority of Countdown to 2030 countries. However, over the course of five years, both Ethiopia and Uganda made substantial improvements in *immunization* and *maternal and newborn care* coverage. The CCI for the Congo, Mali, Mauritania and Nigeria decreased, mostly due to a decline in coverage for *family planning needs satisfied* and *case management of sick children*.

The CCI and its component interventions clearly demonstrate variation in the coverage of immunization and other health services, even among countries with a higher CCI. This shows us that although women, children and their caregivers are making contact with the health system, missed opportunities remain for integration between services (see Section B below).

Fig. 3.4: Comparison in Composite Coverage Index (CCI) and coverage for four CCI components in 10 Countdown countries[a] with two rounds of data since 2010 (year of data collection indicated for each country)



[a] Countdown to 2030 countries with available data since 2010.
Source: Countdown 2030 Master Databases, WUENIC, DHS and MICS data.

The limitations of using the modified CCI as an indicator for integration were described in previous GVAP reports. For this report, CCI calculations for 16 Countdown countries[10] could not be done, as they did not have household survey data available since 2010 or were missing data.

A key achievement of Countdown to 2015 was driving consensus around priority interventions and key coverage and outcome indicators for reproductive, maternal, newborn and child health. Now Countdown to 2030 aims to tracks coverage of health interventions proven to reduce maternal, newborn and child mortality and also calls for accountability from governments and development partners. It aims to identify knowledge gaps and propose new actions to achieve universal coverage for the health of women, children and adolescents. The updated CCI calculations, however, show that while some countries have made progress in the coverage of health interventions, other countries suffer from persistent gaps and inequalities across the continuum of care. Therefore, it is imperative that reproductive, maternal, newborn, child and adolescents' health continue to be prioritized, and that countries strive for a more comprehensive and integrated health agenda.

B) Reducing missed opportunities for vaccination (MOV) through integration

A missed opportunity for vaccination (MOV) refers to any contact with health services by an individual (of any age) who is eligible for vaccination (e.g. unvaccinated or partially vaccinated and free of contraindications to vaccination), but that does not result in the person receiving one or more of the vaccine doses for which he or she is eligible.

In 1988, WHO published a methodology for assessing MOV through health facility exit interviews. In 2017, the WHO launched the updated MOV methodology, which included simpler methods and a qualitative component. Most importantly, the methodology now aims to link and translate the findings of MOV assessments into actionable solutions to reduce MOV, particularly at the health-facility level where vaccination services are provided.

Since its revision, MOV assessments have been conducted in 10 countries in the WHO regions of Africa, Eastern Mediterranean and South-East Asia. To date, the MOV assessments have shown that increased integration could increase immunization coverage by simply improving links between immunization programmes and other services.

[10] Azerbaijan, Bolivia (Plurinational State of), Botswana, Democratic People's Republic of Korea, Djibouti, Eritrea, India, Madagascar, Morocco, Nicaragua, Papua New Guinea, Solomon Islands, South Africa, South Sudan, Uzbekistan, Venezuela (Bolivarian Republic of)

Many people who visit health facilities could be eligible for vaccine doses, particularly children and women of reproductive age. Therefore, it is important that each contact someone has with a health facility is used as an opportunity to screen their vaccination status and to either provide all of the appropriate vaccinations or to refer them to immunization services ("*screen and vaccinate*", or "*screen and refer to vaccination area*").

Home-based records are key tools to facilitate this type of service integration. Home-based records serve as both a reminder to caregivers about the vaccination schedule for themselves or their child, and are also an opportunity for health workers to both screen for vaccine eligibility and provide health education during delivery of immunization. Training health workers from different services on how to review home-based records, educate about the importance of retention of home-based records, and provide catch-up vaccination to those eligible has the potential to have a major impact on increasing immunization coverage.


PREFEITURA DE SÃO PAULO
SAÚDE
Esta criança esta em atraso vacinal
Procure a unidade de saúde mais próxima de sua casa
Telefone
Local
Peso em gramas
Tipo de parto

4. COUNTRY OWNERSHIP: NITAGs

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

TARGET	Functional NITAGs in all Member States by 2020.
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.
DATA SOURCES	• WHO-UNICEF Joint Reporting Forms (JRFs). • 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.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 4.1.

Box 4.1: Descriptions of indicators, results, data sources and highlights

For additional information, see: http://www.who.int/immunization/sage/national_advisory_committees/en/ and http://www.nitag-resource.org/.

For background information, methodology and data limitations please see the 2017 GVAP Secretariat report.

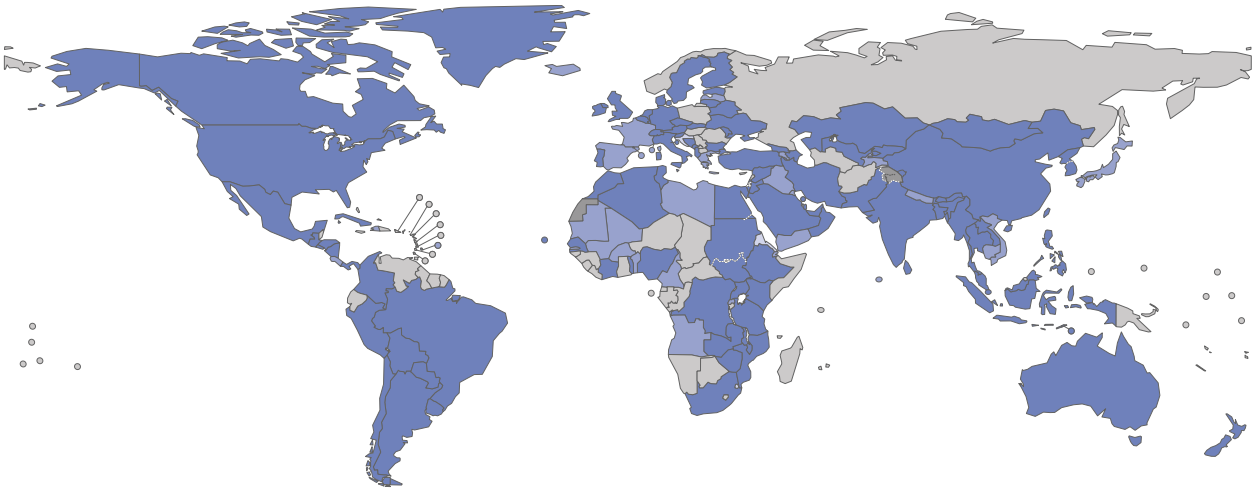
A) Status of the GVAP NITAG indicator, 2017

As of 27 June 2018, data for 186 Member States were available for the analysis. In total 134 Member States declared having a National Immunization Technical Advisory Group (NITAG). All but three of those reported the existence of a NITAG with a formal legislative or administrative basis. In total 98 Member States reported a NITAG meeting all six process indicators (see indicator definition), of which 66 are low- and middle-income countries (Fig. 4.1). This is a 58% increase compared to 2010, when only 41 countries reported having a NITAG meeting all six process indicators. More remarkably, it is a 20% increase since the previous year (Fig.

4.2). An additional 20 countries[1] reported meeting the six process indicators in 2017 in comparison with 2016, mainly located in the European and African Regions. Conversely, four countries reporting functional NITAGs in 2016 failed to do so in 2017. The cause of these drop-outs for three of these countries was due to the fact that the NITAGs did not meet in 2017.

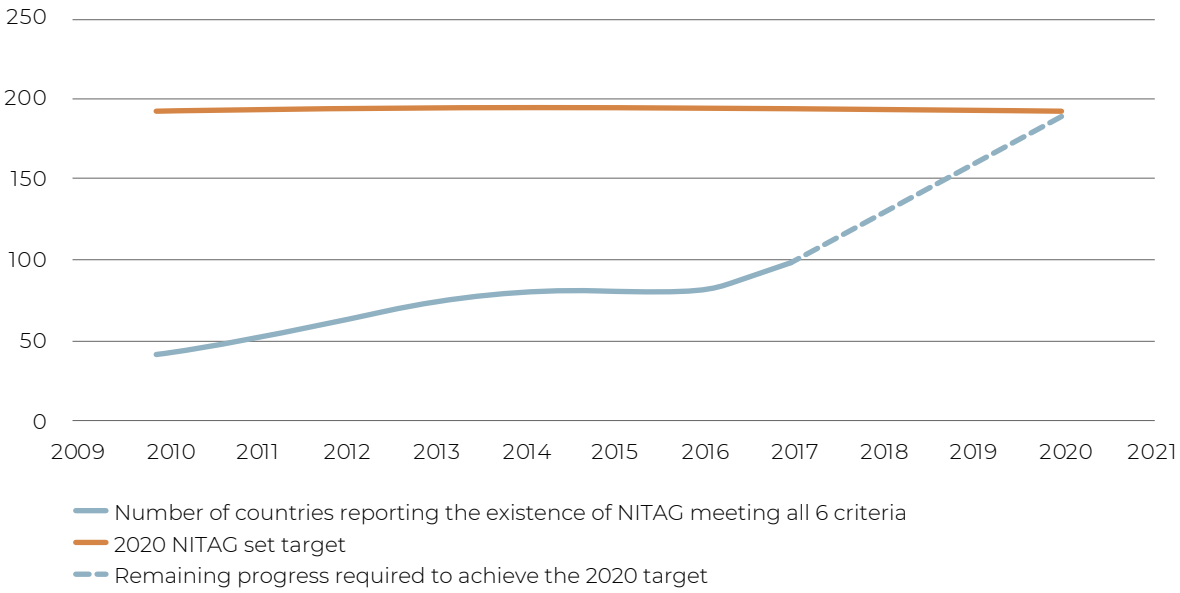
Although the slope of the current trajectory is still insufficient to meet the GVAP 2020 target of a functional NITAG supporting every country, it shows a very encouraging trend, which demonstrates the countries' eagerness to develop independent evidence-based capacities for decision-making in immunization. The significant improvement on the NITAG GVAP indicators underscores the dynamism of the NITAG community and the support offered by the global NITAG network to build sustainable national capacities.

Fig. 4.1: National Immunization Technical Advisory Groups in 2017



98 countries meeting the six NITAG criteria
131 countries having a NITAG with administrative or legislative basis
131 countries reporting the existence of a NITAG with terms of reference
134 countries reporting the existence of a NITAG
No NITAG/not available
Not applicable

Fig. 4.2: Time trend in the establishment of NITAGs meeting all six process criteria with remaining progress required to reach the 2020 target, 2010–2017



[1] Bhutan, Bolivia (Plurinational State of), Bosnia and Herzegovina, Cabo Verde, China, Comoros, Democratic Republic of the Congo, Italy, Kyrgyzstan, Lao People's Democratic Republic, Luxembourg, Malawi, Malaysia, Montenegro, Myanmar, Nicaragua, San Marino, Saudi Arabia, Togo, Ukraine

B) Strengthening global and regional NITAGs – Update 2017–2018

Over the past year significant milestones were achieved in NITAG support, including increased global attention to the progress made in establishing and strengthening NITAGs. For example, a dedicated session on support to NITAGs featured for the first time on the Strategic Advisory Group of Experts on Immunization (SAGE) agenda at its April 2017 meeting, highlighting the importance of NITAGs as core institutions for the success and sustainability of national immunization programmes. SAGE stressed inter alia the need for regional and global collaboration and called on partners, donors, countries and the global immunization community to continue the support.

The SAGE recommendations were further reinforced by the World Health Assembly resolution WHA70.14, urging Member States to strengthen the governance and leadership of national immunization programmes. Resolution WHA70.14 also called on the Director-General of the World Health Organization (WHO) to support Member States in strengthening NITAGs in cooperation with regulatory authorities, to inform decisions related to immunization programmes based on national context and evidence. Member States again at the Seventy-first World Health Assembly in 2018 noted that NITAGs not only support decision-making but also can contribute significantly to building in-country ownership of and credibility for immunization programmes.

Inaugurated in Berlin in 2017, the Global NITAG Network (GNN) aims to strengthen NITAG collaboration at the global level. Its objective is to support NITAGs in particular through direct collaboration, training support and peer-to-peer exchanges to fulfil their national advisory role. The next meeting will be organized by the Public Health Agency of Canada in December 2018.

Following a SAGE meeting in April 2018, a NITAG side meeting successfully took place with representatives from 19 countries. Two major themes shaped the agenda: priority setting and evaluation. WHO and global partners are reinforcing collaboration to provide tailored support to NITAGs and develop new training materials including interactive sessions on how to issue an evidence-based recommendation, best practices to document NITAG work and guidelines to deal with conflicts of interest.

The Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) initiative recently discontinued its activities after completing a 10-year project and the Agence de Médecine Preventive–Health Policy and Institutional Development (AMP-HPID) collaborating centre also closed. An evaluation of the SIVAC initiative conducted by the London School of Hygiene and Tropical Medicine concluded that the project achieved its objectives: NITAG development and strengthening of immunization decision-making at country level, fostering partnerships, and creating training and support materials, tools, and a web-based platform. Nevertheless, progress must be sustained, particularly in the WHO regions where the SIVAC initiative was most active – the African, Eastern Mediterranean and South-East Asia Regions. Via the GNN and the NITAG resource centre, WHO and major international technical partners such as the US Centers for Disease Control and Prevention (CDC) are progressively providing that technical assistance to the NITAGs in the countries in those regions.

In line with the SAGE recommendation to consolidate regional capacities, WHO regional offices support the participation of NITAG members in their respective Regional Technical Advisory Group (RTAG) meetings and organize NITAG side meetings. This support allows NITAG members to network and exchange information on best practices. In December 2017 the Regional Office for Africa organized for the first time a side session dedicated to NITAGs during its RTAG meeting in Johannesburg. Similarly, NITAG members representing every WHO region are invited to attend SAGE meetings.

Further efforts by WHO regional offices have strengthened NITAGs as well. For example, the Regional Office for Africa initiated a regional training session to build technical capacities to support new NITAGs in the region while the Regional Office for Europe piloted revised NITAG training materials during a workshop in Copenhagen attended by representatives from four Eastern European countries. In addition the Regional Office for Africa promoted the NITAG evaluation tool to its Member States, several of which used it to assess their committees. The Regional Office for Europe and other partners such as the West African Health Organization (WAHO) and the US-CDC used a different approach – contracting consultants to conduct evaluations in eight countries. Alongside, a simplified tool was also developed that recently-established NITAGs can use to assess themselves.

Peer-to-peer support was instrumental in the launch of the Chinese NITAG (NIAC). Representatives from NITAGs in the USA, the United Kingdom of Great Britain and Northern Ireland and Sweden were invited to China to share their expertise in establishing working groups. Other international collaborations include collaboration between developing countries (e.g. the Senegalese NITAG supporting NITAG training in Cameroon), between developed and developing countries (e.g. the twinning of Haiti and Belgium NITAGs) and between developed and developed countries (e.g. the ongoing process of Nordic countries to create a subregional network). Other notable regional initiatives include an inception meeting in 2018 of the first subregional Technical Advisory Group, the Caribbean Technical Advisory Group.

Strong NITAGs provide a solid basis for resilient and credible national immunization programmes. It is imperative that the progress seen in 2017 can be maintained – this includes ensuring that partners capitalize on the SIVAC initiative's achievements and that new and developing NITAGs obtain the necessary technical support to be able to provide independent evidence-based expertise.

5. VACCINE HESITANCY AND DEMAND FOR IMMUNIZATION

STRATEGIC OBJECTIVE 2: INDIVIDUALS AND COMMUNITIES UNDERSTAND THE VALUE OF VACCINES AND DEMAND IMMUNIZATION AS BOTH THEIR RIGHT AND RESPONSIBILITY

Indicators SO2.1 and SO2.2: Vaccine hesitancy indicators

Vaccine hesitancy is defined as the 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).

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 years.
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 hesitancy 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.
DATA SOURCES	All 194 countries within the six WHO regions included both indicators in their 2017 WHO-UNICEF Joint Reporting Form (JRF) to collect country data for 2016 (referred to as 2016 JRF data).

A) Status of the vaccine hesitancy indicators, 2017

The Strategic Advisory Group of Experts on Immunization (SAGE) endorsed two indicators to assess vaccine hesitancy worldwide as part of the Decade of Vaccines Global Vaccine Action Plan (GVAP). After pilot testing, these indicators were first introduced in the 2014 JRF and thus, to date, four years of data have been collected – 2014, 2015, 2016 and 2017 (Table 5.1). This has provided the

opportunity to assess how reporting on reasons for vaccine hesitancy has changed over time.

Table 5.1: Response rate globally, per indicator question, for each year of gathered data

	2014	2015	2016	2017
Countries that submitted the JRF	180	183	184	191
Countries that provided at least one reason for hesitancy	**73%**	**79%**	**83%**	**83%**

As of 27 June 2018, 191 WHO Member States had submitted their 2017 JRF data. Of these 191 countries, 165 had responded to at least one vaccine hesitancy question and 159 had provided at least one reason for vaccine hesitancy. The percentage of countries that provided at least one reason for vaccine hesitancy by the deadline for inclusion into the report was 83% (Table 5.1), the same as for 2016. Table 5.2 shows the response rate by WHO region.

Table 5.2: Response rate per WHO region, 2017

	All regions n (%)	African n (%)	Americas n (%)	Eastern Mediterranean n (%)	European n (%)	South-East Asia n (%)	Western Pacific n (%)
Countries providing at least one reason for vaccine hesitancy	159 (83)	44 (94)	31 (91)	15 (71)	43 (83)	8 (73)	18 (69)
Countries that submitted the JRF and did not provide a reason	32 (17)	3 (6)	3 (9)	6 (29)	9 (17)	3 (27)	8 (31)
Total countries that submitted the JRF	191	47	34	21	52	11	26

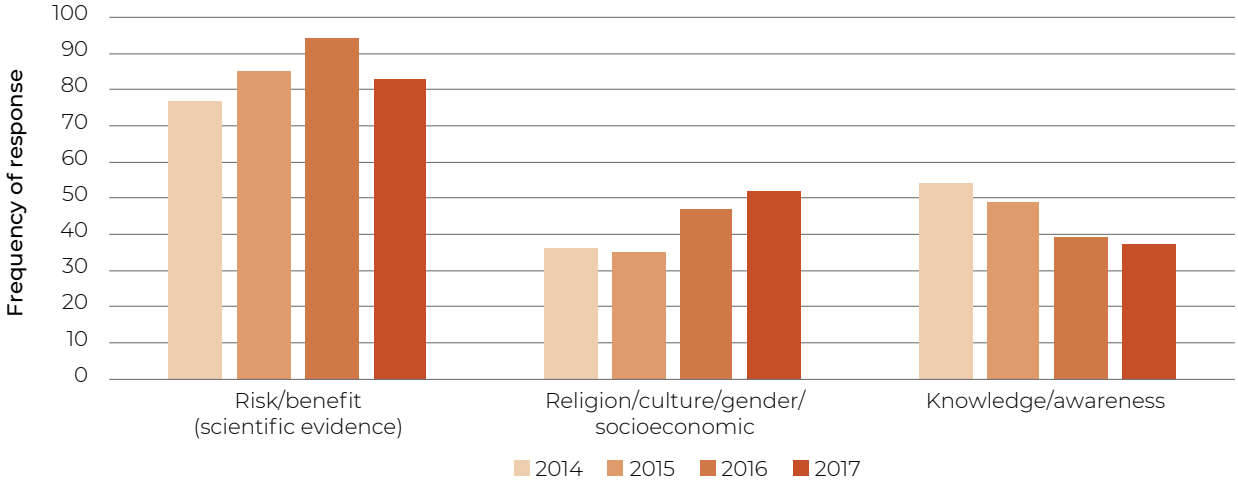
1) Top three reasons for vaccine hesitancy (Indicator 1)

The top three reasons provided for vaccine hesitancy were grouped according to the matrix of determinants[1] of vaccine hesitancy, which assembles the reasons into three major categories: contextual influences, individual and group influences and vaccine and vaccination-specific issues. Each category consists of four or more subgroups. Reasons were then ranked based on their frequency.

The top three reasons for vaccine hesitancy across all WHO regions have remained the same for all four years of data. These are, in decreasing frequency for 2017 data: a) risk/benefit (scientific evidence); b) religion, culture, gender, socioeconomic; and c) lack of knowledge and awareness of vaccination and its importance. The rank order has changed across 2014–2017, with knowledge and awareness decreasing as a reason (Fig. 5.1).

[1] MacDonald N, the SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: definition, scope and determinants. Vaccine. 2015; 33(34):4161–4.

Fig. 5.1: Top three reasons for vaccine hesitancy globally, 2014–2017

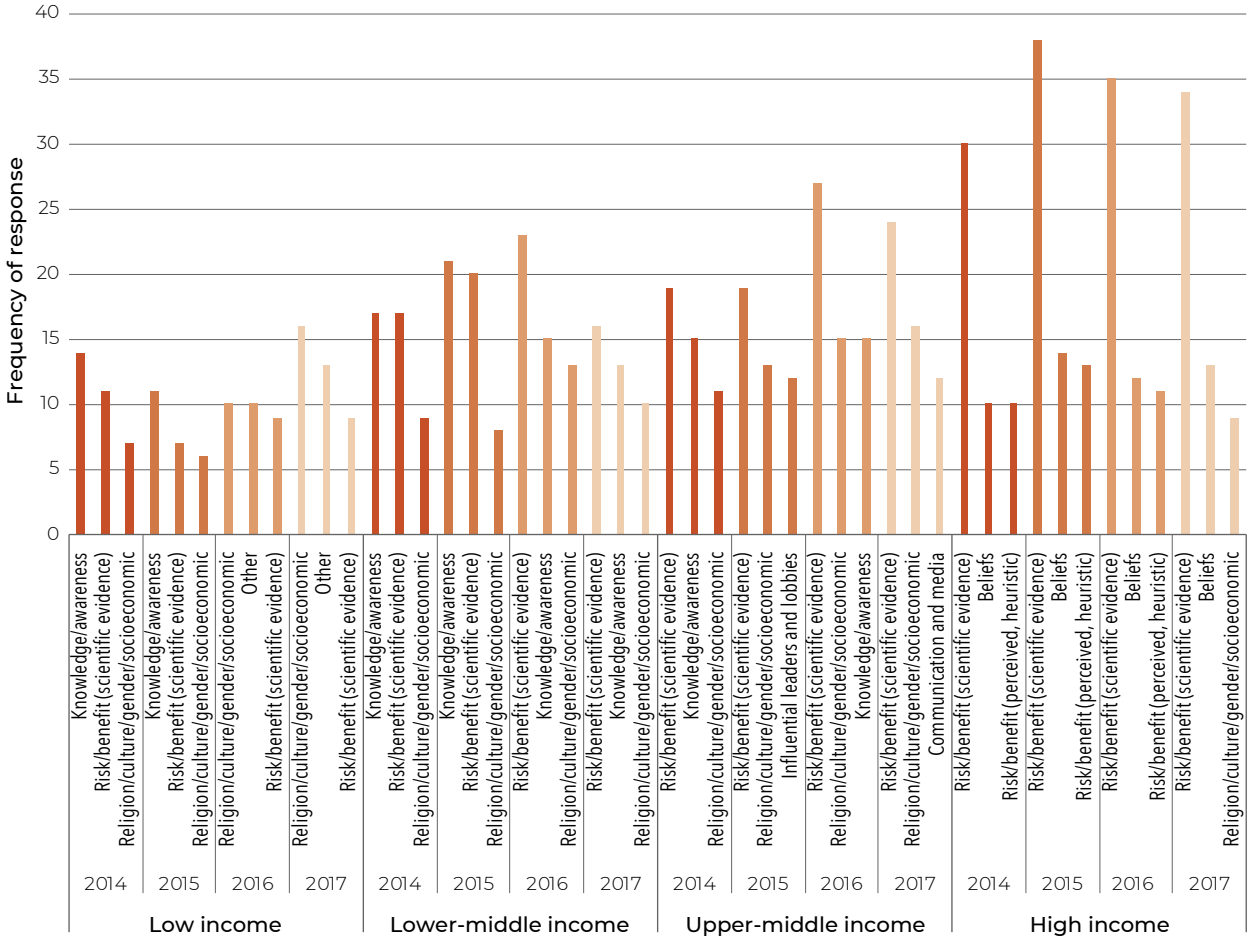


It should be noted that a frequency of response over 80 means that this response was provided over 80 times across all countries in a given year. Of the 1536 reasons given over the four years, risk/benefit (scientific evidence) represented under 30%, but was nevertheless the greatest proportion of responses overall. A further note: of the 10 most populous countries globally[2], only five provided a response.

Only seven countries reported no hesitancy (four of which are in the Eastern Mediterranean Region). The total number decreased from 13 countries that reported no hesitancy for 2016.

The reported reasons were compared by country income level (Fig. 5.2) (low income, lower-middle income, upper-middle income and high income, according to the World Bank classification)[3,4].

Fig. 5.2: Top three reasons for vaccine hesitancy by country income level, 2014–2017



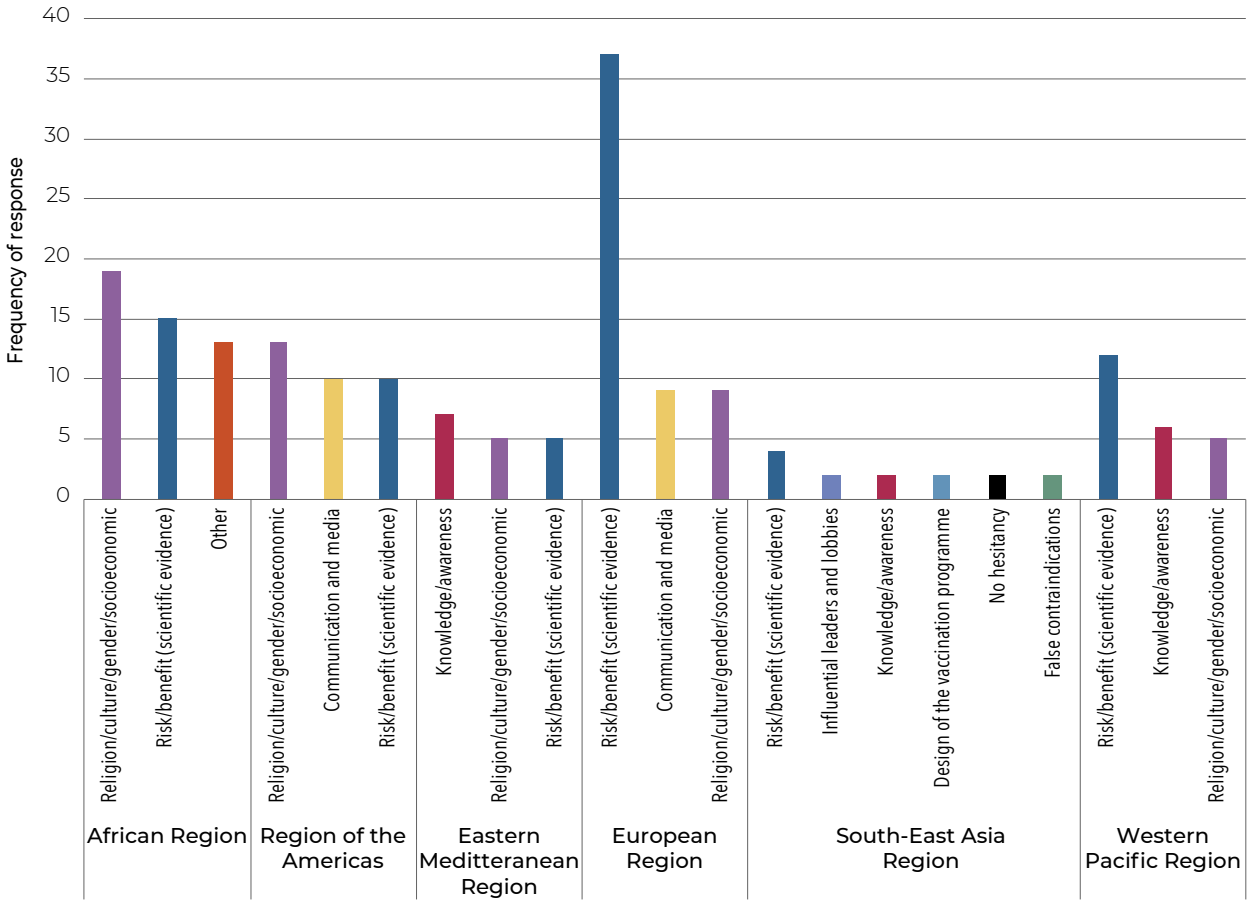
[2] The 10 most populous countries in order are: China, India, United States of America, Indonesia, Brazil, Pakistan, Nigeria, Bangladesh, Russian Federation and Mexico.

[3] World Bank income classification: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-group

[4] The Cook Islands and Niue had populations that were too small to classify by income level.

The responses were also stratified by WHO region with differences seen across regions (Fig. 5.3). The South-East Asia Region had a wider mixed list of top three reasons as no one reason predominated.

Fig. 5.3: Top three reasons for vaccine hesitancy by WHO region, 2017



2) Assessments of vaccine hesitancy (Indicator 2)

There was a slight increase in the number of countries that have completed an assessment since 2014 – 71 of 194 Member States stated assessments had been completed in the past five years (compared to 56 in 2014) (Table 5.3). Further analysis revealed that 26 countries reported having performed a new assessment in the past year. Overall however only a small percentage of countries (37%) had completed an assessment in the past five years, which is relatively unchanged from 2016 when it was 34%.

Table 5.3: Reported assessments of vaccine hesitancy by WHO region, 2017

Assessments of vaccine hesitancy	All regions n (%)	African n (%)	Americas n (%)	Eastern Mediterranean n (%)	European n (%)	South-East Asia n (%)	Western Pacific n (%)
Assessment	71 (37)	22 (47)	6 (17)	6 (29)	27 (51)	4 (36)	6 (22)
No assessment	78 (40)	16 (34)	23 (66)	8 (38)	18 (34)	2 (18)	11 (41)
Question not completed	45 (23)	9 (19)	6 (17)	7 (33)	8 (15)	5 (46)	10 (37)
No. of countries that submitted JRF	191 (98)	47 (100)	34 (97)	21 (100)	52 (98)	11 (100)	26 (96)
Total	194 (100)	47	35	21	53	11	27

3) Discussion

Compared to past years, overall the responses were similar in categories and directions of trends, with some minor changes. More assessments had been done, fewer countries reported no hesitancy, and responses were more often more detailed than in previous years; this suggests an increased understanding of the concept of hesitancy and/or local factors underlying hesitancy in the country. Overall, hesitancy is reported in the vast majority of countries but no single reason predominates overall. The category of knowledge/awareness is less prominent now than in previous years.

The limitations to the analysis remain similar to previous years: difficulty in categorizing responses where two different options were possible, responses that were too brief to categorize, and responses that had two or more categories within the same response.

In coming years it may be valuable to eventually consider potential revisions to how the JRF assesses vaccine hesitancy. With four years of reporting on reasons for vaccine hesitancy, recurrent themes have emerged. Possible revisions may include updates to the matrix that is used to categorize responses to more directly reflect the diversity of responses that are being reported globally. Such revisions would help to ensure that any detail embedded within a country's response could be adequately captured during the categorization process.

Indicator SO2.3: Percentage of countries that include in their immunization programme actions to promote or sustain public demand for vaccines and vaccination services

TARGET	Assess what the country's immunization programme does to promote or sustain public (individuals' and communities') demand for vaccines and vaccination services and what other activities were implemented to stimulate and sustain public demand for vaccines and vaccination services.
DEFINITION OF INDICATOR	**Indicator 1: In 2016, what did the country's immunization programme (at national or lower levels) do to promote or sustain public (individuals' and communities') demand for vaccines and vaccination services (directly or indirectly, alone or in coordination with/through partner agencies and/or CSOs)?** • Question 1: Implementing activities (e.g. training) to prepare for, prevent, manage or communicate about adverse events following immunization (AEFIs) or other vaccine-related events (e.g. address rumours)? (Yes/No) • Question 2: Partnering with local leadership and/or CSOs to enhance the quality and accountability of services, including seeking out community concerns? (Yes/No) • Question 3: Training health workers on interpersonal communication skills? (Yes/No) **Indicator 2: Did the country's immunization programme (at national or lower levels) implement any other activities (directly or indirectly, alone or in coordination with/through partner agencies and/or CSOs), do anything else to stimulate and sustain public demand for vaccines and vaccination services? Please describe up to three activities.** • Question 1: Please describe up to 3 activities. (Free text fields)
DATA SOURCES	All 194 countries within the six WHO regions included both indicators in their 2017 JRF to collect country data for 2016 (referred to as 2016 JRF data).

B) Status of the vaccine demand GVAP indicators, 2017

The report on this indicator has not been done this year for two main reasons. Firstly, no definition of vaccine demand was included in the JRF, and thus each country may have interpreted the concept of demand differently. The definition will be added to the JRF in 2019, and this will help to ensure a common understanding of the concept. Secondly, to date no matrix for the classification of the responses to the demand indicator has been developed, unlike for vaccine hesitancy. A formalized matrix would facilitate grouping and analysis of the different themes listed by countries in response to the query. It is expected that partners will develop this matrix in the coming months, in time for the analysis of the 2018 data.

6. SURVEILLANCE

STRATEGIC OBJECTIVE 4: STRONG IMMUNIZATION SYTEMS ARE AN INTEGRAL PART OF A WELL-FUNCTIONING HEALTH SYSTEM

Indicator SO4.4: 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

TARGET	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.
DEFINITION OF INDICATOR	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. For this report the focus is on sentinel surveillance for rotavirus and invasive bacterial vaccine-preventable diseases.
DATA SOURCES	Data reported by countries participating in the WHO-coordinated Global Rotavirus Surveillance Network and Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Network; data reported annually through the WHO-UNICEF Joint Reporting Form (JRF); other data reported to WHO on surveillance.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 6.1.

Box 6.1: Descriptions of indicators, results, data sources and highlights

Data sources:

WHO Global Invasive Bacterial Vaccine-Preventable Disease and Rotavirus and Pediatric Diarrhea Surveillance Networks Bulletin, July 2018: https://mailchi.mp/046b8f12e001/who-ib-vpd-and-rotavirus-surveillance-bulletin-june-1566245?e=225412eff9.

New and under-utilized vaccines implementation (NUVI) – Resources for monitoring and surveillance: http://www.who.int/immunization/monitoring_surveillance/resources/NUVI/en/.

For background information and methodology used for the GVAP surveillance indicator, see the previous GVAP Secretariat report.

A) Status of the GVAP vaccine-preventable disease surveillance indicators, 2017

The World Health Organization (WHO) recommends that countries conduct active, case-based, sentinel surveillance for rotavirus and invasive bacterial vaccine-preventable diseases (IB-VPDs) for children hospitalized with acute watery diarrhoea (for rotavirus) and meningitis or pneumonia/sepsis (for IB-VPDs, commonly including *Streptococcus pneumoniae*, *Neisseria*

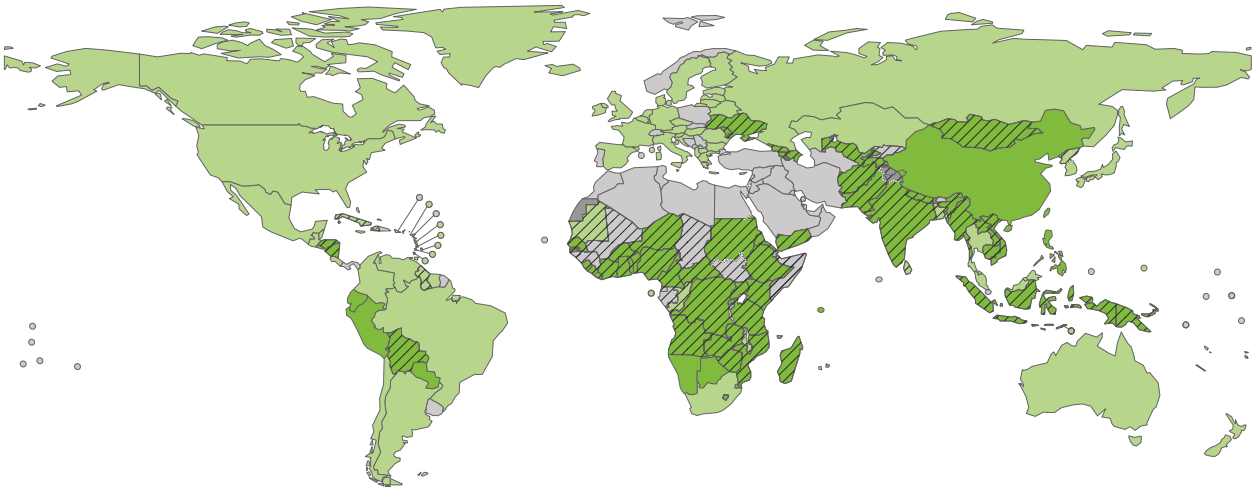
meningitidis and *Haemophilus influenzae*). (WHO vaccine-preventable disease surveillance standards are available at http://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en/). Overall, 69% of countries report conducting surveillance for rotavirus and 79% of countries report conducting surveillance for IB-VPDs (Table 6.1 and Figs. 6.1 and 6.2). Of those, 61 and 54 countries report sentinel surveillance data to WHO for rotavirus and IB-VPD, respectively, as part of the WHO-coordinated Global Rotavirus and IB-VPD Surveillance Networks, which focus on Gavi-eligible and other low- and middle-income countries. The number of countries in the global networks is similar to last year, with three additional countries reporting rotavirus surveillance data and three fewer countries reporting IB-VPD surveillance data. Of the 73 countries that have ever been eligible for Gavi support, 49 have reported rotavirus surveillance data to WHO, and 38 (78%) of those have introduced or plan to introduce rotavirus vaccine by the end of 2018. Of the 24 countries that have ever been eligible for Gavi support but have never reported surveillance data to WHO, only half (12 of 24) have introduced rotavirus vaccine (P=0.02 compared with countries that report surveillance data to WHO).

In 2017, a high percentage of countries (80%; 48 of 60) that reported rotavirus surveillance data to WHO as part of the global networks had at least one site meeting minimum performance standards (≥ 10 months of data at site level and ≥ 80 annual cases at country level). A slightly lower percentage of countries (70%; 38 of 54) that reported IB-VPD surveillance data to WHO had at least one site meeting minimum performance standards (≥ 10 months of data at site level and ≥ 80 annual cases of meningitis or ≥ 400 annual cases of meningitis/pneumonia at country level). All countries reporting to WHO were low- or middle-income countries, except for one high-income country excluded from this rotavirus calculation. The Global Rotavirus Surveillance Network (GRSN) is operating in enough countries to meet the target for this GVAP indicator (≥ 75%), but the countries in which the Global IB-VPD Surveillance Network (GISN) is operating is slightly under the target; these numbers are similar but slightly lower than last year.

Table 6.1: Countries conducting surveillance for rotavirus and invasive bacterial vaccine-preventable diseases, 2017

Disease	Part of WHO-coordinated global surveillance network n (% of total)	Conducts surveillance but not part of WHO-coordinated global surveillance network n (% of total)	No reported surveillance n (% of total)
Rotavirus	61 (31%)	72 (37%)	61 (31%)
IB-VPDs	54 (28%)	100 (52%)	40 (21%)

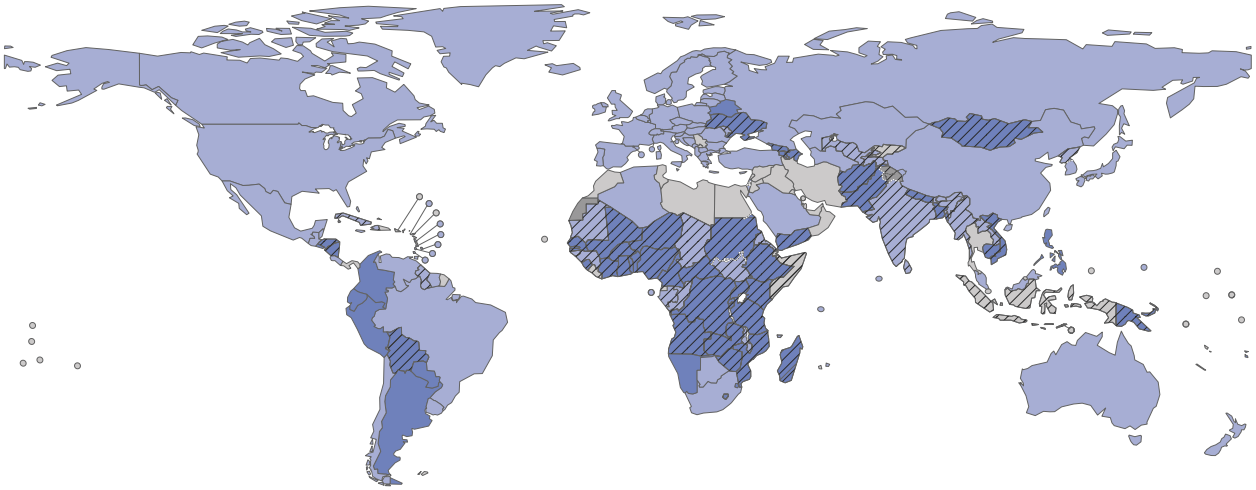
Fig. 6.1: Countries conducting rotavirus surveillance, 2017



Countries in the WHO Global Rotavirus Surveillance Network (GRSN) (61 countries)
Countries conducting Rotavirus Surveillance but not reporting to GRSN (72 countries)
GAVI eligible countries
Not available
Not applicable

Source: WHO/IVB 2017

Fig. 6.2: Countries conducting IB-VPD surveillance, 2017



Countries in the WHO Global IB-VPD Surveillance Network GSN (54 countries)
Countries conducting IB-VPD surveillance but no reporting to GSN (100 countries)
GAVI eligible countries
Not available
Not applicable

Source: WHO/IVB 2017

B) Update on vaccine-preventable surveillance activities, 2017–2018

Rotavirus and IB-VPD surveillance continue to be critical to providing evidence for vaccine introduction, monitoring programme impact, and, at least in the case of IB-VPD, providing support for identification of potential outbreaks. The WHO-coordinated global surveillance networks were initially supported by Gavi to allow Gavi-eligible countries to make evidence-based decisions about vaccine introduction and impact. Among countries that have ever been eligible for Gavi support, an association was found between countries that conduct rotavirus surveillance and report data to WHO and countries that have introduced or are planning to introduce rotavirus vaccine by 2018. This supports the idea that countries use surveillance data to make decisions about vaccine introduction and to monitor vaccine programme impact. In addition, the WHO-coordinated Global IB-VPD Surveillance Network has helped enhance laboratory capacities to identify and characterize the strains of vaccine-preventable diseases in outbreaks settings. The IB-VPD regional reference laboratories have supported countries in identifying pneumococcal and meningococcal outbreaks in the African meningitis belt.

Surveillance for both syndromes is being leveraged to test for additional vaccine-preventable diseases and diseases for which there are vaccines in development. Rotavirus surveillance has expanded in many countries to include surveillance for all cases of children hospitalized due to paediatric diarrhoea, including bloody and persistent diarrhoea. This reflects the need for data on the etiology of severe paediatric diarrhoea in the era of rotavirus vaccine introduction and the development of new enteric vaccines, such as *Shigella*, enterotoxigenic *Escherichia coli* (ETEC) and norovirus.

Surveillance for IB-VPD remains a priority because of the ongoing need to identify the remaining burden of pneumococcal disease and concerns about serotype replacement. Sentinel surveillance is the minimum recommended type of surveillance for pneumococcus; however, sentinel surveillance may not be sufficient in all settings and different types of surveillance may be needed. Bacteriology surveillance laboratory capacity is limited in many countries, so improving bacteriology will help not only the three pathogens commonly tested for as part of IB-VPD surveillance but also other bacterial vaccine-preventable diseases, such as diphtheria, pertussis and typhoid. For *Streptococcus pneumoniae* and typhoid, antimicrobial resistance is a growing concern that should be monitored through surveillance and can be prevented through vaccination.

WHO and partners are developing a strategy for comprehensive VPD surveillance, which comprises country, regional and global systems that are required to meet the minimal recommended standards for surveillance of a set of all mandatory and priority VPDs, including sentinel surveillance for rotavirus and IB-VPDs, with integration of surveillance functions across diseases when possible. One concern is that the majority of VPD surveillance, including sentinel surveillance for rotavirus and IB-VPDs, relies on infrastructure for poliomyelitis surveillance. As poliomyelitis is getting closer to eradication, VPD surveillance capacities must be maintained even though financial support for many poliomyelitis activities is declining. Consistent, sustainable support and funding of rotavirus and IB-VPD surveillance at the country level and continued coordination and monitoring at regional and global levels will be critical over the next couple of years, as highlighted by The Strategic Advisory Group of Experts on Immunization (SAGE) in its 2017 GVAP assessment report and recommendations[1].

[1] http://www.who.int/immunization/web_2017_sage_gvap_assessment_report_en.pdf

7. SUSTAINABLE FINANCING AND SUPPLY FOR IMMUNIZATION

1) Introduction

The World Health Organization's (WHO) 13th general programme of work – approved by the Seventy-first World Health Assembly – foresees achievement of universal health coverage (UHC) as one of three key goals, in line with the Sustainable Development Goals (SDGs): "WHO's work on UHC will be fully aligned with SDG target 3.8, which focuses on achieving UHC, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all."[1]

At the Seventy-first World Health Assembly, Member States discussed a report by the WHO Director-General on "Addressing the global shortage of, and access to, medicines and vaccines". Over 60 Member States spoke about sustainable supply and financing for both medicines and vaccines as a key obstacle to access. Member States then mandated WHO to design a roadmap to facilitate access to medicines and vaccines, including actions and activities for the period 2019–2023.[2]

To develop this roadmap WHO has started work across the organization, which addresses the pharmaceutical and vaccine value chain from research and development (R&D) and innovation to manufacturing, regulation, pricing, financing, supply chains and end use or products. The roadmap will be costed and submitted to the Executive Board and at the World Health Assembly in 2019. The roadmap is an important opportunity to leverage past World Health Assembly resolutions, regional resolutions, and the Strategic Advisory Group of Experts on immunization (SAGE) recommendations to further support and encourage ongoing efforts (described in detail in Chapter 7 of last year's GVAP Secretariat report) and bringing coherence across a series of inter-linked workstreams and enhancing realistic resourcing of priority actions. In parallel to this effort, WHO has also taken action to address the 2017 SAGE GVAP recommendations on sustainable supply and financing, which are discussed below.

2) Middle-income countries

WHO supports middle-income countries by leveraging all opportunities to promote the exchange of information, the sharing of lessons learned and peer-to-peer support. Brief highlights from each WHO region follow.

- **European Region:** In alignment with European Vaccine Action Plan and Health 2020, the Regional office for Europe facilitated the 20 February 2018 signing of a Statement of Intent by 13 Ministers of European middle-income countries for the development and implementation of a five-year immunization framework for south-eastern Europe.
- **The South-East Asia and Western Pacific Regions:** A close collaboration between WHO, Thailand National Vaccine Institute and the Association of Southeast Asian Nations (ASEAN) led to the adoption of the ASEAN Vaccine Security and Self-reliance framework in 2016. WHO regional offices are now working closely with ASEAN on implementation (e.g. leveraging the more developed infrastructure of Thailand and Singapore to explore pooled procurement options).
- **African Region:** Leveraging the Addis Declaration on Immunization (2016)[3], the Regional Office for Africa is developing a regional action plan for middle-income countries; the first meeting was held in Brazzaville, the Congo, 9–11 April 2018.
- **Region of the Americas:** The Pan American Health organization (PAHO) has continued its efforts to support middle-income countries through a revolving fund and related technical support – including a review of the revolving fund operations for further enhancement.
- **Eastern Mediterranean Region:** The region is experiencing major challenges in several conflict-affected middle-income countries (Syrian Arab Republic, Iraq), including inadequate funding and very few human resources resulting in

1 http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_4-en.pdf
2 http://www.who.int/medicines/access_use/road-map-medicines-vaccines/en/
3 http://immunizationinafrica2016.org/ministerial-declaration-english/

significant delays in carrying out EPI activities and very high costs of implementation. The Regional Office for the Eastern Mediterranean has been instrumental in supporting those countries but is still struggling to ensure vaccination activities are included within national emergency plans and related resource mobilization efforts. Another major issue is the support to middle-income countries receiving large numbers of refugees such as Egypt, Iraq, Lebanon and Jordan, which are struggling to provide immunization services to those extra populations from their own limited resources.

- **Global perspective:** In order to support regional efforts, WHO headquarters is planning to re-establish a "middle-income countries task force" to lead information sharing and coordination among different initiatives and inform immunization planning after 2020.

3) Vaccine supply

Vaccine supply is a critical component of immunization activities in middle-income countries. WHO is assisting middle-income countries in the analysis of current and anticipated vaccine supply and demand for routinely used vaccines to identify risks to access (in particular shortage and affordability). In particular, substantial progress has been made to enhance the vaccine market information available to countries, and further investments have been made through the launch of a new global initiative: Market Information for Access to Vaccines – MI4A[4]. MI4A provides a unique global perspective on vaccine markets, covering all countries and vaccines with the objectives to:

- enhance the understanding of global vaccine demand, supply and pricing dynamics and identifying affordability and shortage risks;
- convene all relevant global health partners to contribute to the development of policies, strategies, and guidance to address the identified risks;
- strengthen national and regional capacity for improved access to vaccines supply.

Countries are actively using this information to inform procurement processes. Information is also being used to inform a WHO-led dialogue on Fair Pricing of Vaccines,[5] the set up and launch of a WHO medicine and vaccines shortage notification system,[6] the launch of vaccine access programmes (e.g. a "humanitarian mechanism" granting reduced pricing for pneumococcal conjugate vaccine (PCV for populations facing emergencies); regional efforts to strengthen country procurement regulations and skills (e.g. in the Regions of Europe, Eastern Mediterranean and South-East Asia).

The following subchapters describe progress on the different GVAP indicators and provide additional insight into recent activities on three dimensions of sustainable supply and financing: i) product innovation for enhanced coverage and equity (chapters on vaccines of assured quality, prequalified devices and technologies and controlled temperature chain); ii) availability (chapters on shortages and stock outs); and iii) affordability (chapters on price and financing).

- Subchapter 1: Percentage of doses of vaccine used worldwide that are of assured quality (indicator SO5.1)
- Subchapter 2: Number of vaccine delivery technologies (devices and equipment) that have received WHO prequalification (indicator SO6.5)
- Subchapter 3: All Member States commit to immunization as a priority: domestic expenditures for immunization per person targeted (Indicator SO1.1)
- Subchapter 4: Vaccine price & procurement report 2018
- Subchapter 5: Stock outs: Availability of vaccines for routine immunization at national (Indicator SO5.2) and subnational levels including country performance towards supply chain fundaments
- Subchapter 6: 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)

Subchapter 1: 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)

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 7.1.

Box 7.1: Descriptions of indicators, results, data sources and highlights

WHO Global Benchmarking Tool for evaluation of national regulatory systems: http://www.who.int/medicines/regulation/benchmarking_tool/en/.

[4] www.who.int/immunization/MI4A
[5] http://www.who.int/medicines/access/fair_pricing/en/
[6] http://apps.who.int/iris/handle/10665/259670

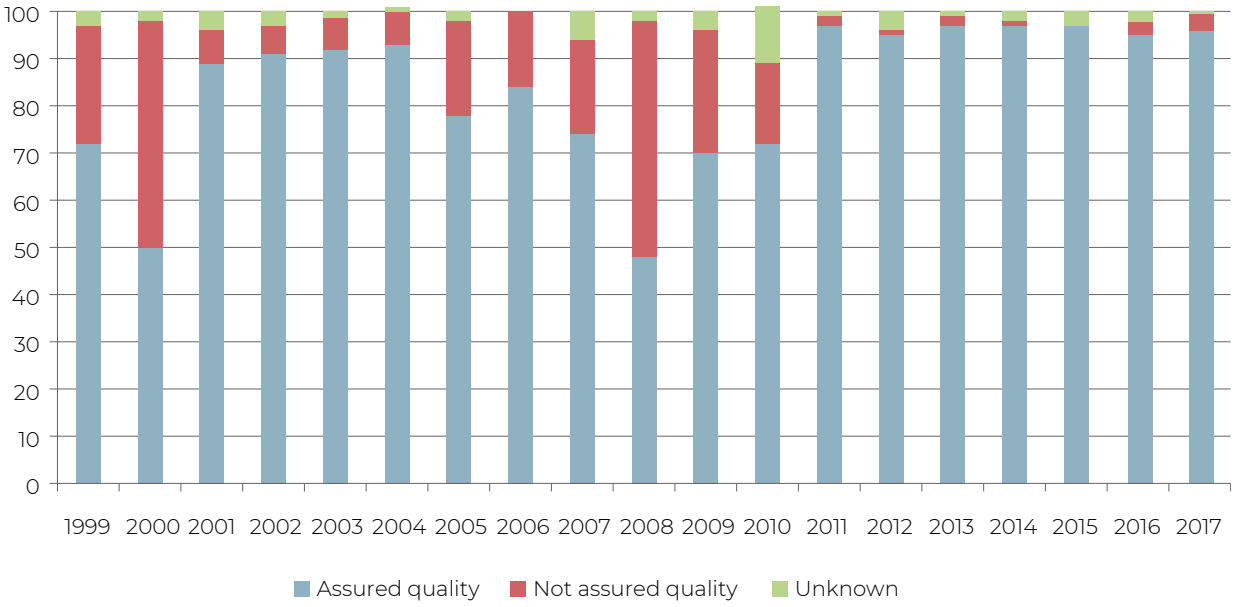
A) Status of the vaccine quality GVAP indicator, 2017

As of June 2018 there were 43 vaccine-producing Member States globally that met the WHO criteria. Of those countries, 37 had a functional national regulatory authority (NRA), as assessed by WHO, compared to 36 countries in June 2017. The NRA of the Russian Federation was declared functional after the Russian authorities implemented a set of corrective actions based on the results of the WHO assessment conducted in April 2016. Twenty-two of the vaccine-producing Member States were manufacturing one or more WHO-prequalified vaccines by the end of 2017 (same as 2016). Likewise, among the 151 Member States that do not produce vaccines, 29 had functional NRAs (same as 2017).

Globally in 2017, 70% of the population (around 5.1 billion people) lives in a country with a functional NRA (66 countries in total). The remaining 30% of the world's population nevertheless have access to WHO-prequalified vaccines through their national immunization programmes, as those vaccines are produced and their quality controlled in countries with functional NRAs. This trend is stable as compared with the previous year. Overall in 2017, 96% of the globally-available doses of vaccines used in national immunization programmes are of assured quality (compared to 95% in 2016) (Fig. 7.1).

While the 4% gap is expected to decrease in 2018 due to additional vaccine-producing countries with functional NRAs, there are still several challenges to reach to the target of 100% assured quality vaccine. These challenges are mainly due to inconsistent vaccine production by local manufacturers, lack of sufficient commitment and strategic plans to strengthen further the concerned regulatory authorities and inadequate human and financial resources at country level. In addition, there are two or three countries in which the functionality of the NRA is at risk and further support is needed to maintain its status in 2018. The major challenges in those countries are related to insufficient enforcement of regulations for local manufacturers as well as inadequate post-marketing regulatory oversight.

Fig. 7.1: Percentage of vaccines of assured (blue) versus non-assured (orange) quality used worldwide, 1999–2017[a]



[a] Doses of vaccines reported mainly from country's lot release and WHO-UNICEF Joint Reporting Form (JRF).
Source: World Health Organization/Essential Medicines and Health Products, as of July 2018.

B) Highlights of activities in the field of vaccine quality and regulatory aspects, 2017–2018

Efficient regulatory mechanisms with streamlined processes and predictable timelines facilitate access to vaccines. The WHO regulatory systems strengthening programme is working with Member States to support and build national regulatory system capacities for medical products including vaccines. This includes the promotion of good regulatory practices, reliability, regulatory cooperation, convergence, transparency, independence, networking and collaboration. The WHO Global Benchmarking Tool is a means by which WHO evaluates regulatory systems through a comprehensive and systematic benchmarking approach. The tool identifies strengths and areas for improvement, facilitates the formulation of an institutional development plan to build upon strengths and address the identified gaps, aids in the prioritization of institutional development plan interventions and helps to monitor progress and achievements.

Revision V of the Global Benchmarking Tool is currently used for benchmarking of vaccine regulatory systems (the revision is based on the outcomes of two international expert consultations in January and December 2015). The Global Benchmarking Tool is currently being revised; draft VI was open for public consultation in January and February 2018. The numerous comments received reflect the interest of Member States, partners and other stakeholders (including industry) for the maintenance and improvement of this tool. WHO is currently working on the compilation, review and response to the comments in collaboration with

expert regulators from all WHO regions. Revision VI of the tool is expected to be published in October or November 2018.

WHO support also extends to Institutional development plans: China, Egypt, India, Indonesia, Serbia and Viet Nam have implemented plans and these are being monitored by WHO through field visits, training and workshops. In addition, the NRAs of Thailand, Indonesia, the Republic of Korea and Viet Nam will be reassessed in 2018. WHO has extended its regulatory support to several African Regional Economic Communities as well, including the Intergovernmental Authority on Development, Economic Community of West African States and the East African Community through several self-benchmarking workshops.

In the context of WHO's support to Member States in strengthening their regulatory systems, WHO conducted two workshops on sensitization towards a quality management system for NRAs from 10 to 13 October 2017 in Harare, Zimbabwe and 17 to 20 April 2018 in Ouagadougou, Burkina Faso for selected Anglophone and Francophone countries of the WHO African Region. As a result of these workshops, Member States requested WHO develop guidelines for the establishment and maintenance of quality management systems for NRAs. These guidelines are now being developed, and are expected to be published by 2019.

Subchapter 2: 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)

TARGET	None specified.
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) specification system as of 31 December 2017, as compared to the number of prequalified products on 31 December 2010, which was 163 products. **Note:** The definition 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.
DATA SOURCES	The WHO PQS 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 2017. The recording of the date after each change of a product's status ensures the quality of data.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 7.2.

Box 7.2: Descriptions of indicators, results, data sources and highlights

For additional information, see: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/index.aspx

A) Status of the prequalification GVAP indicator, 2017

Use of prequalified cold chain equipment and vaccine delivery devices continues to increase – over the past eight years there has been a 100% increase in the total number of products used (Table 7.1). There are now 326 products prequalified from a total of 76 manufacturers.

Table 7.1: Number of prequalified products per year and per category between 2008 and 2017

Prequalified products	Year										Increase (%)
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2010– 2017
Cold rooms and related equipment	0	1	3	3	3	3	3	4	4	4	33%
Refrigerators and freezers	0	8	14	23	33	36	44	51	74	78	457%
Cold boxes and vaccine carriers	0	2	31	32	34	37	39	41	42	43	39%
Water packs	0	1	15	16	18	17	17	17	17	17	13%
Temperature monitoring devices	7	10	11	12	17	22	24	31	33	40	264%
AD syringes for immunization	21	31	30	27	29	33	36	39	39	39	30%
Waste management equipment	5	9	10	10	10	10	11	12	12	12	20%
Therapeutic injection devices	22	35	49	60	72	80	84	89	89	93	90%
Total	55	97	163	183	216	238	258	284	310	326	100%

AD, auto disable

B) Highlights of prequalification activities, 2017–2018

McKinsey & Company was hired by WHO to conduct an external review of the WHO Performance, Quality and Safety (PQS) unit in 2017. The main purpose of the review was to evaluate the extent to which the current functional and organizational structure of the PQS unit is able to meet the needs and demands of the end-users and stakeholders for the regulatory value chain for cold chain equipment and injection devices. Alongside this, the review sought to identify the set of options available that addressed both change/enhancement opportunities and ownership options for the future. The following means were used:

- defining current regulatory value chain activities and describing the role of the various stakeholders in lower-middle-income countries, including the PQS unit, standards setters and regulatory agencies, testing laboratories and donors/procurers;
- comparing lower-middle-income countries and high-income countries to understand the need for different technology, different standard setting/regulatory activities and market shaping activities;
- defining which bodies (international bodies or national bodies from high-income countries) could potentially take a stronger role in lower-middle-income countries and what "best practices" may look like (e.g. for laboratory accreditation and re-assessment);
- capturing stakeholder requirements and expectations along the regulatory value chain (including information from the WHO Expanded Programme on Immunization (EPI), countries, the UNICEF Supply Division/Programme Division, Gavi, the Vaccine Alliance (Gavi), manufacturers, testing laboratories, etc.), which highlight strengths and weaknesses, and options for the future;
- determining a set of options for various stakeholders, which they could potentially use to perform some of the tasks in the value chain from standard setting to post-market monitoring (including trade-offs), and which regulatory value chain activities could be enhanced and how.

The PQS unit is currently finalizing an improvement plan following the recommendations of the review.

Subchapter 3: All Member States commit to immunization as a priority: domestic expenditures for immunization per person targeted (Indicator SO1.1)

STRATEGIC OBJECTIVE	All Member States commit to immunization as a priority.
TARGET	Increasing trend in country allocation to national immunization programmes.
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. The number of live births is used as a proxy for persons targeted as standard denominator available for all countries.
DESCRIPTION OF DATA SOURCES	1. The JRF financing indicators: government expenditure on routine immunization; government expenditure on vaccines; percentage of routine immunization costs funded by government. 2. World Bank: income classification; US Consumer Price Index; currency exchange rates. 3. Gavi: Gavi co-financing country grouping. 4. UN World Population Prospects 2017: live birth data.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 7.3.

Box 7.3: Descriptions of indicators, results, data sources and highlights

For more information, see:

http://apps.who.int/gho/cabinet/gvap.jsp

http://www.who.int/immunization/programmes_systems/financing/data_indicators/en/

Annex 7.1 below contains information about data quality.

A) Status of the domestic expenditure for immunization GVAP indicator, 2017

1) Methodology

The methodology employed for this indicator remains largely unchanged from the 2017 GVAP Secretariat report. Three periods have been chosen for comparison: the baseline (2010–2011) and the most recent two-year periods (2014–2015 and 2016–2017). In order to be included in the analysis, a country needed to have reported data for at least one year in each of the three study periods: 2010–2011, 2014–2015 and 2016–2017. Therefore, a consistent set of countries is maintained across the entire period of analysis (2010–2017). For the comparative analysis, the average expenditure of each two-year period was calculated.

Country-reported expenditures were converted from local currency amounts to US dollars, by using the annual average exchange rates available from the World Bank's World Development Indicators. The analysis covers a considerable timespan (2010–2017). In order to take into account inflation, and allow for valid comparisons between time periods, nominal dollar values for each year were converted to 2017 constant dollars using the United States Consumer Price Index (CPI).

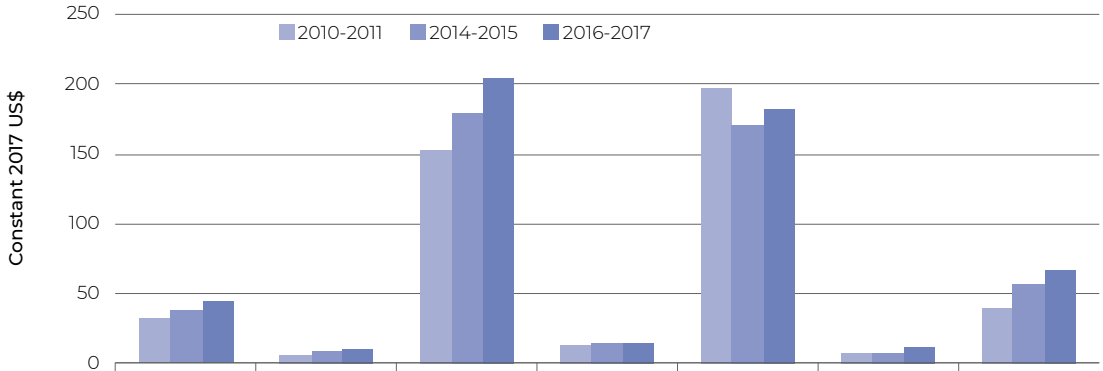
A total of 124 Member States satisfied the reporting criteria and were included in the analysis. Complementing the comparison of routine immunization expenditures was an analysis of government expenditures on vaccines, as well as the percentage of total routine immunization expenditures funded by government.

2) Results

The results of the analysis show that global government expenditures on routine immunization and vaccines per live birth (Fig. 7.2 and Fig. 7.3 respectively) grew over the period of analysis (2010–2017) – a testament to Member States' commitment to immunization. Since the baseline period, global expenditures on routine immunization per live birth grew by 35% (from US$ 33 to US$ 44), while vaccine

expenditures saw a rise of greater magnitude, increasing by 43% (US$ 26 to US$ 37).

Fig. 7.2: Government expenditure on routine immunization per live birth[a], by WHO region

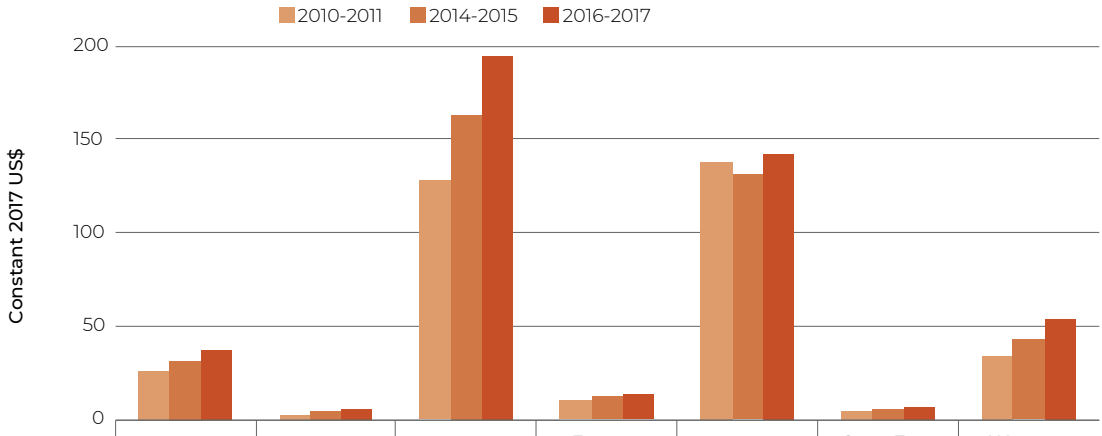


	Global	African	Americas	Eastern Mediterranean	European	Sout-East Asia	Western Pacific
2010-2011	33	6	154	13	196	7	39
2014-2015	38	9	180	14	170	7	56
2016-2017	44	10	204	14	182	11	67
Change 2010-11 & 2016-17 (%)	35%	74%	33%	13%	0%	62%	75%
No. of countries	124	39	30	10	19	11	15
No.of countries reporting increase	78	25	22	7	8	8	8

[a] Population-weighted average

All regions but the European Region increased their routine immunization spending per live birth between 2010–2011 and 2016–2017 (Fig. 7.2); and during the same periods an increase in vaccine expenditures per live birth was recorded across all regions (Fig. 7.3). In the Western Pacific Region routine immunization spending rose by 75% over the period of analysis (from US$ 39 to US$ 67); this represents the largest percentage growth of all the WHO regions. The African Region reported a 74% growth in routine immunization spending, an increase due in part to the region's greater domestic contributions to vaccine procurement, which increased by 130% over the same periods (from US$ 2 to US$ 5 per live birth) (Fig. 7.3). While other regions recorded more modest growth in routine immunization expenditures, the European Region exhibited a fall between 2010–2011 and 2014–2015, which recovered slightly in the most recent period. In some instances, vaccine expenditure increases can be seen to be related to increases in the birth cohort, national vaccine schedules and the introduction of new and underused vaccines. It should also be noted that the price of some vaccines, such as pentavalent vaccine, have declined over the 2016–2017 period.

Fig. 7.3: Government expenditure on vaccines per live birth[a]



	Global	African	Americas	Eastern Mediterranean	European	Sout-East Asia	Western Pacific
2010-2011	26	2	128	10	138	4	34
2014-2015	31	5	163	12	131	5	43
2016-2017	37	5	194	13	143	6	54
Change 2010-11 & 2016-17 (%)	43%	130%	51%	23%	3%	58%	58%
No. of countries	122	39	30	10	18	10	15

[a] Population-weighted average

In terms of absolute expenditures, there are extremely large disparities between regions. In 2016–2017, the total routine immunization expenditure outlay of the Region of the Americas (US$ 204 per

live birth) and the European Region (US$ 182 per live birth), was over fifteen times greater than that of the African and South-East Asia Regions (US$ 10 and US$ 11, respectively). The reasons for these disparities are numerous. For one, the European Region and the Region of the Americas have a larger proportion of high-income countries, which have comparatively higher domestic budgets for health spending, and are not particularly reliant on external funds for immunization (over 85% of routine immunization expenditure is funded by government in the European Region for example (Table 7.2). Additionally, these two regions also have a lower proportion of Gavi-supported countries, so more countries face higher vaccine prices, which could partially explain their higher routine immunization expenditures.

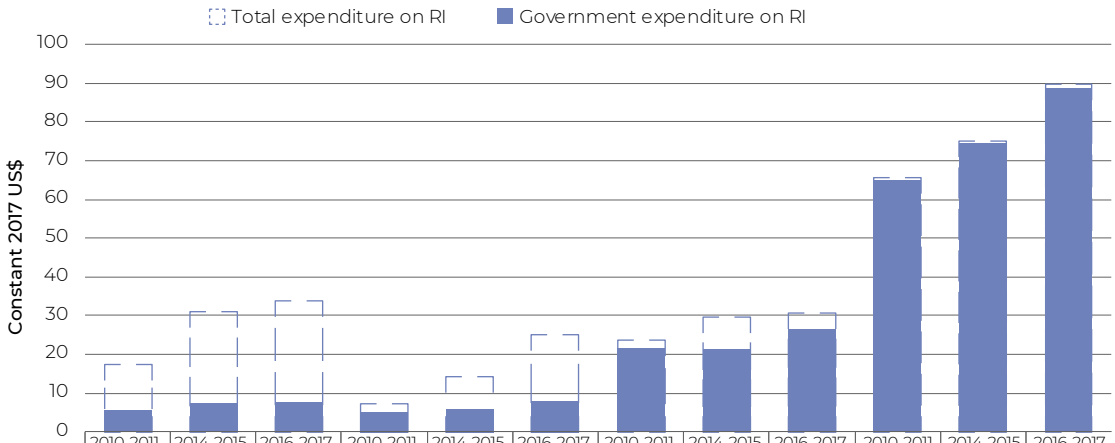
Table 7.2: Percentage of routine immunization expenditures funded by governmenta

Percentage of routine immunization expenditures funded by government					
WHO region/ WHO region or World Bank income group	2010–2011	2014–2015	2016–2017	Change 2010–11 & 2016–17 (%)	No. of countries
African	47	27	25	-47%	36
Americas	98	99	97	-1%	30
Eastern Mediterranean	71	49	41	-43%	10
European	79	79	85	7%	18
South-East Asia	90	60	51	-44%	11
Western Pacific	93	94	96	4%	14
Global	**78**	**61**	**57**	**-28%**	**119**
Low income w/Gavi support	31	24	22	-27%	25
Middle-income w/Gavi support	69	40	32	-54%	23
Former Gavi, fully self-financing by 2018	90	71	86	-5%	14
Middle income w/o Gavi support	99	99	99	0%	41
High income	93	100	100	8%	16
All Gavi-eligible countries	68	43	37	-46%	62

[a] Population-weighted average

The *percentage* of routine immunization expenditures funded by government fell in the African, Eastern Mediterranean and South-East Asia Regions, despite the increase of expenditure in *absolute values*, demonstrating a greater reliance on external funds over the period of analysis (Table 7.2). This is likely a result of the introduction of new and underused vaccines into country immunization schedules, with financial support for these vaccines coming primarily from Gavi (Fig. 7.4). The large increases in external funding in these regions caused the global average share of government expenditure in total routine immunization to fall from 78% in the baseline period to 57% in 2016–2017 period (Table 7.2).

Fig. 7.4: Government expenditure on routine immunization (RI) per live birth[a], by income classification and Gavi support



	Low Income w/ Gavi support			Middle Income w/ Gavi support			Middle income, former Gavi now fully self-financing			Middle Income-Non Gavi		
	2010-2011	2014-2015	2016-2017	2010-2011	2014-2015	2016-2017	2010-2011	2014-2015	2016-2017	2010-2011	2014-2015	2016-2017
Total expenditure on RI	17	31	34	7	14	25	24	29	31	66	75	90
Government expenditure on RI	5	7	8	5	6	8	21	21	26	65	74	89
Percentage funded by government	31%	24%	22%	69%	40%	32%	90%	71%	86%	99%	99%	99%
No. of countries	25			23			14			41		

[a] Population-weighted average

Between 2010 and 2011 and 2016 and 2017, currently Gavi-supported countries increased their routine immunization spending respectively by 41% (from US$ 5.4 to US$ 7.5 per live birth) and 58% (from US$ 5.0 to US$ 7.9 per live birth) for low-income and middle-income countries. Middle-income countries without Gavi support displayed somewhat more modest growth in spending, rising by just 36%. High-income countries (not displayed in Fig. 7.4) increased their government expenditure on immunization by 48% to an average of US$ 790 per live birth. Growth in vaccine expenditures largely drove the increase in routine immunization expenditures seen across all income groups.

Alongside the increases to domestic spending, external funding for immunization continued to grow at a faster rate in currently Gavi-supported countries, having the effect of reducing between 2010 and 2011 and 2016 and 2017 the percentage of routine immunization costs funded by government respectively, from 31% to 22% in low-income and from 69% to 32% in middle-income countries. Middle-income countries formerly supported by Gavi but now fully self-financing – having transitioned from Gavi support in 2018 or prior – did fund a greater share of their routine immunization expenditures than other Gavi-eligible countries (Fig. 7.4). However, over the period of analysis the proportion of expenditures funded by government declined from 90% to 86%, the opposite of what would be expected for these countries (Table 7.2). Annex 7.2 contains routine immunization data by country and WHO region.

B) Activities related to supporting domestic expenditure for immunization, 2017–2018

In continuation of the previous year's efforts, WHO and partner organizations have maintained their advocacy and support for countries to ensure adequate and reliable access to sustainable immunization financing. While external investment for immunization has continued to grow, these funds remain predominantly available to countries with low-income and lower-middle-income status. The importance of developing an understanding of immunization expenditures and financing flows is apparent for all countries, including those with middle-income status, as they strive to appropriately plan and budget their available resources in order to maintain progress towards ambitious immunization targets and goals.

Over the past year, WHO and UNICEF have continued to provide technical assistance to countries in the development of comprehensive multi-year plans (cMYPs) for immunization, which provide costed multi-year strategies and operational plans for immunization. Recently the focus has shifted to enhancing country capacity which has led to a greater number of countries producing cMYPs independently, supported by available WHO-UNICEF resources such as planning guidelines and e-learning materials.

In 2017 a total of 26 countries developed new cMYPs, setting out a comprehensive immunization strategy for the next five years. In addition, a number of countries conducted EPI reviews and evaluated their previous years immunization activities and updated their cMYPs to address unforeseen domestic issues and include amended strategies. Eleven Gavi-eligible countries developed new CMYPs: six countries were in the initial self-financing/co-financing group (all in the African Region) and five in the preparatory transition group. Six countries in the accelerated transition co-financing group developed new cMYPs and two countries which have fully transitioned from Gavi support also developed cMYPs. Furthermore, seven middle-income countries (not eligible for Gavi support)

developed cMYPs, showing the importance attributed to cMYPs as a step towards sustainable immunization financing.

Annex 7.1: Data quality and country-specific data

There has been an improvement in both the number of countries reporting data and its overall quality since 2010. However, the reporting statistics would suggest that the number of countries providing data on routine immunization spending has fallen slightly since last year, and the number of data points judged to be inconsistent have increased year-upon-year since 2015 (Table A.1.1, Fig. A.1.1). The bulk of these trends occur predominantly in the European, South-East Asia and Western Pacific Regions.

The current process for reporting on the JRF financing indicators entails a rigorous screening process for all country-reported data, to ensure that all data when finally analysed is of sufficient quality to provide meaningful results. Inconsistencies in reported data are identified as values that did not meet (six) pre-specified rules of internal consistency for the JRF financing indicators, or when data values were obviously divergent from previous or subsequent trends. In addition, reported data are verified against additional sources of information such a cMYP baseline costs, and Gavi co-financing and new vaccine support disbursement amounts (where applicable). In certain cases, data points are estimated by WHO, based on these additional sources of information or on the data time-series trend. Countries are then provided with detailed feedback and given the opportunity to correct and resubmit their financing indicator data, with the support of WHO regional offices.

Fig. A1.1: Percentage of countries with missing and inconsistent data on government expenditure on routine immunization, 2010–2017

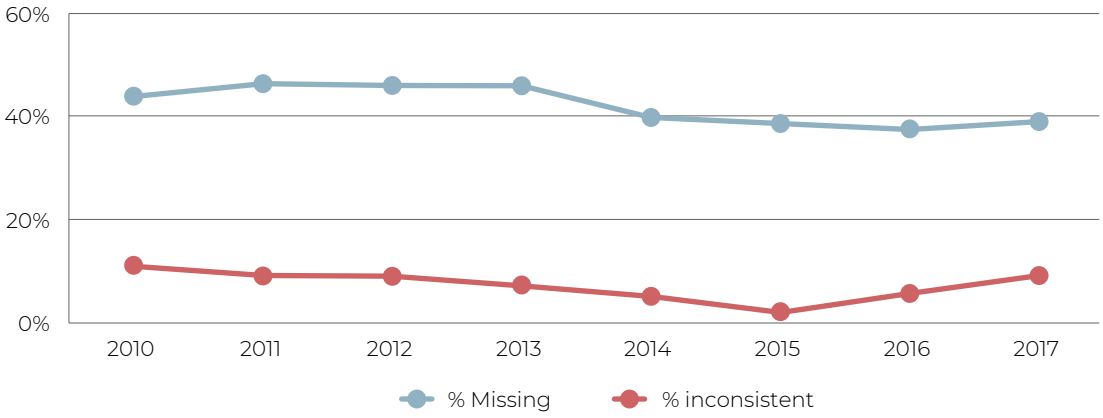


Table A1.3: Number of countries with missing and inconsistent data for government expenditure on routine immunization, 2010–2017

WHO region	2010	2011	2012	2013	2014	2015	2016	2017
African	19	21	24	17	14	12	10	10
Americas	12	9	8	11	8	7	9	9
Eastern Mediterranean	14	15	15	14	14	10	10	11
European	39	41	38	40	36	35	33	39
South-East Asia	6	5	5	4	1	1	3	5
Western Pacific	15	16	16	16	14	14	18	18
Total no. of countries with missing data	**84**	**90**	**89**	**88**	**77**	**75**	**72**	**75**
% missing	44%	47%	46%	46%	40%	39%	37%	39%
Total no. of countries with inconsistent data	**21**	**17**	**17**	**14**	**10**	**4**	**11**	**17**
% inconsistent	11%	9%	9%	7%	5%	2%	6%	9%

WHO and partners continue to advocate for improved country reporting for the JRF financing indicators through improved linkages between the country-led System of Health Accounts supported by WHO. As more countries adopt the methodology for eliciting immunization expenditures through the System of Health Accounts, it is expected that this will contribute to improved reporting of JRF financing indicator data, alongside improvements in quality and accuracy (see section II).

Annex 7.2: Tables on GVAP financing indicators by country, WHO region and World Bank income classification

In the tables that follow, Member States are listed in order of magnitude of change in average expenditures between 2010 and 2011 and 2016 and 2017. For the sake of brevity in the tables below the World Bank's income classification[7] for economies has been shortened: low-income country (LIC), lower-middle-income country (LMIC), upper-middle-income country (UMIC) and high-income country (HIC). Where "(Gavi)" appears in the tables, this means the Member State is eligible for Gavi support.

Table A2.1: Government expenditure[a] on routine immunization per live birth by country, African Region

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Equatorial Guinea	UMIC	1.45	5.24	14.01	Increasing	867%
Seychelles	HIC	26.69	149.80	130.42	Increasing	389%
Nigeria	LMIC (Gavi)	3.88	12.20	18.20	Increasing	369%
Botswana	UMIC	26.56	126.65	118.20	Increasing	345%
Uganda	LIC (Gavi)	2.00	9.48	7.68	Increasing	283%
Senegal	LIC (Gavi)	4.90	3.96	12.09	Increasing	147%
Niger	LIC (Gavi)	1.72	4.67	4.13	Increasing	141%
Burundi	LIC (Gavi)	0.83	1.74	2.00	Increasing	140%
Mauritius	UMIC	109.78	87.44	260.50	Increasing	137%
Madagascar	LIC (Gavi)	0.94	3.83	2.22	Increasing	137%
Mauritania	LMIC (Gavi)	5.24	15.68	9.96	Increasing	90%
Mali	LIC (Gavi)	8.43	10.72	15.81	Increasing	88%
Côte d'Ivoire	LMIC (Gavi)	6.20	8.31	11.46	Increasing	85%
Burkina Faso	LIC (Gavi)	6.25	5.30	10.48	Increasing	68%
United Republic of Tanzania	LIC (Gavi)	5.12	9.65	8.17	Increasing	60%
Ethiopia	LIC (Gavi)	11.32	12.69	15.53	Increasing	37%
eSwatini	LMIC	63.90	70.41	86.33	Increasing	35%
Benin	LIC (Gavi)	6.25	4.96	8.16	Increasing	30%
Mozambique	LIC (Gavi)	4.11	4.72	5.25	Increasing	28%
Eritrea	LIC (Gavi)	2.99	3.04	3.54	Increasing	18%
Kenya	LMIC (Gavi)	4.67	3.29	5.38	Increasing	15%

[7] https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2017-2018

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Lesotho	LMIC (Gavi)	9.35	10.46	10.74	Increasing	15%
Congo	LMIC (Gavi)	4.01	13.02	4.57	Increasing	14%
Central African Republic	LIC (Gavi)	0.80	0.70	0.89	Increasing	11%
Democratic Republic of the Congo	LIC (Gavi)	0.66	1.10	0.68	Increasing	3%
Zimbabwe	LIC (Gavi)	16.89	26.90	16.53	Decreasing	-2%
Sao Tome and Principe	LMIC (Gavi)	71.16	74.13	67.89	Decreasing	-5%
Guinea-Bissau	LIC (Gavi)	2.26	1.67	2.14	Decreasing	-5%
Togo	LIC (Gavi)	19.88	10.82	17.73	Decreasing	-11%
South Sudan	LIC (Gavi)	1.21	1.53	1.02	Decreasing	-16%
Guinea	LIC (Gavi)	2.68	4.81	2.23	Decreasing	-17%
Chad	LIC (Gavi)	4.07	4.10	3.15	Decreasing	-22%
Cameroon	LMIC (Gavi)	7.84	5.91	5.87	Decreasing	-25%
Rwanda	LIC (Gavi)	6.58	10.51	4.64	Decreasing	-29%
Sierra Leone	LIC (Gavi)	3.33	6.25	1.79	Decreasing	-46%
Zambia	LMIC (Gavi)	36.83	14.35	11.29	Decreasing	-69%
Malawi	LIC (Gavi)	5.80	2.28	1.55	Decreasing	-73%
Comoros	LIC (Gavi)	15.39	5.01	3.12	Decreasing	-80%
Gabon	UMIC	46.43	15.86	6.34	Decreasing	-86%

[a] 2017 Constant US$

Table A2.2: Government expenditure[a] on routine immunization per live birth by country, Region of the Americas

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Saint Vincent and the Grenadines	UMIC	23.47	35.59	509.58	Increasing	2071%
Dominica	UMIC	29.41	45.38	541.27	Increasing	1741%
Dominican Republic	UMIC	18.08	38.81	59.39	Increasing	229%
Guyana	UMIC (Gavi)	69.06	123.05	176.98	Increasing	156%
Saint Lucia	UMIC	31.93	80.98	64.60	Increasing	102%
Guatemala	LMIC	34.51	81.92	69.03	Increasing	100%

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Paraguay	UMIC	103.58	111.44	196.40	Increasing	90%
Panama	UMIC	312.11	376.07	569.69	Increasing	83%
Brazil	UMIC	214.72	267.99	355.06	Increasing	65%
Bahamas	HIC	128.10	178.43	207.34	Increasing	62%
Grenada	UMIC	48.74	54.87	76.69	Increasing	57%
Bolivia (Plurinational State of)	LMIC (Gavi)	52.59	63.50	72.61	Increasing	38%
Argentina	UMIC	177.44	342.03	234.19	Increasing	32%
Uruguay	HIC	173.35	203.95	222.97	Increasing	29%
Nicaragua	LMIC (Gavi)	80.45	97.40	101.99	Increasing	27%
Saint Kitts and Nevis	HIC	27.94	17.49	35.10	Increasing	26%
Venezuela (Bolivarian Republic of)	UMIC	68.64	86.62	82.07	Increasing	20%
Belize	UMIC	64.70	52.93	76.44	Increasing	18%
Cuba	UMIC (Gavi)	185.05	216.14	213.89	Increasing	16%
Mexico	UMIC	132.40	121.63	145.24	Increasing	10%
Honduras	LMIC (Gavi)	59.98	63.50	63.62	Increasing	6%
Peru	UMIC	195.13	174.90	203.52	Increasing	4%
Ecuador	UMIC	168.28	153.18	153.75	Decreasing	-9%
Colombia	UMIC	110.55	121.25	97.08	Decreasing	-12%
Barbados	HIC	233.40	357.03	199.04	Decreasing	-15%
Chile	HIC	235.51	194.43	198.77	Decreasing	-16%
Costa Rica	UMIC	300.57	212.89	240.29	Decreasing	-20%
El Salvador	LMIC	122.93	108.37	69.24	Decreasing	-44%
Jamaica	UMIC	133.06	36.40	47.47	Decreasing	-64%
Suriname	UMIC	120.84	29.89	29.05	Decreasing	-76%

[a] 2017 Constant US$

Table A2.3: Government expenditure[a] on routine immunization per live birth by country, Eastern Mediterranean Region

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Iran (Islamic Republic of)	UMIC	13.17	28.93	36.64	Increasing	178%
Lebanon	UMIC	42.08	73.52	111.34	Increasing	165%
Djibouti	LMIC (Gavi)	37.27	84.29	90.08	Increasing	142%
Jordan	LMIC	68.89	101.30	137.58	Increasing	100%
Sudan	LMIC (Gavi)	2.86	4.53	4.39	Increasing	53%
Afghanistan	LIC (Gavi)	2.35	2.05	3.01	Increasing	28%
Tunisia	LMIC	23.30	28.24	26.67	Increasing	14%
Pakistan	LMIC (Gavi)	9.71	5.41	6.85	Decreasing	-29%
Egypt	LMIC	25.32	24.90	16.35	Decreasing	-35%
Yemen	LMIC (Gavi)	5.24	4.43	0.76	Decreasing	-86%

[a] 2017 Constant US$

Table A2.4: Government expenditure[a] on routine immunization per live birth by country, European Region

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Georgia	LMIC (Gavi)	33.51	63.87	123.33	Increasing	268%
Uzbekistan	LMIC (Gavi)	9.62	6.56	26.37	Increasing	174%
Armenia	LMIC (Gavi)	18.17	95.73	46.71	Increasing	157%
Kazakhstan	UMIC	92.16	190.42	223.55	Increasing	143%
Republic of Moldova	LMIC (Gavi)	16.35	38.91	26.68	Increasing	63%
Kyrgyzstan	LMIC (Gavi)	6.87	8.27	8.24	Increasing	20%
Finland	HIC	450.23	393.02	494.80	Increasing	10%
Bulgaria	UMIC	379.95	290.19	405.98	Increasing	7%
Belarus	UMIC	72.18	47.26	70.71	Decreasing	-2%
Ireland	HIC	1,610.02	1,547.35	1,541.15	Decreasing	-4%
Andorra	HIC	821.57	729.61	720.61	Decreasing	-12%
Turkey	UMIC	205.59	172.24	179.04	Decreasing	-13%
Netherlands	HIC	692.24	615.42	597.12	Decreasing	-14%
Hungary	HIC	329.66	227.63	279.93	Decreasing	-15%

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Tajikistan	LMIC (Gavi)	6.13	4.90	5.18	Decreasing	-16%
Estonia	HIC	228.64	150.14	178.91	Decreasing	-22%
Iceland	HIC	349.50	290.50	256.16	Decreasing	-27%
Azerbaijan	UMIC (Gavi)	39.43	29.50	25.81	Decreasing	-35%
Denmark	HIC	1,059.21	436.09	334.04	Decreasing	-68%

[a] 2017 Constant US$

Table A2.5: Government expenditure[a] on routine immunization per live birth by country, South-East Asia Region

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Myanmar	LMIC (Gavi)	0.97	8.39	12.64	Increasing	1207%
Thailand	UMIC	32.17	74.95	108.85	Increasing	238%
Nepal	LIC (Gavi)	6.89	8.32	12.83	Increasing	86%
Democratic People's Republic of Korea	LIC (Gavi)	9.64	24.92	15.74	Increasing	63%
India	LMIC (Gavi)	4.24	3.98	6.61	Increasing	56%
Maldives	UMIC	22.02	30.83	29.48	Increasing	34%
Indonesia	LMIC (Gavi)	12.86	10.81	16.94	Increasing	32%
Bangladesh	LMIC (Gavi)	8.15	9.12	9.56	Increasing	17%
Timor-Leste	LMIC (Gavi)	13.42	16.22	10.56	Decreasing	-21%
Sri Lanka	LMIC (Gavi)	38.63	17.63	27.01	Decreasing	-30%
Bhutan	LMIC (Gavi)	16.03	6.49	4.48	Decreasing	-72%

[a] 2017 Constant US$

Table A2.6: Government expenditure[a] on routine immunization per live birth by country, Western Pacific Region

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Lao People's Democratic Republic	LMIC (Gavi)	1.95	35.83	27.20	Increasing	1293%
Republic of Korea	HIC	119.09	1,012.25	972.57	Increasing	717%
New Zealand	HIC	943.48	1,328.37	1,644.93	Increasing	74%
China	UMIC	19.01	20.71	31.03	Increasing	63%

Country	Income classification	Average 2010–11	Average 2014–15	Average 2016–17	Trend 2010–11 & 2014–15	Percentage change 2010–11 & 2016–17
Philippines	LMIC	23.99	26.43	33.44	Increasing	39%
Mongolia	LMIC (Gavi)	22.83	36.56	29.53	Increasing	29%
Viet Nam	LMIC (Gavi)	6.61	9.33	8.10	Increasing	22%
Vanuatu	LMIC	19.45	16.02	22.37	Increasing	15%
Australia	HIC	1,127.51	1,011.04	1,102.19	Decreasing	-2%
Cambodia	LMIC (Gavi)	8.53	6.69	7.94	Decreasing	-7%
Tonga	UMIC	20.38	18.05	18.25	Decreasing	-10%
Malaysia	UMIC	88.46	37.46	64.06	Decreasing	-28%
Papa New Guinea	LMIC (Gavi)	6.98	8.75	3.09	Decreasing	-56%
Solomon Islands	LMIC (Gavi)	63.80	15.84	20.95	Decreasing	-67%
Marshall Islands	UMIC	106.65	28.78	28.47	Decreasing	-73%

[a] 2017 Constant US$

Subchapter 4: Vaccine price & procurement report 2018

Indicator	Goal
1. Transparency: number of countries sharing price information by WHO region	Monitor country progress in sharing price data over time.
2. Annual average or unit vaccine prices as data permits, including: • price trends: evolution of annual average price over time; • volume & price: relationship of vaccine prices with volumes purchased, segmented by level of income; • price segmentation: relationship between income level and vaccine prices. 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.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 7.4.

Box 7.4: Descriptions of indicators, results, data sources and highlights

For additional information on vaccine price, see: www.who.int/immunization/MI4A.

A) Background

In response to global calls for greater vaccine price transparency and affordability (see last year's GVAP Secretariat report), WHO has continued to invest in its Vaccine Product Price Procurement project (V3P) blending this into an expanded initiative called Market Information for Access (MI4A). MI4A continues to collect information and study vaccine-pricing dynamics (as did V3P), but expands understanding to broader vaccine market dynamics, identifying affordability and shortage risks. This work complements that of many other immunization partners active in vaccine markets (such as UNICEF, the PAHO Revolving Fund, Gavi, the Bill & Melinda

Gates Foundation, CHAI Foundation, PATH) and broader WHO efforts to enhance access to essential medicines. The MI4A initiative publishes various global vaccine market reports, which can be found on its website (see Box 7.4). The section below only provides an update on GVAP pricing indicators, building on last year's report. For further information, MI4A reports should be consulted.

Note: Throughout this subchapter, countries will be grouped to reflect elements that have an important link to price: financing (i.e. whether or not they receive Gavi financial support for vaccine purchase or are eligible to procure vaccine through the PAHO Revolving Fund), income (to reflect their ability to pay) and procurement policy (i.e. whether or not they self-procure vaccines). Details on the categories can be found in last year's report. For the sake of brevity, the term "non-Gavi, non-PAHO countries" is used in this subchapter. This refers to middle-income countries that are neither eligible for Gavi support nor have access to the PAHO Revolving Fund (i.e. lie outside the Region of the Americas).

1) Indicator 1: Transparency: number of countries sharing price information by WHO region

In total, 144 countries reported price data in 2018 and are included in the following analyses. Thanks to active regional engagement with countries, 16 countries reported to V3P for the first time this year, contributing to increased reporting in the African Region and the Region of the Americas. Reporting from the Western Pacific, South-East Asia, Eastern Mediterranean and European Regions decreased slightly from 2017 to 2018; the reasons are being investigated, but are likely linked to simple delays in reporting. Overall, reporting rates have remained stable from 2017 to 2018, maintaining a substantial increase over the launch years (2014 for V3P: only 25 countries and 2016 for MI4A: 51 countries).

Across all years, the V3P database captures price data for 84% of the world's countries and 95% of the world birth cohort. Importantly, high (89%) and increasing (up from 87% last year) reporting coverage has been achieved among middle-income countries neither supported by Gavi nor eligible to access the PAHO Revolving Fund, which face the greatest information gaps and are a main target of MI4A. Important progress was made in high-income countries, where the share of country reporting increased substantially from last year (from 47% in 2016 to 59% in 2017, with price data received for 29 of 49 total countries).

2) Indicator 2a: Price trends – evolution of annual average price over time

Following the methodology[8] used in previous reports, the change in prices over time for countries, as well as PAHO and UNICEF, was analysed and compared to the annual average of the global inflation rate over the same period of time (Table 7.3).

Table 7.3: Evolution of average vaccine price over time, by procurement mechanism and vaccine type

	Self-procurement		Pooled-procurement	
	Non-Gavi, non-PAHO countries *(2013/14–2017) Data source: JRFs*		PAHO countries *(2013–2017) Data source:* PAHO	Gavi countries *(2013–2017) Data source:* UNICEF
	HICs	MICs		
Increase in average price	Three vaccine types (18%): BCG, PPSV, Seasonal Influenza	Four vaccine types (44%): DT, HepB, Td, TT	Six vaccine types (26%): DT, DTaP, DTaP-Hib-IPV, MMR, MR, Varicella	Two vaccine types (13%): DT, TT
Stable (+/- 15%) average price	Five vaccine types (29%): DTaP-Hib-IPV, Hib, IPV, Td, Tdap	Three vaccine types (33%): BCG, MMR, Rota	Eleven vaccine types (48%): BCG, DTwP, HepA, HepA (adult), Hib, IPV, PPSV, Rota, Seasonal Influneza, Td, YF	Nine vaccine types (56%): BCG, bOPV, DTwP, HepB, HPV, MMR, MR, Td, YF

[8] Country data were analysed for the period 2013–2017, while data from UNICEF and PAHO were analysed for the period 2010–2018 (based on annual average of the global inflation rate, consumer prices (annual %), as available from the World Bank World Development Indicators: http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators#. The average global annual inflation rate *(Ir)* was used as the threshold to define the three ranges presented in Table 7.3: 2.19% per year for the period 2013–2017 and 3.02% per year for the period 2010–2018. Increase or decrease in average vaccine price *(P)* was then compared to the inflation rate, to determine how both nominal and real prices have evolved over time.

	Self-procurement		Pooled-procurement	
Decrease in average price	Nine vaccine types (53%): DTaP-HepB-Hib-IPV, DTaP-IPV, HepA, HepB, HPV, MenC, MMR, PCV, Varicella	Two vaccine types (22%): PCV, Seasonal Influenza	Six vaccine types (26%): DTwP-HepB-Hib, DTwP-Hib, Hep B (adult), HPV, PCV, Rabies	Five vaccine types (31%): DTwP-HepB-Hib, IPV, Measles, PCV, Rota
Total	17 vaccine types (100%)	9 vaccine types (100%)	23 vaccine types (100%)	16 vaccine types (100%)

Notes:

1. In the first column with country data, the analysis only includes high-income countries and non-Gavi, non-PAHO middle-income countries, as defined at the beginning of the subchapter, with vaccine price data available for 2013 (or 2014) and 2017. Prices are public-sector prices. Note that the database in 2013 and 2014 contained mainly data shared by countries of the European Region (they represented 92% and 70% of the participating countries in 2014 and 2015, respectively). The analysis includes vaccine types for which countries had registered at least three records in both 2013 (or2014) and 2017 (representing 17 vaccine types for high-income countries and 9 for middle-income countries).
2. The analyses presented in the two right-hand columns of the table are based on 15 and 14 vaccine types purchased by PAHO and UNICEF, respectively.

YF, yellow fever; JE, Japanese encephalitis; TT, tetanus toxoid; PPSV, pneumococcal polysaccharide vaccine; TBE, tick-borne encephalitis; Td, tetanus diphtheria.

With more data and improved methodology, conclusions have evolved over previous reports. The trend in price over time varies by vaccine for each country group and procurement mechanism. A comparison of price over time shows stable or decreasing price for the majority vaccines procured by high-income countries and stable or increasing prices for non-Gavi, non-PAHO middle-income countries. Vaccine prices for PAHO and UNICEF have largely remained stable or decreased.

3) Indicator 2b: Volume & price: relationship of vaccine prices to volumes purchased, segmented by level of income

To better understand the relationship between vaccine price and volume purchased, an analysis of the linear correlation between volume and price was conducted on 145 vaccine types differentiated by presentation sizes (e.g. 10- and 20-dose BCG). These were analysed separately by country category (Gavi-supported countries, non- Gavi, non-PAHO middle-income countries and high-income countries). Of these 145 vaccines, only six showed a statistically significant and positive correlation between volume purchased and price; hepatitis B 10-dose showed a negative correlation.[9] The correlations seem to be mainly driven by outliers. Further investigative analysis will be conducted to determine if this is the case.

4) Indicator 2c: Price segmentation: relationship between income level and vaccine prices. Minimum–maximum price range by country level of income

An analysis of the Pearson's correlation between gross national income (GNI) per capita[10] and price was conducted on 53 vaccine types in 54 non-Gavi, non-PAHO middle-income countries and high-income countries for which a GNI per capita was available from the World Bank. The correlation analysis was only conducted when at least 10 observations were available and the result considered statistically significant when returning a Pearson's correlation P-Value ≤ 0.05.

For 26 vaccine types there were too few records to perform the analysis. For 6 of the remaining 27 vaccine types reviewed, no statistically significant correlation was found: bOPV, DTaP–Hib–IPV, DTwP–HepB–Hib, MR, rabies, TdaP. Last year's analysis showed 12 vaccine types with no correlation. The remaining 21 vaccine types displayed a positive correlation between GNI per capita and price. The number of vaccines with strongly positive correlation increased to 10 (from 6 last year). Results are presented in Table 7.4. Note that the pool of vaccines analysed varies by year.

[9] The correlation analysis was only conducted when at least 10 observations (N ≥ 10) were available and the result considered statistically significant when returning a P-value ≤ 0.05.

[10] GNI per capita, Atlas method (current US$), as available from the World Bank World Development Indicators: http://data.worldbank.org/indicator/NY.GNP.PCAP.CD.

Table 7.4: Correlation between GNI per capita and vaccine price in non-Gavi, non-PAHO middle-income countries and non-PAHO high-income countries, 2017

Indicator	Vaccine type Vaccine (N=number of records in the analysis)		
Strongly positive correlation r ≥ 0.6 → 10 vaccine types	Measles (N=12)	MenACYW-135 (N=10)	MMR (N=38)
	Seasonal influenza (N=64)	PCV (N=38)	PPSV (N=12)
	Rotavirus (N=16)	TBE (N=14)	Td (N=32)
	Varicella (N=10)		
Moderately positive correlation 0.3 ≤ r ≤ 0.6 → 11 vaccine types	BCG (N=36)	DT (N=16)	DTaP–HepB–Hib–IPV (N=24)
	DTaP–IPV (N=19)	DTwP (N=14)	HepA (N=34)
	HepB (N=76)	Hib (N=23)	HPV (N=28)
	IPV (N=32)	TT (N=18)	

TBE, tick-borne encephalitis; Td, tetanus diphtheria

Table 7.5 illustrates the range in vaccine prices paid by each income group by averaging the ratio of the minimum and maximum price for each vaccine type within income groups. Middle-income countries that were not part of a pooled-procurement mechanism displayed the highest price variance, with an average multiplier factor of 35.9 between the lowest and highest vaccine price. By comparison, high-income countries paid, on average, only 12.2 times more for the most expensive vaccine than the lowest-priced vaccine. This important result shows again opportunities for enhanced pricing policies in middle-income countries to expand access to vaccines.

Table 7.5: Average multiplier factor between the lowest and highest price of a vaccine type, by country category, 2017

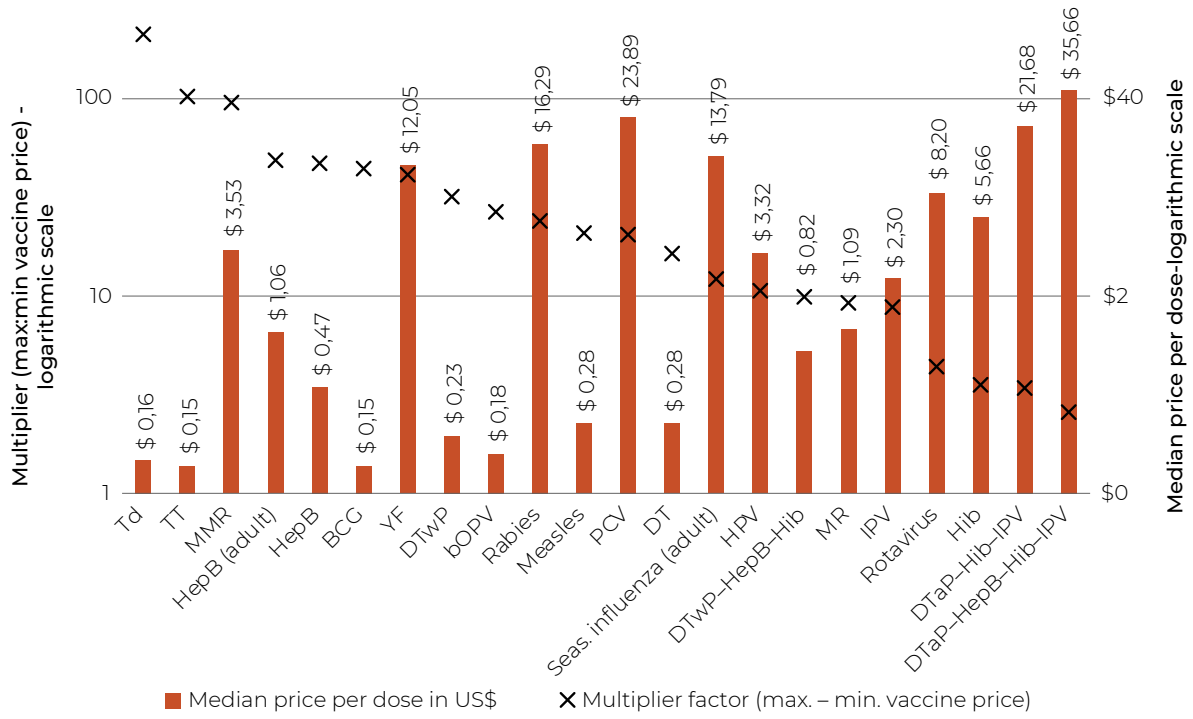
Category	Average multiplier factor between minimum and maximum price
Gavi-eligible	9.0
PAHO Revolving Fund-eligible	4.7
Non-Gavi, non-PAHO middle-income countries	35.9
High-income countries	12.2
Across all categories	15.2

Notes:
- Values with fewer than four data points per income group per vaccine type were excluded.
- Includes 37 vaccine types.

Fig. 7.5 shows the multiplying factor and median price per dose by vaccine type for non-Gavi, non-PAHO middle-income countries. Tetanus diphtheria, TT and MMR contributed most significantly to the high price variance in non-Gavi, non-PAHO middle-income countries, with multiplying factors of 210, 101 and 96, respectively. However, these vaccine types had relatively low median prices (US$ 3.53 for MMR, US$ 0.16 for tetanus diphtheria, and US$ 0.15 for TT).

In comparison, non-Gavi non-PAHO middle-income countries reported a median price per dose of more than US$ 10 for PCV, rabies vaccine, HPV and yellow fever vaccine, and these vaccines also displayed considerable price variance, with multiplying factors ranging from 12 to 40; non-Gavi, non-PAHO middle-income countries pay high and wide-ranging prices for PCV, rabies vaccine, HPV and yellow fever vaccine.

Fig. 7.5: Multiplier factor between the lowest and highest price, by vaccine type, non-Gavi, non-PAHO middle-income countries



Notes:
- Multiplier displayed by an orange X and median price displayed in blue bars.
- Values with fewer than four data points per income group per vaccine type were excluded.
- Includes 22 vaccine types.

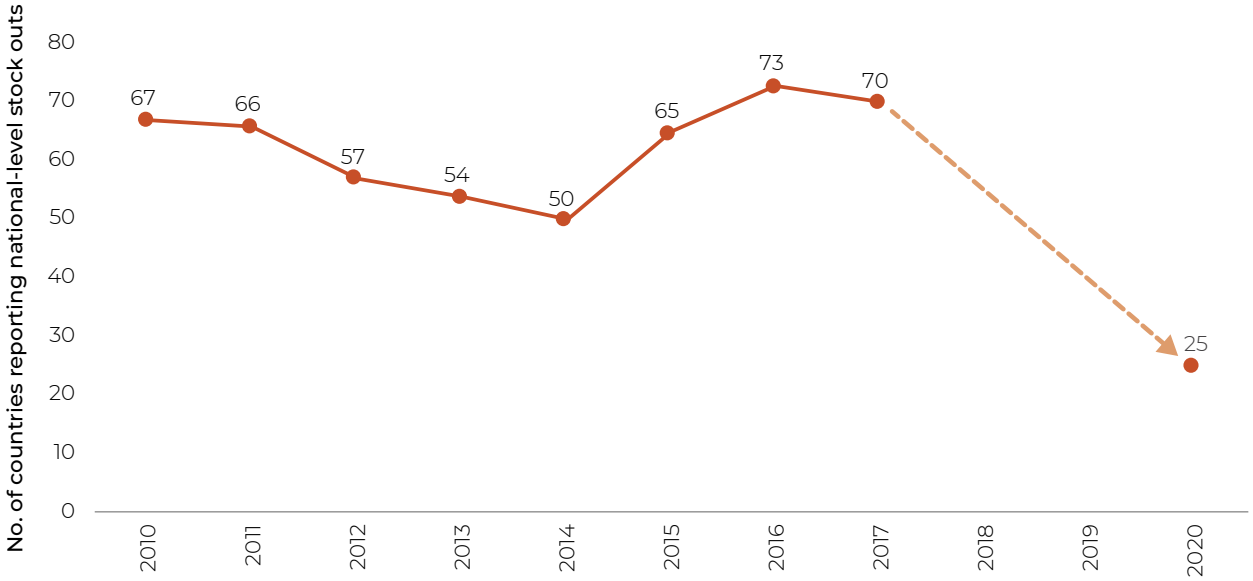
Subchapter 5: Stock outs: Availability of vaccines for routine immunization at national (Indicator SO5.2) and subnational levels including country performance towards supply chain fundaments

TARGET	Two thirds reduction in countries reporting national-level stock outs by 2020 (from 2010 level).
DEFINITION OF INDICATOR	Number of countries reporting a national-level stock out of at least one vaccine for at least one month.
DATA SOURCES	WHO-UNICEF Joint Reporting Form (JRF).

A) Update on National-level stock outs GVAP indicator, 2017

In 2017 a total of 70 countries (36% of Member States) reported a national-level stock out for at least one vaccine. Compared to 2016, this represents an improvement to the situation where 73 countries (or 38%) had reported national-level stock outs. Nevertheless, the world is still far from the global target of only 25 countries with stock outs by 2020 (Fig. 7.6).

Fig. 7.6: Trend towards the GVAP 2020 target



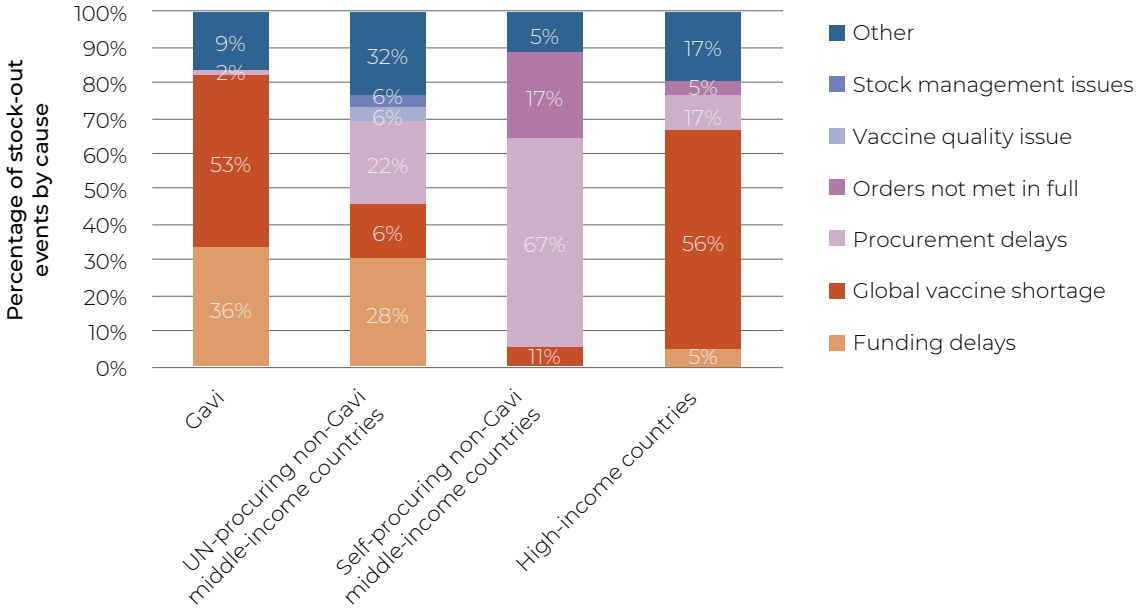
In 2017 a total of 111 national stock-out events were reported in the 70 reporting countries. Countries averaged 1.6 stock-out events in 2017 – an average that has decreased since 2016. The average duration of a stock-out event was estimated at 3.9 months (the median duration is 2.8 months) – this represents an increase in average and median duration compared to 2016 (the average duration was 1.7 months and median duration was 1.3 months in 2016). While multiple stock outs within a year are not uncommon, the majority of countries reporting stock outs (50, or 71%) reported only one stock-out event at national level in 2017.

The reporting of national-level stock outs in 2017 was greatest in the African Region (25 countries affected, or 36%). The European Region and the Region of the Americas each represented 20%. Although national-level stock outs were reported by countries in all income groups, the concentration is greatest in Gavi-eligible countries (43% of stock-out events) and in non-Gavi middle-income countries (41%).

1) Causes of national-level stock outs

An analysis of causes of stock outs was performed (please refer to the 2014 GVAP Secretariat report for methodology). The results of this analysis indicate that in 2017, overall, product unavailability on the global market accounted for 37% of the causes of national-level stock outs as reported by countries. An equal proportion of stock outs (41%) were due to funding or procurement delays. Nevertheless, different patterns were observed in different groups, similarly to last year. Of note, the importance of procurement delays increased in self-procuring middle-income countries.

Fig. 7.7: Causes of national stock out by adjusted income group[a], 2017



[a] Data on stock-out causes were available respectively for 33 Gavi-supported countries, 14 UN-procuring non-Gavi middle-income countries, 8 self-procuring non-Gavi middle-income countries and 15 high-income countries. One or more causes may have been declared by each of the countries.

2) Subnational-level stock outs

A total of 69 countries reported experiencing stock outs at subnational level. Of these 69 countries, 61 (88%) indicated that the district-level and national-level stock outs were linked – that the national stock out resulted in vaccines being unavailable at district level. For the remaining 12% of countries that reported a district-level stock out, the stock outs were caused by other factors – for example, a breakdown of the distribution system, orders not being met in full or poor stock management at lower levels of the supply chain. District-level stock outs led to an interruption of vaccination services in 54 of the 69 countries.[11]

Subchapter 6: 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)

TARGET	None specified.
DEFINITION OF INDICATOR	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.
DATA SOURCES	Reports from national regulatory authorities.

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 7.5.

Box 7.5: Descriptions of indicators, results, data sources and highlights

The CTC Strategic Roadmap, various guidelines and additional literature on CTC are available online: http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/

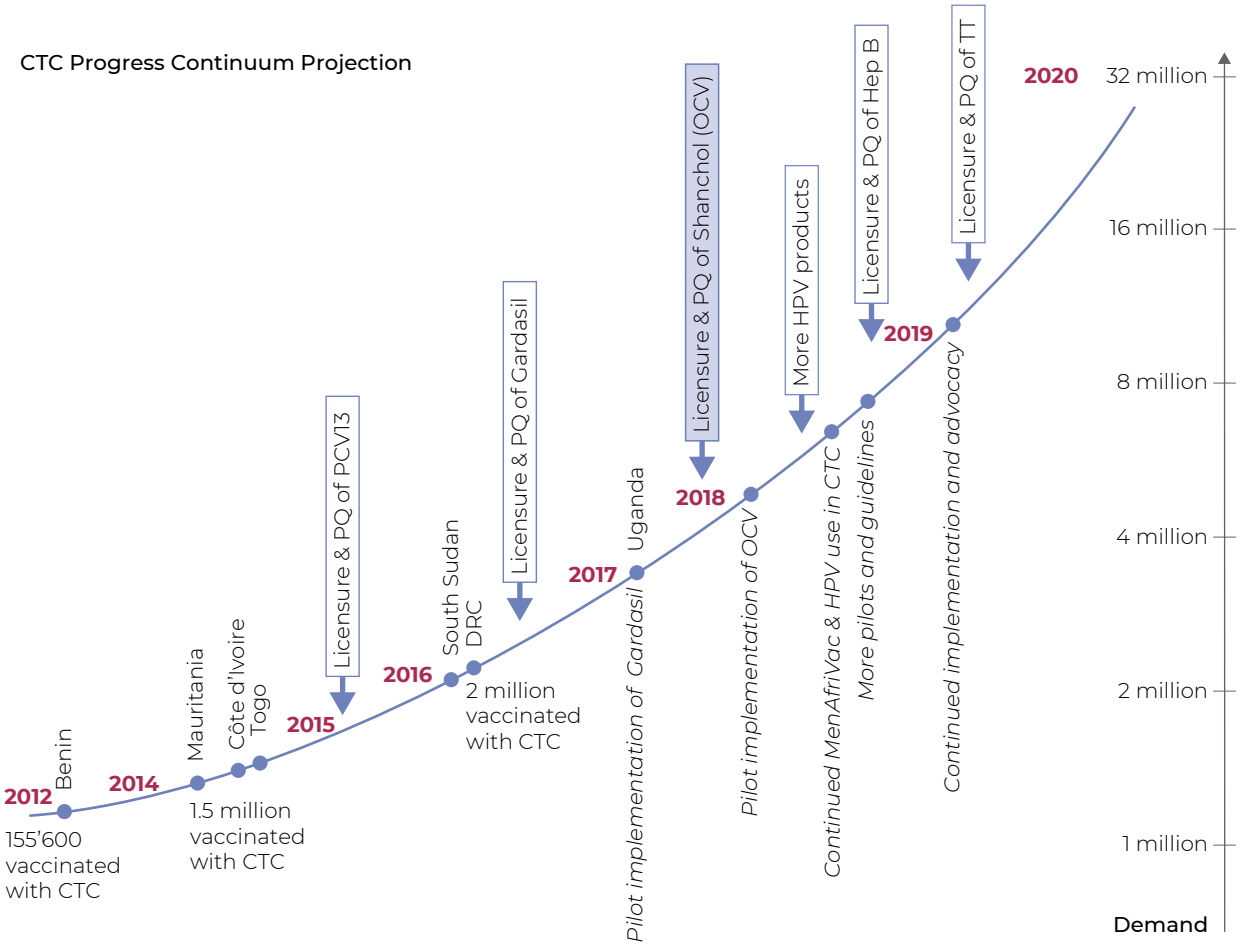
A) Status on controlled-temperature chain GVAP Indicator, 2017

Significant milestones were reached during 2017 for each of the four priority vaccines which the controlled temperature chain (CTC) agenda focuses on, representing important momentum in the advancement of this innovation, as well as key opportunities to document and learn from expanding experience (Fig. 7.8). With respect to the specific indicator SO6.4, there has been a noteworthy increase in the 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, thanks to the long-awaited prequalification in January 2018 of Shantha's Shanchol oral cholera vaccine (OCV) for use in a CTC. As of 30 April 2018, three vaccines (Gardasil, MenAfriVac and Shanchol) are licensed and WHO prequalified under CTC conditions, with an additional hepatitis B product under review. This achievement was the outcome of an ongoing effort to facilitate dialogue across immunization stakeholders, and ensure the right guidance and inputs are received as early on in the product development process as possible.

Of equal note has been the programmatic progress in the form of planning efforts for a pilot implementation of OCV with CTC in collaboration with the Global Task Force for Cholera Control (GTFCC) and Médecins Sans Frontières (MSF). This past year also saw the successful CTC pilot delivery of a human papillomavirus (HPV) vaccine in Uganda, which provided a valuable opportunity to document and assess the implementation methodology along with lessons learned. The latter were then incorporated into a draft set of guidelines for HPV-CTC decision-making and implementation. As the successes at county-level multiply, the message to industry has become clearer: there is a growing interest and demand to use vaccines out of the cold chain, as part of a broader call for more technological innovations that help improve immunization coverage and equity. Vaccine manufacturers are responding positively, as indicated by the commitment of multiple manufacturers to seeking licensure and prequalification of CTC-compatible vaccines. This has also been the recent case for several manufacturers of the two other priority CTC vaccines: hepatitis B birth dose (HepB-BD) vaccine and tetanus toxoid-containing vaccines, which puts the CTC agenda well on track to meeting the objectives set out in the CTC Strategic Roadmap for Priority Vaccines, finalized in September 2017 in alignment with GVAP time frames.

[11] While the subnational stock out indicators provide valuable insights, the magnitude of the problem is difficult to gauge without an understanding of how many districts were affected.

Fig. 7.8: Projection of the CTC progress continuum



B) Update on controlled-temperature chain-related activities 2017-2018

The CTC agenda is sustained by three central principles: adhering to a clear and consistent strategy; being driven by country needs; and ensuring lessons are learned and appropriately applied. Under the stewardship of the CTC working group, which operates as a subgroup to the Immunization Practices Advisory Committee (IPAC), WHO developed the *CTC Strategic Roadmap for Priority Vaccines*. This document defines the necessary activities required to meet objectives for CTC within the current GVAP timelines. These consist mainly of:

- improving stakeholder involvement, advocacy and alignment on CTC work streams;
- increasing the base of evidence in support of CTC and characterizing the value proposition of CTC with respect to improving immunization coverage and equity;
- developing operational guidance and communication tools in support of CTC practices;
- supporting efforts towards the licensure and prequalification of appropriate vaccines for CTC.

As the CTC objectives have become more concrete and focused, so have efforts to generate more guidance and evidence on the delivery of vaccines through a CTC, while increasing advocacy efforts both with industry and countries, and better engaging partner institutions to boost momentum around CTC use. The most fruitful and notable recent outcome of these efforts has been the CTC prequalification of OCV, Shanchol, from the India-based Shantha Biotechnics, in January 2018. However, just as was the case for this OCV product, continued CTC licensure and uptake efforts must be steered by the right drivers, namely the need to overcome recognized and documented barriers to high immunization coverage and equity.

Understanding country needs and demand should always be the starting point of any effort to pursue innovation. This is because meeting those needs should propel both the development of that innovation, as well as its ultimate uptake. Keeping this overarching programme-based objective in mind is one of the challenges of the CTC agenda, a challenge confronted by many technological innovations for immunization. The CTC-Working Group and its WHO-based secretariat has had to resist the temptation to seek immediate successes in the form of easing the upstream parameters that can yield an individual vaccine's successful licensure, which in turn would translate into a higher rate of success against this particular GVAP indicator. However, the appeal of this kind of upstream success must be balanced against the larger prospects of success and potential impact of CTC as a general practise at country level. As IPAC recommended in 2013, it is important that CTC be recognized and protected as a brand, with a view to ensuring its long-term success and impact. The CTC branding, as it pertains to a well-defined set of vaccine management practices, is particularly

of value from the perspective of the health worker whose burden this innovation is meant to alleviate. Should vaccines be licensed for CTC that cannot easily be delivered in a manner that truly produces public health advantages or should the practice be tailored excessively for each individual vaccine, then the benefits of the CTC brand are eroded through increased confusion and risk of error and failure. In the programme context, the long-term success of CTC therefore depends on how effectively the potential pitfalls and failures are minimized; failing to do so would tarnish CTC as a practise and compromise its continued uptake and ability to bring benefits to an immunization programme. Success will be achieved in part by ensuring health worker needs are not forgotten during the product development process, but also by carefully documenting lessons learned and applying them to subsequent efforts.

As with any innovation, the failures and challenges experienced are as important as the successes, since both allow an understanding of the complex web of factors that conspire in order for that innovation to actually be adopted and have impact. Recognizing, documenting, and analysing the barriers to success have been an invaluable part of the CTC agenda and are expected to play a critical role in improving the rate of successful licensures and implementation linked to CTC. In the case of Shanchol OCV, key lessons concerning the regulatory pathway have been drawn and rendered beneficial to other vaccines. This has occurred in the pilot CTC delivery of Meningitis A and HPV vaccines as well, consequently reflected in adapted implementation guidelines for each of the respective antigens. As these efforts start to bear their fruits, the CTC agenda has proven that bringing an innovation to realization is a carefully-paced process, relying on a shared vision and strategy, a well-defined need and demand at the country programme level and extensive experience on which to build and fine-tune the strategy.

8. VACCINE SAFETY

TARGET	No target set.
DEFINITION OF INDICATOR	Number of countries reporting at least 10 AEFI cases for per 100 000 surviving infants.
DATA SOURCES	WHO-UNICEF Joint Reporting Forms (JRFs).
DATA AVAILABILITY AND QUALITY	See the 2016 GVAP Secretariat report.

For additional information please refer to the documents or websites listed in Box 8.1.

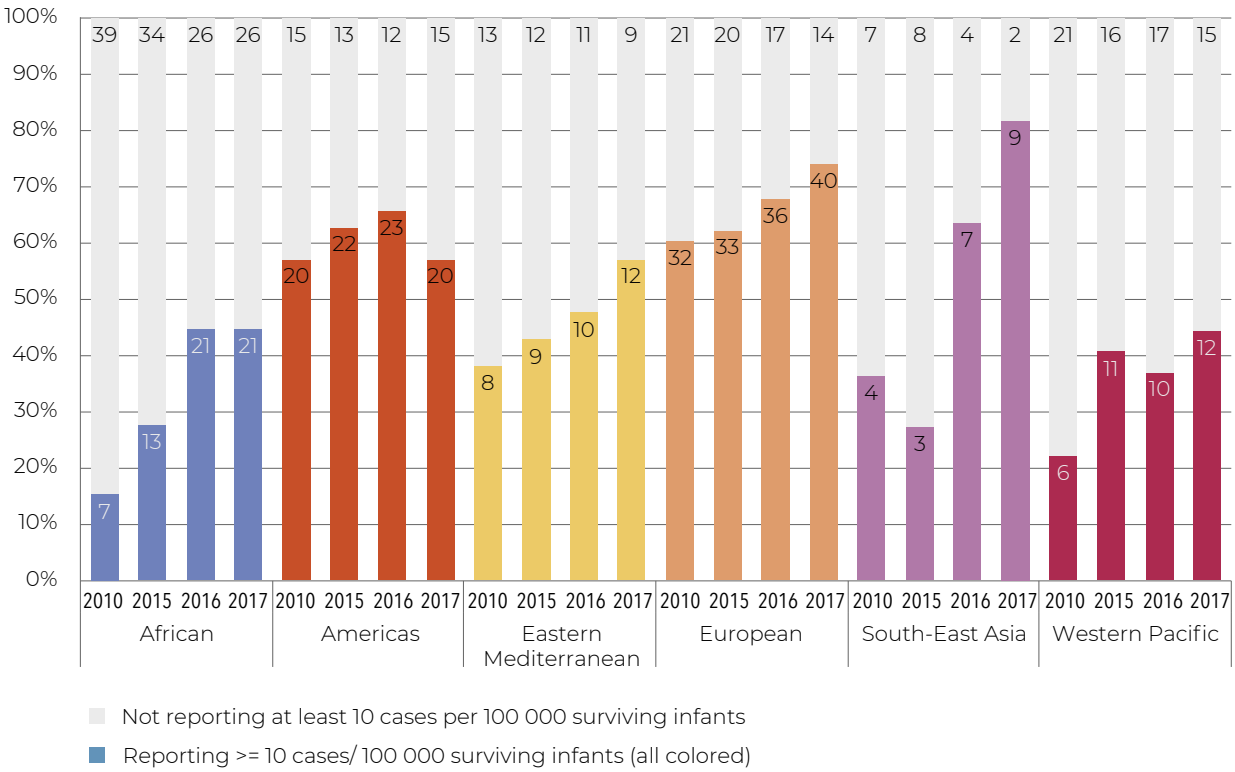
Box 8.1: Descriptions of indicators, results, data sources and highlights

For more information, see: http://www.who.int/vaccine_safety/en/ and the Global Vaccine Safety Initiative – 2017 annual meeting report.

A) Status of the vaccine safety GVAP indicator, 2017

In 2017, a total of 114 countries met the vaccine safety indicator. As compared to 2010, all regions have experienced an increase in the number of Member States reporting at least 10 adverse events following immunization (AEFI) per 100 000 surviving infants (Fig. 8.1 and Fig. 8.2). This increase has been quite steady and consistent in most regions over the past three reporting years. The improvement in 2017 is particularly significant in the South-East Asia Region where 9 of 11 countries achieved the indicator compared to 4 of 11 in 2010. The improvement in AEFI reporting from the Eastern Mediterranean and the European Regions has been steady and sustained: in the former it increased from 8 countries in 2010 to 12 of 21 in 2017, and in the latter from 32 to 40 countries of 53 in the same time period. In 2017, the Western Pacific Region recorded the highest number of its countries (12 of 27) that report over 10 AEFI cases per 100 000 surviving infants since 2010. After improved reporting in 2016 compared to previous years, the performance of the African Region has remained unchanged (21 countries) in the past two years. The Region of the Americas is the only exception to this trend; it showed a decrease from 23 to 20 countries between 2016 and 2017. This is due to the fact that several countries, with well-established vaccine safety surveillance systems, had not communicated their data for 2017 on time to include in the present analysis.

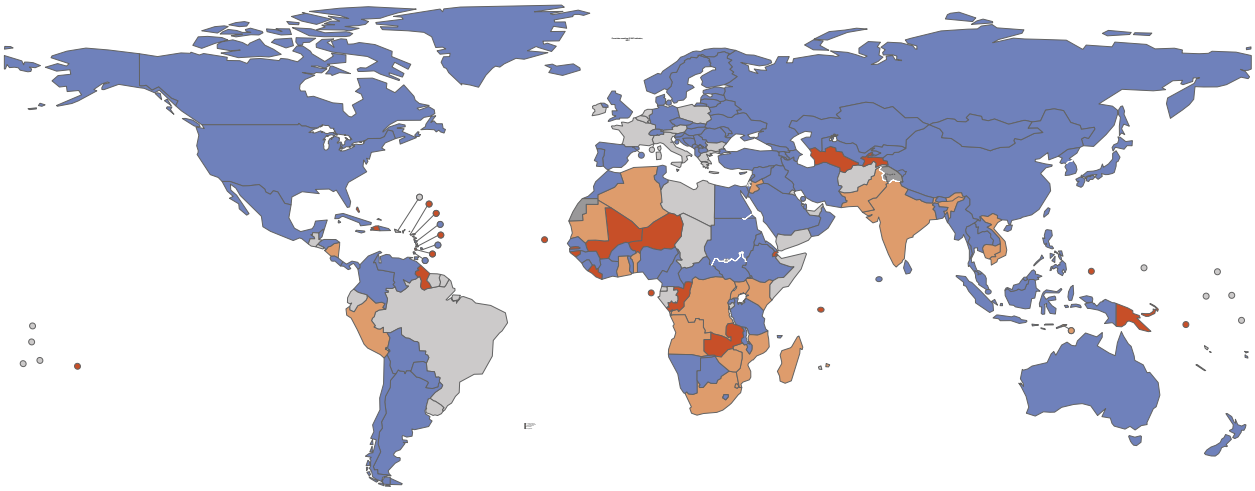
Fig. 8.1: Percentage and number of Member States reporting[a] at least 10 per 100 000 AEFI cases by WHO region 2010, 2015–2017



[a] Based on WHO-UNICEF JRF reports received.

The sustained increase in the number of countries achieving the GVAP indicator over the past three years is a reflection of the continued capacity building efforts undertaken in 2015–2017, particularly in Gavi-eligible countries, in all World Health Organization (WHO) regions. As Fig. 8.2 shows, upper-middle-income- and high-income countries remain committed to reporting AEFI.

Fig. 8.2: Number of AEFI reported per 100 000 surviving infants by Member States in 2017



≥ 10 AEFI/100 000 surviving infants (114 Member States or 59%)
1-9 AEFI/100 000 surviving infants (20 Member States or 10%)
0 AEFI/100 000 surviving infants (24 Member States or 12%)
Not available (36 Member States or 19%)
Not applicable

Source: WHO/UNICEF coverage estimates, 2017 revision.

B) Highlights of the activities in the field of vaccine safety, 2017–2018

The multipronged approach to strengthen vaccine safety as enshrined in the eight strategic objectives of the Global Vaccine Safety Blueprint has been a key driver for improvement of AEFI reporting. During the 2017 Global Vaccine Safety Initiative meeting in Kuala Lumpur, Malaysia, Member States and partner agencies showcased the innovations and strategic approaches that were instrumental for the success of vaccine pharmacovigilance in their respective countries[1]. During the meeting participants shared their experiences in the areas of building vaccine confidence, addressing safety crises during vaccination campaigns, addressing anti-vaccine lobbies, improving AEFI investigations, developing innovative pharmacovigilance systems and the key role of vaccine safety communications.

Use of existing in-country health information systems to strengthen vaccine safety monitoring has led to an increase in the number of countries reporting. One innovative example is the use of free, open source software for data management (DHIS2) for the development of web-based reporting of individual AEFI cases. This platform also allowed for developing a training module on AEFI data management called "Harmonia". This module provides guidance for countries to develop their own vaccine adverse events information monitoring systems (VAEIMS) tailor-made to local requirements (see details below).

Another key development during 2017 was the strengthening of linkages between the Global Advisory Committee on Vaccine Safety (GACVS) and the Global Vaccine Safety Initiative. Stronger links between the two major arms of the WHO vaccine safety work should help further disseminate GACVS's independent, authoritative, scientific advice about vaccine safety. Likewise, the capacity-building work from the Global Vaccine Safety Initiative and its impact on the quality assurance of national immunization programmes is further validated by GACVS. The Global Vaccine Safety team at WHO continues to develop ICT tools to build capacity for training, signal detection, AEFI investigation, vaccine safety crises communication and a AEFI causality assessment that are available to all Member States. These innovative approaches aim to improve the quality of vaccine safety data collected and allow for timely and relevant interventions to maintain confidence in immunization programmes.

1) Vaccine Adverse Events Information Management System & Harmonia – history, geography and architecture

Accurate and complete vaccine safety data are essential for decisions related to use of vaccines. In 2009, the global network for was established in 12[2] countries. Based on the feedback obtained from the postmarketing surveillance of vaccines network, the GACVS in June 2012 suggested a set of 25 core variables for AEFI surveillance to be used by both national regulatory authorities and immunization programme staff.

The incorporation of the core variables into the WHO global AEFI guidelines in 2013 was an impetus for countries to standardize AEFI reporting forms that enable:

- easy collection of a minimal set of comparable information;
- pooling of passive AEFI surveillance data;
- creation of electronic tools for data collection, collation transmission and analysis;
- standardized information collection from all levels of hierarchy and from all countries;
- sharing of information.

Countries expressed the need for a vaccine-specific data management tool in addition to the identification of the core variables. VAEIMS was conceptualized and developed to address this gap. The objective of VAEIMS is to provide specifications that facilitate the efficient collection, collation, transmission, analysis and feedback of vaccine safety-related data (AEFI data) from the periphery of the health care system to the district and state (province) level, and ultimately to establish national databases. This can then be used for processing and conversion of data to information for action. VAEIMS also enables countries to monitor performance and measure surveillance indicators as outlined in the Global Vaccine Action Plan.

With support from WHO, several countries have piloted VAEIMS platforms or are in the process of developing them. One important lesson learned through the pilot programmes is that country-specific health information management platforms require software solutions to be adapted to their existing systems. Several countries indicated the need for web-based approaches that include both online and offline platforms, and the use of parallel technologies such as mobile devices (i.e. smartphones and tablets).

The DHIS 2 is the preferred health management information system in over 60 countries, particularly in lower-middle-income countries across four continents. Since June 2017, several countries are now piloting VAEIMS on a DHIS2 platform using the WHO standard AEFI reporting form. The use of DHIS2 enables data to be entered on any type of device, including desktops, laptops, tablets, smartphones and feature phones. It is being used as a flexible, web-based open-source information system with excellent visualization features including GIS, charts and pivot tables. The key feature is availability of an attractive user-interface that is identical and adaptable to the reporting form of any country. The end user has only to populate the national AEFI reporting form to instantaneously generate modules with epidemiology graphs, tables and line lists. In addition, the "anytime, anywhere" access to reported events and automations like drop-down menus and filters minimizes errors, provides reminders and offers real-time data to data-entry focal persons as well as decision-makers like supervisors and programme managers.

[1] See Global Vaccine Safety Initiative – 2017 annual meeting report.
[2] Albania, Brazil, China, India, Islamic Republic of Iran, Kazakhstan, Mexico, Senegal, Sri Lanka, Tunisia, Uganda and Viet Nam

WHO offers technical support to countries seeking to develop their own VAEIMS adapted to existing data systems and with local maintenance capability. Bridging AEFI data to the global database maintained by the programme for international drug monitoring is another feature for which technical support can be provided. Currently experience with VAEIMS platforms is available from Sri Lanka, the Islamic Republic of Iran, two Indian states, Malawi, Mongolia and Bangladesh.

WHO used the opportunity of VAEIMS safety databases to develop an AEFI data management training module called the Harmonia AEFI data management training platform. This comprehensive training package uses WHO's 25 core variables and standard AEFI reporting form. It incorporates a complete one-day training curriculum with an agenda, presentations and group work. Harmonia includes 180 "simulated" cases and a database for health workers to train and practice. These virtual cases enable end users to better understand field realities such as vaccine safety crises, their link to AEFI data and the challenges in addressing safety communications in such situations.

In addition to Member States, the VAEIMS concept, architecture and implementation is supported by the US Food and Drug Administration, the US Centers for Disease Control and Prevention, Gavi, the Vaccine Alliance and the Bill & Melinda Gates Foundation.

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9. RESEARCH AND DEVELOPMENT

Note: as this chapter discusses the latest advances in research and development (R&D), trademarked products are by necessity discussed. This inclusion does not imply that WHO recommends or otherwise endorses such products over any other (generic) products of equal efficacy, or products that may be derived from them.

STRATEGIC OBJECTIVE 6: COUNTRY, REGIONAL AND GLOBAL RESEARCH AND DEVELOPMENT INNOVATIONS MAXIMIZE THE BENEFITS OF IMMUNIZATION

Progress towards development of tuberculosis, malaria and HIV vaccines (Indicator SO6.1)

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 9.1.

Box 9.1: Descriptions of indicators, results, data sources and highlights

For information on the background of tuberculosis, HIV and malaria vaccines please refer to the 2016 GVAP report.

Progress towards development of tuberculosis vaccines

1) Overview of current efforts

Bacille Calmette–Guérin (BCG) is a live, attenuated vaccine that is the most widely administered neonatal vaccine worldwide. BCG has been shown to be moderately effective in preventing death and serious extrapulmonary tuberculosis (TB) in infants and young children, such as TB meningitis and miliary TB. For BCG delivered after birth, however, protection does not last into adolescence and adulthood to prevent transmissible, pulmonary TB.

Research to date suggest that a robust cellular immune response is required for protection against *Mycobacterium tuberculosis* (*Mtb*) infection and disease, and hence current clinical TB vaccine candidates are predominantly 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. The role of antibody-mediated control of *Mtb* is an area of increasing interest, however, and may influence future TB vaccine design.

At least 16 of these candidates have advanced into clinical studies in the past 10 years, including 13 current candidates. These clinical candidates encompass a variety of platforms, such as: mycobacterial whole cells or whole-cell extracts; viral-vectored candidates; and fusion protein subunits with TH1-inducing adjuvants (see Table 9.1 for additional information). DNA vaccines are still in preclinical development.

Due to the widespread administration of BCG 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. In parallel, however, recombinant BCG and MTBVAC vaccines are being studied as replacements for BCG, both to improve the vaccine safety profile in HIV-exposed

infants and to induce a more efficacious and/or more durable immune response. 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. Proof-of-concept trials that use clinical end-points are by necessity large and expensive.

An initial Phase IIb proof-of-concept efficacy trial that randomized 2797 BCG-vaccinated infants to receive either control or MVA85A did not show better efficacy than BCG alone against TB disease or infection. A Phase IIb trial in 3573 HIV-uninfected adults with latent *Mtb* infection in Africa seeks to determine the ability of the GlaxoSmithKline-Aeras M72 + AS01E to prevent TB disease; the results of this trial will soon be available.

In addition to these large-scale, proof-of-concept trials, smaller innovative trial designs are being explored to evaluate the biologic activity of vaccine candidates in special populations. The first of these tested whether H4:IC31 or BCG re-vaccination can prevent sustained infection, as opposed to disease, by *Mtb*. This study concept required only 330 subjects per arm rather than the two thousand or more that would be needed in classic, proof-of-concept trials. Moreover, the trial demonstrated that while initial infection with *Mtb* could not be prevented, BCG re-vaccination was able to prevent sustained infection as measured by reversion to a negative QFT-GIT test, illustrating the feasibility of this trial approach. A second trial in 400 subjects was recently completed and used an innovative design based on prevention of recurrence (POR). The goal of this trial was to investigate the ability of the ID93 vaccine to prevent the 4–6% relapse and/or reinfection rate typically observed following treatment of active TB; the results of this trial will soon be available.

2) Opportunities and challenges

Despite recent advances in the field, factors slowing progress include the lack of correlates of protection that can guide vaccine design or animal experiments, or that can be used as a credible end-point in early human studies; and limited knowledge about the impact prior sensitization to mycobacteria (immune priming) has on vaccine efficacy.

To identify the "best" *Mtb* antigens or the most promising vaccine constructs, and allow better differentiation among vaccine candidates, mouse, guinea pig and non-human primate models are being refined to better approximate both natural infection by *Mtb* as well as human disease due to *Mtb*. Using low-dose challenges, sophisticated imaging techniques and novel vaccine candidates, the non-human primate model is emerging as a potentially useful tool to better understand potential correlates of vaccine-induced protection and select vaccine candidates that could be validated in humans. Models of natural infection, such as human-to-guinea pig as well as macaque-to-macaque transmission, are also being investigated. Furthermore, the use of novel mouse models including the Collaborative Cross[1] mice, diversity outbred mice and so-called "dirty" mice (standard laboratory mice that have been cohoused with pet store mice and exposed to bacteria and viruses) are also being explored as models to assess the immune responses to *Mtb* and vaccination. Moreover, systems immunology studies appear promising in identifying markers of risk and protection, and offer a more comprehensive approach to assessing host responses to infection and disease.

3) Current promising leads, strategies and technologies

For the selection and differentiation among vaccine candidates early in the development process, head-to-head comparisons of candidates in animal and early human studies would be optimal. However, this approach requires a diverse and robust pipeline of candidates that is dependent on significant innovation in TB vaccinology.

A variety of innovative constructs are being developed by expert consortia utilizing a number of approaches, such as focusing on the role of antibody-mediated mechanisms in protection 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 range of immunologic responses that can be triggered by TB vaccine candidates. While these programmes progress, efforts are under way to develop an engineered *Mtb* strain that can safely be used in human challenge studies and that allows measurement of the bacterial burden in blood or urine.

One example of the success of cross-cutting research is the development of cytomegalovirus (CMV)-vectored candidates that 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 where the host first encounters the pathogen. Other noteworthy approaches include candidates based on the intranasally administered, attenuated para-influenza viruses for induction of mucosal immunity as well as candidates based on promising technologies such as self-replicating RNA candidates and electroporated DNA vaccines. Systematic studies of combinations using common antigens to elucidate the role of antigen-delivery platforms are also under way.

4) Future directions

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 (POI) in adolescents, POR in recently-treated TB patients, and prevention of disease (POD) in latently-infected individuals.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276648/

- 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 antibodies 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 common antigens, and test immunogenicity and safety in humans.
- Determine the role of non-tuberculous mycobacteria exposure on TB vaccine responses.
- Build prototype human challenge strains and test them in animals for further re-iterations.
- Identify novel protective antigens that are not immunodominant during latency or treatment.
- Build a consensus for a global portfolio advisory capability that can influence the candidate pipeline and resource allocation.

Mid-term goals (by 2023)

- Determine whether the novel BCG replacement candidates are safer and/or more effective than BCG in HIV-unexposed and exposed infants.
- Determine whether at least two new vaccine candidates protect against sustained *Mtb* infection in adolescents in a high-risk infection setting.
- 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 POI trial or a POR trial, into Phase IIb POD efficacy trials.

Long-term goals (beyond 2023, 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+, diabetics; 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 and antibody-based vaccines such as polysaccharide conjugates, glycolipids, etc.).

5) Discussion

Discussions at the 2018 Global Vaccine and Immunization Research Forum (GVIRF) included progress towards vaccines against TB. Considering the large reservoir of latently-infected persons who may develop active, transmissible disease, key target populations that may benefit from preventative vaccines now include adolescents and adults – key sources of *Mtb* transmission. This is in addition to infants and young children in whom prevention of initial infection is targeted. The WHO established preferred product characteristics set development goals for vaccines for these populations. Since a growing global clinical pipeline of TB vaccine candidates requires innovative trial designs to estimate efficacy while enrolling a modest number of volunteers, Phase II POI trials are being explored to de-risk candidates earlier in clinical trials and at lower costs, thus making optimal use of the still limited global vaccine trials capacity.

Rational advancement of vaccine candidates in the context of global portfolio management and prioritization for access to clinical trial support could be facilitated through the application of stage gating criteria that are being developed by some members of the TB vaccine community and are expected to be generally accessible in the summer of 2018. To support addition of new and more diverse clinical candidates to the clinical pipeline, investments in discovery research, animal model development and establishment of immune correlates and biomarkers are also needed. Assays emerging from these studies will be useful in experimental medicine studies that may utilize vaccines as tools to understand the role of delivery platforms, adjuvants and novel antigen combinations in eliciting specific immune response that may translate into POI, POD or POR. Ultimately, to facilitate evaluation of advanced candidates in Phase III efficacy trials, immune correlates of risk will be required to identify persons at highest risk of disease and consequently lower the number of volunteers that are required to arrive at statistically significant trial outcomes. In TB vaccine development it remains a priority to maintain a diverse pipeline of candidates through discovery research, targeted studies for the elucidation of correlates of vaccine protection and disease risk, to take advantage of enabling technologies and trial designs to help de-risk candidates, and to ensure sufficient clinical trials capacity to conduct late-stage clinical trials.

Table 9.1: Development status of current vaccine candidates

Approach	Organization(s)	Candidate name	Phase I	Phase IIa	Phase IIb	Phase III
Whole-cell or whole-cell extracts	Anhui Zhifei Longcom	Vaccae				X
	Serum Institute of India, Max Planck, Vakzine Projekt Management, TuBerculosis Vaccine Initiative	VPM 1002				X
	Cadila Pharmaceuticals, Indian Council of Medical Research	MIP				X
	Geisel School of Medicine at Dartmouth, Global Health Innovative Technology Fund	DAR-901			X	
	Archivel Farma	RUTI		X		
	Biofabri, TuBerculosis Vaccine Initiative, University of Zaragoza, Aeras	MTBVAC		X		
		BCG revaccination		X		
Protein subunits with adjuvants	GlaxoSmithKline, Aeras	M72 + AS01E			X	
	Statens Serum Institut, Valneva, Aeras	H56: IC31			X	
	Sanofi Pasteur, Statens Serum Institut, Aeras	H4: IC31		X		
	Infectious Disease Research Institute, Wellcome Trust	ID93 + GLA-SE		X		
Viral-vectors	Research Institute for Biological Safety Problems	TB/FLU-04L		X		
	McMaster University, CANSINO BIOLOGICS Inc.	Ad5Ag85A	X			
	University of Oxford	ChAdOx185A/ MVA85A (ID/IM/Aerosol)	X			

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Progress towards development of malaria vaccines

1) Background

According to the latest WHO World Malaria Report, 91 countries reported a total of 216 million malaria cases (95% confidence interval [CI]: 196–263 million), and an estimated 445 000 malaria deaths in 2016. Although malaria case incidence has fallen globally since 2010, the rate of decline has stalled and even reversed in some regions since 2014. Mortality rates have followed a similar pattern. Fifteen countries – all but one in sub-Saharan Africa – carry 80% of the global malaria burden, with children aged under 5 years and primigravid women disproportionately impacted.

2) Opportunities and challenges

The lack of a dual market for malaria vaccines remains a major challenge in accelerating development, as the public and/or philanthropic sector supports the majority of development costs. Further, the experience with the RTS,S/AS01 malaria vaccine has highlighted the need for this support to extend beyond the traditional safety, efficacy and manufacturing quality assessments, to include implementation assessments, which has been under-appreciated. The global health community should be aware of the potential additional financial requirements associated with gaps between licensure and widespread use; these may include sustaining manufacturing and delivering post-approval plans (i.e. risk management plans/pharmacovigilance) to meet regulatory and policy obligations, which can involve great costs. For products such as malaria vaccines in low- and middle-income countries, where use is associated with limited prospects for financial return, innovative financing mechanisms need to be set up to support the final steps towards availability and use, and to avoid major delays in realizing the impact of new tools in communities where they are most needed.

In 2013, the WHO Malaria Vaccine Technology Roadmap, which currently guides *P. falciparum* and *P. vivax* vaccine development efforts in alignment with global health goals, was updated, and supplemented shortly thereafter by WHO: Preferred Product Characteristics. The community will benefit from an update in the Roadmap over the next one to two years, in part to reflect changing malaria epidemiology, as well as the advancement of a first malaria vaccine into a pilot project.

Controlled human malaria infection (CHMI) models continue to serve a critical role in the early assessment of malaria vaccine candidates. In addition to sporozoite challenge models, which have accelerated the development of pre-erythrocytic vaccines for several decades, recent advancements in the development of asexual blood-stage and parasite transmission models are offering similar potential to vaccines targeting asexual and sexual stages of the parasite life-cycle.

3) Promising leads, strategies and technologies

The current pipeline of malaria vaccines in development (the "Rainbow Tables") is available at the WHO website.

Pre-erythrocytic vaccines

In January 2016, WHO formally adopted the joint recommendation of SAGE/MPAC for pilot implementation of the RTS,S vaccine in three to five settings in sub-Saharan Africa. The Malaria Vaccine Implementation Programme, a country-led, WHO-coordinated initiative, was established to generate the necessary evidence on the feasibility of delivering the required four doses of RTS,S, the vaccine's potential role in reducing childhood deaths, and safety in the context of routine use.

Ghana, Kenya and Malawi were selected, based on a competitive process, as partner countries for implementation of the vaccine through routine immunization services in selected areas of moderate-to-high malaria transmission. During the pilot implementation, the vaccine will be used as a complementary malaria control tool – added to the core package of WHO-recommended measures for malaria prevention and case management. As the vaccine provides partial protection against malaria, those receiving it will still need to use a bednet, and those who become sick with fever will still need to be tested for malaria, and treated, as appropriate. The vaccine implementation programme plans to reach approximately 360 000 children annually in selected areas across the three countries.

In addition to making the vaccine available to children and providing experience for its possible broad roll out in the future, the Malaria Vaccination Implementation Programme offers the three countries several potential opportunities. Additional vaccination visits for RTS,S could help to increase coverage of routine childhood vaccines and supplements. Collaboration between the immunization and malaria programmes could benefit other potential interventions that require cooperation, including bednet distribution. Financing for the pilot programme has been mobilized through an unprecedented collaboration between three key global health funding bodies:

Gavi, the Vaccine Alliance; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid.

Results from an open extension (Mal-076; see NCT02207816) of the Phase III (Mal-055) efficacy and safety study were recently reported at the 7th Multilateral Initiative Malaria (MIM) Pan African Conference in Dakar (April 2018); the incidence of severe and uncomplicated malaria in three different malaria parasite transmission settings for three additional calendar years was reported. The incidence of severe malaria significantly declined when children grew older (regardless of the study/vaccine group) and vaccine efficacy against severe malaria persisted for seven years following initial vaccination. No rebound effect of severe malaria could be observed during the three additional years of follow-up, and no safety signal was detected in this extension study.

In follow-up to promising CHMI data for a delayed fractional booster dose regimen for RTS,S in which 86.7% [95% confidence interval [CI], 66.8–94.6]; P < .0001) of volunteers were protected against infection, compared to 62.5% [95% CI, 29.4–80.1]; P = .0009) in the standard dose regimen, additional CHMI data (See NCT03162614) and field studies (see NCT03276962 and NCT03281291) have been initiated. The CHMI study, which is expected to report data in late 2018, will inform whether the paediatric (RTS,S/AS01E) formulation can be used effectively in adults, and whether alternative fractional dosing regimens should be considered. The field study will determine whether the fractional booster dose concept translates to an endemic setting, in 5 to 17 month-old children, with respect to prevention of clinical disease and infection, and whether the regimen can be further optimized. Success with respect to prevention of infection could catalyse development of the vaccine for use in all age groups to accelerate *P. falciparum* parasite elimination and prevention of reintroduction.

The evaluation of radiation-attenuated *P. falciparum* sporozoites, delivered by direct intravenous inoculation, is actively ongoing. After encouraging data from CHMI studies using homologous challenge parasites in United States volunteers, the project has transitioned to field efficacy testing. Safety and efficacy results have been reported from a single study conducted in healthy adults living in Mali. The vaccine candidate was safe and well-tolerated; however, immune responses were lower than reported from United States CHMI studies. In the six months following dosing with five sequential immunizations, 37 adults (93%) from the placebo group and 27 adults (66%) from the vaccine group developed *P. falciparum* infection. The estimated vaccine efficacy was 29% (95% CI 0.08–0.47) (*P* = 0.006, proportion affected analysis) and 48% (14–69) (log-rank *P* = 0.01, time-to-infection analysis). At the 7th MIM Conference, results from a safety and efficacy study conducted in adults living in Burkina Faso (see NCT02663700) reported a vaccine efficacy against infection (as measured by thick blood smear) of 38%, during the six months after the last dose in adult volunteers (14/39, 35.6%, were infected from the vaccinated group, compared to 23/40, 57.5%, infected from the control group).

Initial safety and efficacy data from a small CHMI study performed in the United Kingdom of Great Britain and Northern Ireland (see NCT02572388) of the CSP-based R21 vaccine candidate, formulated with Matrix-M1 adjuvant, was reported at the 7th MIM Conference. The short-term efficacy data are similar for those obtained previously for RTS,S/AS01, so it remains to be determined whether this approach will provide a significant advantage, such as via the induction of more durable protective responses. Initial safety and immunogenicity data from a trial in Burkina Faso (See NCT02925403) indicate reduced immune responses compared to those in the United Kingdom-based CHMI study.

Asexual blood-stage vaccines

The RH5 complex has emerged as a promising target for inducing strain-transcending immunity against *P. falciparum* asexual blood stages. In 2017 it was reported that substantial RH5-specific responses were induced in naïve human volunteers, using a viral vector platform, with serum antibody levels greatly exceeding those observed in African adults after years of natural malaria parasite exposure. Earlier this year, it was reported that an RH5 protein-based vaccine, formulated with GlaxoSmithKline's AS01 adjuvant, successfully induced biologically-active antibody responses in human volunteers, as determined by statistically significant reductions in parasite multiplication rate after challenge with infected erythrocytes in a CHMI study. While promising, the modest reductions in parasite multiplication rate (up to 30%) following challenge with < 1000 infected erythrocytes suggest more potent responses may be needed to confer clinical benefit.

Two asexual blood-stage vaccine candidates, targeting VAR2CSA and intended to protect women from pregnancy-associated malaria, recently completed Phase I clinical testing (see NCT02647489 and NCT02658253). Favourable, preliminary safety results and in vitro functional activity of induced antibodies were reported at the 7th MIM Conference in April 2018. Clinical efficacy data are yet to be reported, and consensus to emerge on an ideal development pathway.

The first clinical assessment of a *P. vivax* asexual blood-stage vaccine candidate (PvDBP2), formulated with Glucopyranosyl Lipid A-Stable Emulsion (GLA-SE) adjuvant, was recently completed in India (CTRI/2016/09/007289). Initial data indicate that the vaccine candidate is safe and well-tolerated, with evidence for induction of strain-transcending receptor-blocking antibodies.

Sexual, sporogonic and/or mosquito-stage vaccines

The clinical assessment of vaccine candidates designed to block transmission of parasites from humans to mosquitoes has historically focused on Pfs25 and Pvs25 and been challenged by the promising preclinical data translating into similar levels of transmission-blocking activity in human vaccinees. However, in 2017 a significant milestone was reached with the reporting at the 66th Annual

American Society of Tropical Medicine and Hygiene (ASTMH) meeting of the induction of high-levels of transmission-reducing activity (as measured by the standard membrane feeding assay) in humans, following immunization with four doses of a protein-protein conjugate vaccine (Pfs230-EPA) formulated with Alhydrogel adjuvant (see NCT02334462). More recently, at the 7th MIM Conference, even more promising data were reported for the same vaccine candidate formulated with GSK's proprietary AS01 adjuvant (see NCT02942277) where just two doses of the vaccine were shown to induce strong transmission-reducing activity in Malian adults. Important supplemental data on the durability of immune responses and functional activity, as measured by direct skin feeding, are expected in 2018.

4) Future directions

Short-term goals (within one to two years)

The chronic underfunding of *P. vivax* remains a major concern for the community, with little indication of significant change on the horizon. As mentioned above in *opportunities and challenges*, updating the *Malaria Vaccine Technology Roadmap*[2] should be a goal for the next one to two years.

Progress towards development of HIV vaccines

1) Background

Human immunodeficiency virus type 1 (HIV-1) infection leads to a progressive loss of CD4+ T-cells and an acquired immunodeficiency syndrome (AIDS). The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2016 about 37 million people globally were living with HIV, 1 million people died, and 1.8 million were newly infected; about 64% of these new infections were in sub-Saharan Africa *(1)*. Women and girls account for 59% of the total number of people living with HIV in eastern and southern Africa. HIV is most commonly transmitted through sexual intercourse; the virus can also be transmitted from mother-to-child during pregnancy, delivery or breastfeeding; transmission can also occur via injection of blood. Antiretroviral drugs in various combinations can help control the infection *(2)*, prevent onward transmission of HIV *(3)* and protect prophylactically treated, uninfected persons at risk from infection *(4)*. However, only about half of people living with HIV receive treatment, and among treated individuals- variable percentages of people are virally suppressed *(1)*. Voluntary medical male circumcision can reduce the odds of a man acquiring HIV through heterosexual sex by about 60%; while progress has been made in increasing voluntary medical male circumcision coverage, gaps still *(5)*. Oral pre-exposure prophylaxis (PrEP) is not widely available *(6)*; and it is not yet clear how much access and uptake there will be of this intervention among those at greatest risk for HIV acquisition. Long-acting prophylactic antiretroviral drugs and passive administration of anti-HIV broadly neutralizing monoclonal antibodies (mAbs) are currently being evaluated clinically as HIV prevention modalities, with results anticipated around 2021 *(7,8)*. Ultimately, the development of a safe and effective HIV vaccine remains a global public health priority that is the best hope for curbing the HIV pandemic *(9)*.

Prophylactic HIV vaccine development is stymied by the inherent biology of the virus. In contrast to virtually all other infectious diseases for which vaccines have been successfully developed, there is no precedent for the development of a natural immune response that clears HIV infection; thus, there is no "blueprint" for a protective immune response. HIV has evolved to evade the immune response in multiple ways. As a retrovirus, HIV can integrate into the genome of host cells and hide from the immune system in a latent state. The virus also has an extremely high mutation rate that allows it to rapidly escape from cellular and humoral immune responses; this extreme viral variability is reflected in the predominance of genetically diverse HIV clades in different geographies, as well as the presence of genetically diverse viral quasi-species within each infected individual *(10)*. Additional unique features of the viral surface envelope (Env) protein, the major target of humoral immune responses and vaccine development, impede the development of effective antibody responses. Critical neutralizing epitopes may be recessed on the functional Env spike; antibodies must negotiate a high-density glycan shield on the Env surface in order to engage key protein epitope regions; and nonfunctional forms of Env on the HIV virion or infected-cell surface divert the immune response towards non-neutralizing Env epitopes *(11)*.

2) Overview of current efforts

Current prophylactic HIV vaccine studies are testing hypotheses regarding the potential protective effect of anti-HIV immune responses that mainly fall into three conceptual areas, described below. For each of these approaches, the status of key exemplary investigations is summarized (a list of currently recruiting clinical trials appears in Table 9.2). It is not yet known whether a vaccine will need to elicit one or more of these responses to protect against HIV infection. Therapeutic HIV vaccine research is not covered in this update.

Vaccines that induce anti-HIV antibody responses, which while not directly virus-neutralizing in *in vitro* assays, may still provide protection *in vivo*.

These vaccine approaches, relying on different viral vector- or DNA-primes, followed by subunit Env protein boosts or protein co-administration, build on empirical observations achieved with such regimens. While the approaches may elicit some cellular immune responses, available evidence

[2] http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

suggests that Fc-mediated functional antibody responses may provide the primary mechanism of protection; such responses may include antibody-dependent cellular cytotoxicity *(12)*. (The Env immunogen constructs used here, such as non-native like gp120 or gp140, are to be contrasted with the structure-based bNAb immunogens described in the next section.)

Only one vaccine regimen (out of four evaluated for efficacy), a pox vector prime and gp120 Env protein boost evaluated in the RV144 trial, demonstrated modest evidence of vaccine efficacy (31%) which requires further confirmation. Post-trial analyses led to the identification of immune biomarkers or correlates of infection risk, with a prominent correlate being the levels of binding antibody to the Env V1V2 region *(13)*. To build upon the RV144 trial result, and to evaluate the potential for vaccine efficacy in a high-burden geography, a clade C-based regimen modified with the aim of inducing a higher magnitude and more durable immune response, is being tested in South Africa. A Phase I/II study of the clade C-based regimen (HVTN 100) met the pre-specified immunologic criteria for advancement of the regimen to a Phase IIb/III efficacy trial *(14)*; HVTN 702 started in 2016 and is anticipated to provide primary vaccine efficacy results in 2021 *(15)*. In addition to determining whether this regimen can provide meaningful protection in a high-risk South African population, the trial provides an important opportunity to potentially identify correlates of vaccine protection; confirmation of protection correlates could provide a powerful tool for further iterative vaccine improvement.

Another prime-boost regimen, employing an adenovirus serotype 26 (Ad26) vector and Env gp140 protein, is based on evidence of the partial protective efficacy of the vaccine regimen in a non-human primate immunodeficiency virus challenge model *(16)*. The Ad26/gp140 prime-boost regimen being tested in clinical trials (Ad26.Mos4.HIV vector, clade C gp140 protein) includes several mosaic antigen immunogens representing diverse epitopes from all known HIV strains, and is intended to provide broad coverage of circulating viruses globally. Following evidence of safety and adequate immunogenicity in Phase I/II trials, a Phase IIb trial (HVTN 705) was initiated in several sub-Saharan Africa countries in 2017 *(17)*. HVTN 705 is anticipated to provide vaccine efficacy results in 2022, and provides an important opportunity to again identify correlates of infection risk, as well as to determine the value of the non-human primate challenge model as a predictor of human vaccine efficacy.

The vaccines being tested in both HVTN 702 and HVTN 705 are multi-dose regimens, which could present eventual deployment challenges, especially in resource-limited settings; simplified regimens are highly desirable in the future. A third Phase IIb study, PrEPVacc, assessing the combination of an HIV vaccine (DNA, MVA and Env protein/adjuvant) and PrEP, is also planned *(18)*. Other prime-boost strategies under active clinical investigation are listed in Table 9.2.

Induction of broadly neutralizing anti-HIV antibodies

These approaches, based on structure-based design, aim to elicit antibody responses that are directly virus-neutralizing against a global panel of diverse HIV-1 strains in in vitro assays.

Broadly neutralizing anti-Env antibodies (bNAbs) appear in a subset of HIV-infected individuals, typically years after infection when the virus has achieved an irreversible foothold. A considerable repertoire of monoclonal bNAbs have been isolated and characterized *(19)*; when passively administered, the bNAbs have been demonstrated to provide protection in non-human primate models of HIV transmission *(20)*. A pair of major proof-of-concept clinical efficacy trials will evaluate whether passive administration of one of these mAbs, VRC01, is efficacious in preventing HIV infection in high-risk populations *(8)*. Proof of efficacy in humans would be significant for several reasons. If protection is associated with serum neutralization titers, it may 1) validate the use of ex vivo serum neutralization titers as a biomarker of HIV protection, as well as validate the predictive value of the non-human primate virus challenge model; 2) provide a potential approach to passive immune-prophylaxis in high-risk human subjects; and 3) provide support for the development of active immunization strategies designed to elicit such bNAbs. A number of monoclonal and bi-specific antibodies targeting different epitopes of the Env are now being evaluated alone and in combination (see Table 9.2).

HIV bNAbs often have highly unusual features, not typically found in antibodies to other pathogens, including extensive somatic hypermutation, long heavy-chain complementarity-determining regions, and some bNAbs are autoreactive *(21)*; it is hypothesized that such unusual antibodies are immunologically disfavoured and thus may be difficult to elicit with vaccine immunogens. Nonetheless, the isolated bNAbs and improved Env stabilization and analysis methods have provided critical tools for understanding the structure of the Env trimer as well as the structural characteristics of multiple bNAb epitopes that cover all surfaces of the trimer – the targets of bNAb immunogens *(22)*. These advances have enabled the structure-based design of novel Env immunogens that stably display (mimic) bNAb epitopes *(19)*, including modified Env subunit-, epitope scaffold- and native-like trimer-based approaches. The engineering of immunogens containing sites of Env vulnerability – as defined by the recognition of the available multiple different bNAbs for a given site of vulnerability – is referred to as epitope-based vaccine design.

The highly mutated bNAbs arise from complex evolutionary pathways (ontogenies). Ontogenies for individually isolated bNAbs have been experimentally elucidated by the longitudinal sampling of memory B-cells/antibodies over the course of infection, and/or by the phylogenetic inference of bNAb lineages. This allowed identification of the likely earliest bNAb precursor/ancestor B-cells that would need to be engaged for a given discreet bNAb lineage of interest to target with a vaccine. The design of immunogens that are optimized to bind to and activate the bNAb

precursors of a specific bNAb lineage, combined with boosting immunogens to further "mature" B-cells toward broad neutralization is referred to as antibody lineage-based immunogen design.

There are now several lead concepts about to enter Phase I experimental medicine studies in the coming year. While none of the individual immunogens is anticipated to induce mature bNAbs in humans, their evaluation in Phase I experimental medicine studies will demonstrate whether human subjects can mount the humoral/B-cell responses predicted by the preclinical studies.

BG505.664 gp140 SOSIP is a stabilized native-like trimer; preclinical studies of BG505 SOSIP have demonstrated the induction of strain-specific NAbs in preclinical models, including non-human primates *(23, 24)*. The Phase I study will look for evidence of autologous serum virus neutralization. BG505.664 SOSIP has also been further modified to bind to GL B-cell receptors *(25)*.

eOD-GT8, an engineered protein that mimics the CD4 binding site target of bNAbs, was optimized to bind the GL ancestor IgG of the CD4bs bNAb lineage (VRC01-class) and proof of principle of GL-targeting was demonstrated in human IgG gene knock-in mouse models *(26)*. For the eOD-GT8 clinical trial, the primary immunogenicity analysis will look for evidence of expansion of the CD4bs bNAb lineage (VRC01-like) precursor B-cells; this will be the first time that such a specific B lineage precursor analysis will be applied to a human HIV vaccine study.

426c is a clade C-based modified Env gp120 that has also been engineered to bind to and activate VRC01-class B-cell receptors *(27)* and is headed for Phase I study.

Another approach utilizes non-native-like gp120 immunogens that represent sequential HIV Env evolutionary sequence variants that were associated with the development of neutralization breath in an infected human (HVTN 115; see Table 9.2).

Positive signals in any of these trials will represent an important first step; however, given the complex, multi-step nature of HIV bNAb evolution, it is hypothesized that multi-component, multi-stage immunization strategies will be required for bNAb elicitation.

T-cell immune responses that could potentially mediate effective control or clearance of early infection

While antiviral T-cell responses are not generally anticipated to provide "sterilizing" immunity, a prophylactic cell-mediated immunity (CMI)-inducing vaccine approach for HIV would aim to prevent the establishment of persistent infection by extinguishing the earliest stages of viral replication, prior to the establishment of a long-lived reservoir of latently-infected cells. Due to HIV's extreme variability, it is predicted that CMI must be extremely broad and/or focused on critical regions ("Achilles heels") of the HIV proteome so that the virus is unable to effectively escape by mutating. The vaccine-induced cellular immune responses would likely also need to persist in tissues in an effector state, in order to immediately respond to any nascent infection foci, prior to significant viral replication, systemic dispersion and reservoir establishment.

Approaches to induce responses that HIV would be less able to escape from have included T-cell epitope design approaches that include mosaic and/or conserved region immunogens. Mosaic antigen immunogens are designed to present diverse sequences representing the optimal choice of epitopes from all known HIV strains, for broad coverage of circulating viruses *(28, 29)*. The conserved region approach uses vectored immunogens expressing highly conserved regions of the HIV proteome; if viral escape mutations occur, these are predicted to restrict the mutant virus replicative fitness *(30)*. Hybrid conserved and mosaic immunogen concepts are also being evaluated *(31)*. These mosaic and conserved immunogen designs have been expressed in vectors that may elicit CD4 T-cells and classical major histocompatibility complex (MHC) class I restricted CD8 T-cells, including DNA, chimpanzee adenovirus and modified vaccinia Ankara poxvirus vectors. Other novel approaches that aim to identify critical areas of mutational constraint within the HIV proteome may also lead to the design of novel T-cell-based vaccines.

In a serendipitously-discovered novel mechanism of potential broadening of the T-cell immune response, a fibroblast-adapted rhesus cytomegalovirus (RhCMV) vector carrying several simian immunodeficiency virus (SIV) gene inserts (gag, pol, env) protected over 50% of macaques against persistent infection with a virulent SIV strain; specifically, this approach led to the unprecedented early clearance of an initial detectable SIV viremia *(32)*. Uniquely, the vector was shown to elicit persistent effector-memory CD8 T-cells that had unparalleled breadth and that were "unconventional" in their MHC-restriction and epitope targeting. Rather than eliciting conventional immuno-focused MHC-I-restricted responses, the RhCMV vector elicited CD8 T-cells recognizing multiple SIV peptides across the entire span of the antigen inserts, either in the context of MHC-II or the non-classical, highly conserved MHC-E molecule *(32)*. Current research and development is focused on developing equivalent human cytomegalovirus vectors to evaluate whether such unconventional and broad CD8 T-cell responses can be elicited in humans. Human cytomegalovirus vector manufacturing and process development is currently ongoing and a Phase I trial is anticipated in late 2019.

3) Current opportunities in HIV vaccine research and development

- Improved analytic methods: Novel and improved analysis methods promise to accelerate progress in bNAb immunogen antigen discovery and iterative antigen improvement, product development and the evaluation of vaccine-induced immune responses. Increases in electron cryogenic electron microscopy and X-ray methods resolution have improved the analysis of the HIV Env glycoprotein structures *(22)*, and advances in single-particle cryogenic electron microscopy data processing allow for

rapid assessment of trimer immunogen structural quality. New glycan analysis methods are proving to be invaluable for the design, production and characterization of Env immunogens that more accurately mimic the glycosylated viral Env *(33)*. Advances in high throughput, multi-parameter, and systems immunology approaches allow for increasingly detailed characterization of vaccine-induced immune responses. Methods for HIV bNAb isolation and antibody sequencing have been particularly useful, enabling deep assessment of B-cell lineage engagement by bNAb immunogens, and the opportunity to identify improved immunogen designs that best trigger the sought-after bNAb lineage pathways *(34)*.

- Expanded repertoire of preclinical models: New humanized immunoglobulin mice promise to provide additional insights into the regulation (host control) and induction of bNAbs *(35)*.
- Novel approaches aimed at overcoming the poor and generally transient immunogenicity of HIV Env: These include novel adjuvants and other approaches to induce stronger and/or more durable immune responses, including multimerized/particulate display, controlled/timed release approaches and approaches that mimic the antigen delivery kinetics of natural infection, or extend the duration of antigen exposure *(24, 26, 36)*. Approaches to improve antigen targeting to germinal centres, the sites of immune response induction, are also being evaluated.
- New bNAb epitope targets that may be easier to induce with a vaccine: The HIV fusion peptide was recently identified as a novel vaccine epitope target against which neutralizing antibodies may be more readily elicited *(37)*. The identification of relatively simpler bNAb ontologies (i.e. less mutated bNAb lineages) may provide simpler templates/guides for lineage-based Env vaccine designs; as an example, the CD4bs bNAb lineage, IOMA, is hypothesized be more readily vaccine-elicitable *(38)*.
- Further development of native-like trimers as a platform for epitope structure- and bNAb-lineage-based designs: For example, next-generation Env trimers, engineered to specifically engage GL B-cell IgG receptors, will be poised to contribute to lineage-based vaccine design efforts *(39)*.
- Nucleic acid-based vaccine antigen expression platforms: These include novel RNA-based platforms *(40)*, and could enable the more rapid, iterative evaluation of HIV Env immunogen variants, primarily due to the relative speed and simplicity of nucleic acid- versus protein-immunogen manufacture.
- Human studies: The **potential opportunity to identify correlates of HIV vaccine protection in humans** would be afforded by a positive vaccine efficacy signal in the ongoing efficacy studies HVTN 702 and HVTN 705 (anticipated results around 2021 and 2022). If the prior non-human primate challenge model predictions are confirmed in the human trials, this would support further HIV vaccine efficacy evaluation in the non-human primate challenge model. For the earlier stage vaccine concepts, Phase I experimental medicine studies in humans that employ intensive, hypothesis-focused analyses of host-responses, promise to iteratively inform HIV vaccine design; the above-mentioned eOD-GT8 vaccine study is a good example of the planned study of human bNAb precursor B-cell responses in the human "model".
- An improved, novel simian-human immunodeficiency virus infection model: This model offers the potential to systematically characterize the natural induction of bNAbs against the HIV Env protein in non-human primates, thus potentially providing specific HIV Env templates for bNAb-inducing vaccine design *(41)*.

4) Current challenges in HIV vaccine R&D

- Resources allocated to R&D: The perception that it may be possible to treat our way out of the global epidemic, or that PrEP approaches could significantly reduce the epidemic, could potentially lead to a plateauing or decrease in global HIV vaccine R&D funds. For industry, there are poor market incentives to invest in HIV vaccine R&D.
- Fundamental biologic or scientific impediments: Challenges to discovering an effective HIV vaccine include a still-limited understanding as to which vaccine design and immunization approaches may be successful in inducing the highly unusual bNAbs that have only been observed in a subset of infected individuals after years of HIV infection. It is also important to understand the underlying mechanisms of poor Env immunogenicity and poor duration of anti-Env antibody responses, in order to effectively address these challenges.
- Still-unknown predictive value of non-human primate challenge models: Until efficacy results of ongoing HIV vaccine and passive prophylactic antibody efficacy clinical trials are published, the relevance of the currently favoured non-human primate challenge model in predicting efficacy in humans remains unknown.
- A complex ecosystem of different HIV prevention approaches and concepts-in-testing may pose challenges for the clinical efficacy testing of new HIV vaccines: An increasingly complex array of prevention approaches (including PrEP) and concepts in testing (long-acting prophylactic antiretrovirals) could make it challenging to conduct efficacy studies of next-generation vaccines. Challenges include the design and execution of large, resource-intensive trials that will need to incorporate evolving country standards of HIV prevention, and recruitment and retention of high-risk individuals for lengthy periods of time.
- Post proof-of-concept product development challenges: To prepare for the possibility of a positive HIV vaccine efficacy signal, a host of product development and distribution challenges should be addressed prospectively. These challenges include an uncertain regulatory path to product approval in developing countries, particularly for products not previously approved in the United States or Europe. To ensure availability of a marketable

vaccine when efficacy trials are completed, substantial upfront, at-risk investments need to be considered, including investments to conduct bridging trials (e.g. in adolescents), manufacturing process development, demand forecasting and identifying/building sufficient manufacturing capacity, technology transfer, feasibility studies of vaccine distribution/uptake, and health economics analyses to make the case for vaccine funding relative to funding for other HIV prevention interventions. Post proof-of-concept planning should also address vaccine distribution challenges, especially how to effectively deliver a multi-dose vaccine regimen to adolescent girls and young adult men and women that are at greatest risk of HIV infection in many high-incidence geographies.

- Need for better coordination of efforts and resources in HIV vaccine R&D, including the development of new business models: While the field awaits clear evidence of a robust proof-of-concept (a significant vaccine efficacy signal), no single organization is positioned to address the multiple HIV vaccine R&D challenges, or accept the substantial risks required to have a marketable vaccine ready when efficacy trials are completed. This suggests the need for effective coordination of efforts and resources and the development of new investment cases/ business models to proactively prepare for post proof-of-concept product development requirements, especially for vaccines that may have little market in developed countries.

Table 9.2: Actively-recruiting preventive HIV vaccine and passive immunization clinical trials

Trial	Product	Antigen	Phase	ClinicalTrials.gov identifier
DNA				
HVTN119	p24CE1/2 pDNA and p55^gag pDNA/IL-12 pDNA adjuvant	DNA plasmid expressing M group p24^gag conserved elements and/or p55^gag	I	NCT03181789
DNA + protein				
HVTN111	DNA-HIV-PT123; Bivalent Subtype C gp120/MF59: clade C TV1.C gp120 Env + clade C 1086.C gp120 Env	1) DNA clade C ZM96 gag, 2) clade C ZM96 gp140, and 3) clade C CN54 pol-nef; clade C TV1.C gp120 Env + clade C 1086.C gp120 Env proteins	I	NCT02997969
HVTN115	EnvSeq-1 Envs/GLA-SE +/- DNA Mosaic Tre	CH505 sequenced Envs Clade C (CH505-TF, -w53, -w78, -w100); DNA mosaic env	I	NCT03220724
HVTN124	gp120 (A,B,C,A/E)/GLA-SE, env (A,B,C,A/E)/gag (C)/GLA-SE	env (A,B,C,A/E)/gag (C) DNA Vaccine; gp120 (A,B,C,A/E) Protein Vaccine	I	NCT03409276
HVTN108	DNA-HIV-PT123/Bivalent Subtype C gp120/MF59 or Bivalent Subtype C gp120/AS01B	DNA clade C 96ZM651 gag, 2) clade C 96ZM651 gp140, and 3) clade C CN54 pol-nef; Protein Clade C TV1.C gp120 Env and clade C 1086.C gp120 Env	I/II	NCT02915016
Protein only				
HVTN 122	gp145 C.6980	Env gp145 C.6980 recombinant oligomeric gp145 clade C Env protein	I	NCT03382418
Viral vector - adeno + protein				
HPX2008/ HVTN 705	Ad26.Mos4.HIV/Clade C gp140/aluminium phosphate	Ad26.Mos1.Gag-Pol + Ad26.Mos2.Gag-Pol + Ad26.Mos.1.Env + Ad26.Mos.2.Env; Protein gp140 C	IIb	NCT03060629
Viral vector - pox + protein				

Trial	Product	Antigen	Phase	ClinicalTrials.gov identifier
HVTN107	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/MF59 or alum-adjuvant	Canarypox-ZM96 Env gp120 C, gp41 B, gag B, protease B; TV1 gp120 Env C + 1086 gp120 EnvC proteins	I/II	NCT03284710
HVTN120	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/MF59 or AS01B-adjuvant	96ZM651 gp120 (clade C strain) linked to transmembrane anchor (TM) sequence of gp41 (28 amino acids clade B LAI strain) and Gag and Pro (clade B LAI strain); protein clade C TV1.C gp120 Env and clade C 1086.C gp120 Env with MF59 OR AS01	I/II	NCT03122223
HVTN 702	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/ MF59	Canarypox-ZM96 Env gp120 C, gp41 B, gag B, protease B; TV1 gp120 Env C + 1086 gp120 EnvC proteins	IIb/III	NCT02968849
Viral vector - replicating				
Ad4 HIV	Ad4-EnvCN54; MVA-CN54 or CN54gp140/ MPLA	Live, replication-competent adenovirus 4 vector expressing HIV-1 isolate 97CN54 Env; Non-replicating MVA expressing 97CN54 Env; Recombinant 97CN54 gp140	I	NCT03408262
Passive immunization				
HVTN 704 AMP	VRC-HIVMAB060-00-AB	VRC01 antibody	IIb	NCT02716675
HVTN 703 AMP	VRC-HIVMAB060-00-AB	VRC01 antibody	IIb	NCT02716675
IMPAACT P1112	VRC-HIVMAB060-00-AB	VRC01 antibody	I	NCT02256631
MB66-01	MB66	VRC01 antibody and HSV8 antibody	I	NCT02579083
HVTN 127/HPTN 087	VRC-HIVMAB075-00-AB (VRC07-523LS)	VRC07-523LS antibody	I	NCT03387150
HVTN116	VRC-HIVMAB060-00-AB (VRC01)/VRC-HIVMAB080-00-AB (VRC01LS)	VRC01 antibody and VRC01 modified for FcRn affinity	I	NCT02797171
3BNC117-LS	3BNC117-LS	3BNC117-LS antibody with aa mutations, M428L and N434S, in the Fc domain	I	NCT03254277
MCA-0906	3BNC117 & 10-1074	3BNC117 & 10-1074 antibodies	I	NCT02825797
IAVI T001	PGT121	PGT121 antibody	I	NCT02960581
IAVI T002	PGDM1400, PGT121	PGDM1400 & PGT121 antibodies	I	NCT03205917
123I Radiolabeled 3BNC117	3BNC117	3BNC117 antibody	I	NCT03468582
3BNC117-LS + 10-1074-LS	3BNC117-LS + 10-1074-LS	3BNC117-LS antibody plus 10-1074-LS antibody	I	NCT03554408

Source: (42, 43) and Clinicaltrials.gov.

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Progress towards a universal influenza vaccine (Indicator SO6.2)

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 9.2.

Box 9.2: Descriptions of indicators, results, data sources and highlights

For more information on the background or limitations of currently approved influenza vaccines please refer to 2016 GVAP Secretariat report.

1) General approaches to the development of universal influenza vaccines

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.

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.

As detailed in Table 9.3, the main approaches being explored to develop such vaccines include:

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 been shown to increase the breadth of the response. Adjuvanted vaccines have been demonstrated to be effective against strain drift. Other adjuvant strategies include activating cellular immune responses to promote immune responses similar to those found during natural infection.
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. nucleic acid-based vaccines, notably including ones designed to elicit host responses against conserved internal proteins.
5. live attenuated influenza vaccine, replication-deficient, and novel attenuated virus vaccine approaches that elicit a broadly cross-reactive, longer-lasting host response.
6. vaccines comprising conserved epitopes from external proteins and/or internal proteins such as the nucleoprotein or matrix protein, or fragments of these, in formulations with and without adjuvants. These include highly conserved peptide epitopes or expression of these internal proteins in viral vectors, nanoparticles and fusion proteins.
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.

2) Opportunities and challenges

Opportunities

- Promising results from several laboratories have stimulated significant attention from pharmaceutical companies interested in developing the next generation of influenza vaccines.
- Government interest in the development of universal influenza vaccines is increasing due to the public health need for influenza vaccines with broader protection against antigenically drifted virus, improved efficacy across all age groups and the ongoing need for a proactive and nimble response against potential influenza pandemics. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health in the United States, held a workshop entitled "Pathway to a Universal Influenza Vaccine" that identified gaps and opportunities in influenza research. Building on the workshop, NIAID released "A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases" outlining activities in three main areas of influenza research: transmission, natural history and pathogenesis studies using prospective cohorts; influenza immunity and correlates of immune protection; and strategies in rational vaccine design to elicit broad, protective immune responses.
- New research findings regarding the role of pre-existing immunity, antigenic imprinting and the role of egg-adaptations in vaccine virus strains provide clues about seasonal vaccine efficacy and may lead to new discoveries to further enhance vaccine responses.
- Multiple strategies toward development of vaccines with extended breadth and duration of protection.
- Publication of the WHO preferred product characteristics for next generation influenza vaccines and other recently published research agendas in support of universal influenza vaccine development provide guidance to the community to foster innovation and promote promising new candidate products and approaches.
- Collaborative efforts among members of the research community to share reagents, best practices and findings provide momentum to fill important knowledge gaps and advance the field.
- Studies evaluating HA stem monoclonal antibodies show promise as a prophylactic or therapeutic option.

Challenges

- 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 exposure to influenza, whether via infection or immunization, impacts the immune response to subsequent exposures to different strains. 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.
- Licensure of universal vaccines will require agreement on acceptable outcomes (prevention of infection or severe disease), efficacy of these vaccines and the design of appropriate clinical trials and end-points.

- Data on the burden of influenza disease in low- and middle-income countries is still needed to build political will to support efforts to address influenza as a significant, global threat to public health.
- Better understanding of influenza vaccine uptake and demand is needed to assure manufacturers of the potential market for universal influenza vaccines once they are available.

3) Current promising leads, strategies and technologies

Table 9.3 highlights the status of current influenza vaccine candidates.

Table 9.3: Development status of current vaccine candidates

Organization(s)	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licensed
GlaxoSmithKline (United Kingdom)	Cross-clade antibody responses demonstrated with split-virion, inactivated, AS03-adjuvanted vaccine.				X	X
Novartis (Switzerland)	Adjuvant MF59 allows for broader cross-reactivity against viral strains not included in the vaccine.				X	X
Medicago (Canada)	Recombinant haemagglutinin (HA) expressed as virus-like particle (VLP) in tobacco plants. Requires adjuvant.				X	
BiondVax Pharmaceuticals (Israel)	Multimeric-001 vaccine: recombinant protein, combination of nine conserved linear epitopes from HA, nucleoprotein (NP) and matrix protein (M).			X	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		
Altimmune (United States)	Nasovax: Adenovirus 5, on PER.C6 cell line for vaccine production.			X		
	Long peptides from four core influenza proteins elicits strong T-cell response.			X		
SEEK Group (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		
Vaxart (hAd5 expressing HA/TRL 3) (United States)	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		
Vivaldi Biosciences (United States and Austria)	Replication-deficient influenza virus created by deletion of the interferon-inhibiting NS1 protein.		X	X		
Codagenix (United States)	Live attenuated influenza vaccine using Synthetic Attenuated Virus Engineering.		X			
Cytos Biotechnology (Switzerland)	M2 protein linked to a TLR7 ligand yielding high levels of IgG2c antibodies.		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			

Organization(s)	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licensed
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			
Sanofi Pasteur (formerly Acambis Inc.) (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, Inc. (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) (United States)	PXVX0103 (Ad4-H5-Vtn administered as oral capsules) live adenoviral-based vaccine against avian influenza (H5N1).		X			
Blue Willow Biologics (United States)	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			
NIAID (United States)	Fusion protein between self-assembling ferritin protein and full length HA for nanoparticle presentation of HA.		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				
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 (France) and Vaccine and Gene Therapy Institute (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				
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				

Organization(s)	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licensed
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				
Bionor Holding (Norway)	Peptide-based approach targeting conserved epitopes (Vacc-Flu).	X				
VBI (formerly Variation Biotechnologies) (United States)	Unique technology using a mixture of 8 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				
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) (Belgium)	Recombinant tetrameric protein, M2e-tGCN4 (modified form of the leucine zipper of the yeast transcription factor GCN4 linked to M2e).	X				
University Of Gothenburg (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				

Organization(s)	Approach, target, adjuvant	Preclinical	Phase I	Phase II	Phase III	Licensed
KJ Biosciences LLC (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.	X				
Janssen/Crucell Vaccine Institute and the Scripps Research Institute (United States)	A stable trimeric influenza haemagglutinin stem (headless) as a broadly protective immunogen (mini-HAs).	X				
Novartis (Switzerland)	Synthetic, self-amplifying mRNA, delivered by a synthetic lipid nanoparticle.	X				

4) Future directions

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.

Mid-term goals (by 2020, end of the DoV)

- One or two candidates advanced towards licensure.
- Robust pipeline of vaccine candidates using a variety of approaches advanced in preclinical development, ready to move to clinics.

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.

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Progress towards institutional and technical capacity to carry out vaccine clinical trials (indicator SO6.3)

No report submitted.

GOAL 4: DEVELOP AND INTRODUCE NEW AND IMPROVED VACCINES AND TECHNOLOGIES

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.
DATA SOURCE/COLLECTION	Subject matter experts; landscape reviews; clinical trial databases.
TARGET	Progress towards licensure/launch of one or more such vaccines by 2020.
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.

1) Background

Goal 4 of the Monitoring & Evaluation/Accountability Framework in the Global Vaccine Action Plan 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 above. 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, cytomegalovirus (CMV), respiratory syncytial virus (RSV), group A streptococcus, leishmaniasis and helminth infections. The selected candidate vaccines as a group were generally considered to provide a representative indication of the changing state of the science. The GVAP Secretariat early on consulted with experts, performed a landscape analysis and generated reports for each of the target diseases to establish a baseline.

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, is reported on a biennial basis to SAGE and the World Health Assembly. This third report provides an update on the current status of vaccine candidates since 2016 and presents a forward-looking assessment of potential progress in the Decade of Vaccines and beyond.

2) Overview of current efforts

In 2015, a live recombinant tetravalent vaccine against dengue, Dengvaxia, proposed initially for use in individuals older than 9 years of age, was licensed in Mexico. Since that time, the vaccine has been licensed by additional national regulatory authorities in other dengue-endemic countries, but its implementation has been limited by recent safety concerns. As discussed below, additional dengue candidate vaccines are under development.

Table 9.4 shows the number of candidate vaccines for the seven target diseases currently in active clinical development. As compared to 2016 the number of candidate vaccines in clinical development for dengue, hepatitis C, and Group A streptococcal diseases has remained unchanged. In contrast, the number of vaccine candidates in clinical development for CMV, leishmaniasis and helminth diseases has decreased. The reduction in the number of candidates in clinical development likely reflects the process of rigorous down-selection at the clinical stage rather than a lack of progress. Further, it is important to note that there are substantial basic research and preclinical development efforts in each of the target diseases that will likely produce new candidates for clinical evaluation in the near future, as was observed for RSV. Current efforts encompass a variety of diverse technologies and approaches, ranging from live attenuated (dengue, CMV, RSV) and inactivated vaccines (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, CMV).

Table 9.4: Number of candidate vaccines against selected diseases currently in active clinical development (as of July 2018)

Target disease	Phase I	Phase II	Phase III
Dengue	4	1	2
Hepatitis C	3	1	0
Cytomegalovirus	6	2	1
Respiratory syncytial virus	12	5	1
Group A streptococcal diseases	4	1	0
Leishmaniasis	0	1	0
Helminth diseases[a]	1[b]	2[c]	0

[a] Includes schistosomiasis, hookworm, onchocerciasis and lymphatic filariasis.
[b] For *Schistosoma mansoni* infection.
[c] Includes one candidate vaccine for *Schistosoma mansoni* infection and one for hookworm infection.

3) 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, RSV, hookworm and schistosomiasis. 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.

For some diseases, e.g. leishmaniasis and helminth diseases, additional hurdles include the scientific and technological challenges posed by complex parasite life-cycles, the relatively small vaccine R&D communities, the lack of private sector interest and development partnerships for early translational R&D, and an incomplete assessment of the full public health value of such vaccines. 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.

4) 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) and nanoparticles (RSV vaccines). Candidate vaccines in Phase II trials are based on live attenuated virus (RSV vaccine), recombinant live attenuated virus (dengue vaccine), replication-defective virus (CMV), viral vectored vaccines (hepatitis C, CMV, RSV, Leishmaniasis), DNA vaccines (human CMV), adjuvanted peptide combinations (Group A streptococcus vaccine), adjuvanted

recombinant proteins (human CMV, hookworm, and schistosomiasis vaccines) 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, 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 chapter.

5) Future directions

Short- and medium-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 recommendations for use of the recently licensed dengue vaccine will continue to be evaluated and where applicable, the resulting analysis and lessons learned may be useful to inform licensure of other vaccines against dengue and other target diseases. Also, results from three Phase III trials (for the tetravalent, live attenuated vaccines for dengue and a nanoparticle vaccine for RSV) and Phase II trials of a hepatitis C vaccine and a leishmaniasis vaccine are expected to be available 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.

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.

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 delivery 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 SOURCE/COLLECTION	Subject matter experts, landscape reviews and meeting reports.

1) Overview of current efforts

Blow-fill-seal

The Bill & Melinda Gates Foundation have made two investments in blow-fill-seal (BFS) technology, one to Rommelag which includes development of new BFS vial designs as well as a parenteral vaccine vial design with temperature control. The project work also included a PATH human factors evaluation implemented in Uganda and Viet Nam in 2017 Global Good has also been developing a low volume cold chain ampoule design, which was assessed in the PATH human factors evaluation.

Development of a new Apiject-Rommelag compact auto-disable prefill (CPAD) of this novel container continues to move forward; application to a specific vaccine could potentially occur by 2020. The Bill & Melinda Gates Foundation and other stakeholders have also expressed interest in applying the Apiject design to contraceptive delivery. The other Bill & Melinda Gates Foundation investment has been to Maropack to demonstrate the feasibility and impact on parenteral vaccine potency and stability when using the BFS process for filling. A viral vaccine and a bacterial vaccine are currently under evaluation, with data anticipated to be reported during the latter half of 2018.

Angela Brevetti, another BFS developer, has also been working with Sanofi Pasteur in India on a new, low volume cold chain design for vaccines. To date however, the most advanced BFS application for vaccine packaging is the GlaxoSmithKline effort to package their Rotarix vaccine in a multi-mono dose design. The multi-mono dose design is a strip of five conjoined BFS ampoules, with one VVM. As an ampoule is removed from the conjoined strip, it is immediately open and must be used to deliver the vaccine to an infant. Initial market introduction is anticipated in 2018 or 2019.

Microarray patches

The most advanced example of a microarray patch (MAP) for drug delivery, a zolmitriptan MAP for migraine treatment in development by Zosano Pharma, has successfully completed Phase III clinical testing *(1)*. Proof-of-concept for MAP delivery of vaccines has been demonstrated through publication of the results of three Phase I clinical trials of MAPs delivering seasonal influenza vaccine, including examples from both the dissolving and solid-coated MAP platforms *(2–4)*. Three MAP developers are currently advancing measles–rubella vaccine MAPs towards readiness for clinical studies, and the most advanced candidate has demonstrated immunogenicity and protection of MAP vaccination in preclinical studies, as well as thermostability under CTC conditions *(5)*. Other vaccine MAPs in preclinical development include those for rotavirus, inactivated poliovirus, tetanus toxoid, diphtheria and Ebola vaccines. In-country evaluations of two developers' MAP technologies in Ghana, Benin, Nepal and Viet Nam have assessed acceptability, usability and programmatic fit of this technology platform for vaccine delivery in low-resource settings.

Disposable syringe jet injectors

Successful completion of a study of Serum Institute of India's measles–mumps–rubella (MMR) vaccine with the PharmaJet Stratis device (intramuscular and subcutaneous capable) occurred and was published in early 2018 *(6)*. PharmaJet has been working to support Serum Institute of India's relabeling of their measles-containing vaccines to allow for Stratis delivery in India. The PharmaJet Tropis intradermal delivery-capable device has been under review by WHO for prequalification since early 2017, with prequalification expected by middle of 2018. The WHO Global Polio Eradication Initiative (GPEI) has purchased 5000 Tropis injectors and 5 million cartridges as a stockpile for fractional dose inactivated polio vaccine (fIPV) delivery to be used by countries. Several countries have expressed interest in using the Tropis for fIPV delivery, which could occur in 2018–2019.

Intradermal adapters

Sanavita (acquired Helm Medical GmbH) and West Pharmaceutical Services have worked to produce 4 million intradermal adapters (ID adapters) plus the Sanavita/Helm prequalified Helmject AD syringe 0.1mL 3/8" 27 G needle for use by the GPEI for fIPV delivery. To date countries have not as yet adopted the intradermal adapter, with some countries such as India simply adopting BCG ID syringes for fIPV delivery and others waiting for WHO prequalification to occur. GPEI conducted a study of fIPV delivery that included the ID adapter in Pakistan; it demonstrated user preference for the

ID adapter, as well as a similar immune response as compared to traditional needle and syringe *(7)*. WHO has been working to develop a prequalification specification and validation protocol for ID adapter-capable needle-based injection devices such as the ID adapter, with finalization expected in 2018 and prequalification of the ID adapter possible in 2018–2019.

Barcodes

A cost–benefit study of barcodes has been completed in the United Republic of Tanzania with positive results, and the software systems supporting their use has been scaled nationally. The Gambia is scaling their barcode system nationally this year across the central store, 7 regional stores and 21 hospitals and priority health centres. The 1st African Global GS1 Healthcare Conference on "Track and trace for access to safe medicines" was held in Addis Ababa, Ethiopia in May 2018, with representation from 24 African countries. The Ethiopian Food, Medicine and Health Care Administration and Control Authority co-hosted the event and has set a five-year roadmap for the implementation of barcodes on health commodities including vaccines with batch/lot tracking and serialization. In addition, both Kenya and South Africa have implemented policies requiring GS1 barcodes on the procurement of health commodities that match European Union and United States regulations for pharmaceutical products. Similarly, the Global Health Supply Chain Program of the United States Agency for International Development (USAID) has set timelines for GS1 implementation on tertiary trade items by December 2018, secondary trade items by June 2020 and serialization by June 2022. India also has adopted regulations requiring GS1 standards on the packaging of exported vaccines. Serum Institute of India has applied the GS1 2D barcode on their tertiary packaging, and Biological E has 2D barcodes on their secondary packaging. Manufacturers selling to the United States (e.g. GlaxoSmithKline and Pfizer) have 2D barcodes on their packaging down to the vial level.

Vaccine vial monitor with threshold indicators (VVM-TIs)

WHO has developed draft specifications for threshold indicators (TIs) that apply to vaccine vial monitors (VVMs). In addition, the Temptime VVM-TI technology was independently evaluated in Nepal and Uganda and results were submitted to WHO in February 2017 as documentation supporting prequalification (see Table 9.5). Prequalification is anticipated in 2018.

Table 9.5: Summary of progress for key platform delivery technologies expected to 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 completed with SII MMR vaccine, published in 2018.	Relabeling of Serum Institute of India's measles vaccines for Stratis delivery in India.	February 2013 (Stratis device)	Expected launch in India in 2018.
Tropis 0.1 mL needle-free (intradermal)	PharmaJet	Intradermal delivery of IPV.	CE mark received in June 2016.	Expected in mid-2018.	Expected in 2018–19.
Intradermal adapter	Sanavita/West Pharmaceutical Services	Intradermal delivery of IPV.	USFDA 510(k) clearance in 2013 and CE mark in 2014.	Expected in 2018–19.	Expected in 2018–19.
Blow-fill-seal primary containers	GlaxoSmithKline	Oral delivery of rotavirus vaccine.	Expected in 2018–19.	Expected in 2018–19.	Expected in 2018–19.
Barcodes	Multiple vaccine manufacturers	All vaccines.	NRA approval in at least one low- or middle-income country expected by 2020.	Critical characteristics on secondary and tertiary packaging by 2020.	Continued nationwide expansions expected in 2018–19.

Technology	Manufacturer	Vaccine application	Licensure (NRA)	WHO prequalification	Anticipated launch in country
Vaccine vial monitor with threshold indicator (VVM/ TI)	Temptime	Potentially all vaccines labelled for controlled temperature chain use.	NA	Expected in 2018.	TBD

USFDA, United States Food and Drug Administration.

2) Opportunities and challenges

Although several platform delivery technologies are advancing and some have been launched, the goal is for these innovations to deliver impact by increasing coverage and equity of immunization programmes. This remains a challenge due to cost of development and/or procurement, lack of clarity as to how these potentially more-costly innovations would be used to complement existing vaccines and associated commitment from countries for uptake. Public health stakeholders are working together to better articulate the public health need to inform product development of new delivery technologies. This initiative is known as total systems effectiveness.

Microarray patches

In April 2018, the World Health Organization hosted a product development workshop for measles-containing vaccine MAPs, bringing together global stakeholders, MAP developers and industry representatives. The workshop highlighted the potential benefits a thermostable, easy-to-deliver MR MAP could have in improving stalled coverage rates and supporting measles-rubella elimination goals. However, the workshop also highlighted key product development hurdles—including uncertainty of the clinical and regulatory pathway, the capital investment required for a pilot facility, cost of manufacturing and scale-up and unclear market viability—which will require collaboration and sustained investment to overcome if the timeline to product licensure is to be accelerated.

Blow-fill-seal

Adoption by the broader field of vaccine manufacturers still represents a challenge for this innovation. Questions about the impact of the BFS process on vaccines continue to represent an uncertainty to manufacturers. In addition, the capital investment and facility requirements necessary for implementation and use of the BFS format prove to be daunting for developing country vaccine manufacturers. In applications where the use of a BFS ampoule format for oral delivery, such as rotavirus or cholera vaccine, many manufacturers have instead selected polymer tubes such as what is currently used for Merck's RotaTeq vaccine. Although a recently published cost model has demonstrated that lower cost is possible for BFS in comparison to other packaging formats *(8)*, skepticism remains – hindering the uptake and use of this format and process for vaccine filling by manufacturers.

Disposable syringe jet injectors

The role of disposable syringe jet injectors (DSJIs) in low- and middle-income country immunization programmes remains questionable, with the potential for a greater value proposition in supplemental campaign scenarios. Utilization of a total systems effectiveness modelling approach to assessing potential public health value for intradermal DSJI delivery of IPV has been conducted by PATH, which demonstrated that if intradermal devices enable countries to adopt fIPV, the overall cost of delivery could be reduced compared with full-dose intramuscular delivery with needle and syringe.

Intradermal adapters

To date countries have yet adopted the alternative intradermal devices such as the DSJI or the intradermal adapter for fIPV delivery, with some countries such as India simply adopting less costly 0.1ml AD syringes for fIPV delivery and others waiting for WHO prequalification to occur. The value proposition for low- and middle-income countries use could rest upon the strength of any particular country's immunization programme and confidence in healthcare workers' ability to provide needle and syringe ID injections. Devices such as the ID adapter could have more potential benefit in countries or districts that are not as strong as others comparatively, or in outreach or campaign scenarios.

Barcodes

A number of factors are delaying scale-up of barcodes on secondary and tertiary packaging including lack of strong demand from customers (countries), lack of country readiness and the absence of barcode functionality in logistics/vaccine information management systems. At the global level, there is no longer a formal working group to advance barcodes on vaccines. Such a working group could help to create standards for barcode use and align the stakeholders across the supply chain ecosystem including WHO, the United Nations Children's Fund (UNICEF), vaccine manufacturers and countries. UNICEF's own global supply chain Enterprise Resource Planning system is not yet GS1 compatible; though plans are under way to resolve this.

A limitation to the adoption of the barcode use in the United Republic of Tanzania is the lack of barcodes on secondary packaging for many of the vaccines that are part of routine immunization. While users recognized that barcode scanning reduces data entry errors and saves time, the perception is the lack of products with barcodes does not allow the system to add value. For example, the larger cartons present at the regional level (300 vial packaging) have 2D barcodes, but once broken down for district use, the smaller boxes of 50 vials do not. Manufacturers such as Serum Institute of India have been willing to place 2D barcodes on the 50 count boxes for smaller projects like in the Gambia. If changes to the manufacturing line were made permanent, it would be a giant step forward for barcode coverage across Africa.

Vaccine vial monitor with threshold indicators

The availability of this product is dependent on WHO prequalification of VVM-TIs and WHO/UNICEF requirements of VVM-TIs on specific vaccine types.

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2018 GLOBAL VACCINE AND IMMUNIZATION RESEARCH FORUM (GVIRF): MEETING REPORT

For the definition of each indicator, description of data sources, comments on data quality, description of results, please refer to the documents or websites listed in Box 9.3.

Box 9.3: Descriptions of indicators, results, data sources and highlights

Highlights

- Global research in vaccines and immunization is advancing in many priority areas.
- More innovation is urgently needed to improve vaccine access and coverage.
- Implementation research should be an integral part of R&D for complex interventions.

1) Introduction

In March 2018, WHO, NIAID (part of the US National Institutes of Health), and the Bill & Melinda Gates Foundation convened leading scientists, vaccine developers, and public health officials from around the world for the third Global Vaccine and Immunization Research Forum, held in Bangkok, Thailand. As with previous GVIRF meetings, this conference tracked progress in the GVAP's research and development agenda, identified opportunities and challenges in meeting GVAP goals

and promoted partnerships in vaccine research *(1,2)*. The 2018 GVIRF featured two overarching themes, "innovating for equity" and "end-to-end integration." This report summarizes the forum discussions; presentations and other materials from the 2018 GVIRF can be found at http://www.who.int/immunization/research/forums_and_initiatives/gvirf/forum_2018/en/.

2) Innovating for equity

As presented at GVIRF, innovation is widespread in immunization. Progress is being made in advancing priority vaccines and enabling technologies, developing approaches to improve immunization coverage and impact, and building capacity for innovation, particularly in low- and middle-income countries.

Priority vaccines

HIV

Two pivotal HIV vaccine efficacy trials are under way and expected to provide efficacy data around 2020. First, in a follow-on from the RV144 clinical trial in Thailand that demonstrated safety and modest efficacy for an HIV preventive vaccine, the HVTN702 trial is testing an ALVAC-C prime with an ALVAC-C+ bivalent envelope (gp120 env) protein/MF59 boost (NCT02968849). Second, the HVTN705 trial, which will enrol 2600 women in six African countries, is using an Ad26 vector prime with an Ad26+gp140 env protein boost and aiming for global cross-clade protection (NCT03060629).

HIV immunization strategies will pose delivery challenges because they will target high-risk adult populations that are not routinely vaccinated and require complex vaccination regimens: GVIRF participants noted that implementation research will be crucial to efficiently protecting these populations.

Tuberculosis

The pipeline of TB vaccines includes subunit protein, viral vector, whole-cell inactivated and live-attenuated candidates *(3,4)*. A recent study in adolescents tested two approaches, H4:IC31 vaccine (a recombinant fusion protein with IC31 adjuvant) and BCG re-vaccination (NCT02075203). Early analysis showed that both were well tolerated. BCG re-vaccination demonstrated a statistically significant 45.4% reduction of sustained infection and H4:IC31 gave a statistically significant 30.5% reduction of sustained infection *(5)*. These results are informing further TB vaccine product development. Priorities for TB vaccine research include developing a controlled human infection model and identifying alternative clinical endpoints such as prevention of infection, disease, recurrence or reinfection.

Malaria

Having received a positive scientific opinion from the European Medicines Agency, the first malaria vaccine, RTS,S (GlaxoSmithKline, MosquiRix) is being deployed in pilot studies in Ghana, Kenya and Malawi. These studies are assessing the operational feasibility, safety and impact of RTS,S and will inform WHO recommendations for use *(6)*. GVIRF participants observed that there remains a need for malaria vaccines with high and persistent efficacy that are effective against both *Plasmodium falciparum* and *Plasmodium vivax*, that can interrupt transmission, and that are suitable for use in older children and adults (including pregnant women). A diverse pipeline that includes pre-erythrocytic, blood and sexual stage candidate vaccines and monoclonal antibodies is aiming to address this gap *(7)*.

Influenza

Universal influenza vaccine have been defined as vaccines that are at least 75% efficacious against symptomatic influenza infection, that protect against both group 1 and group 2 influenza A viruses for at least 1 year, and that are suitable for all age groups *(8)*. Universal influenza vaccines would transform both seasonal influenza prevention and pandemic response, as annual revaccination would no longer be necessary and doses could be stockpiled for rapid deployment in the event of a pandemic. Multiple candidates targeting conserved regions of the haemagglutinin protein are in clinical development *(9)*.

Enabling approaches

Vaccine vectors

Two vaccine vectors were highlighted at the conference: CMV-based vectors and plasmid launched live-attenuated vaccines. CMV-based vector vaccines elicit and maintain high frequency "effector memory" T-cell responses in non-human primates. Because they efficiently re-infect and persist despite robust anti-CMV immunity, CMV-based vectors can be used repeatedly to induce responses against successive antigens *(10)* CMV vectored vaccines provide unprecedented protection against simian immunodeficiency virus (SIV. A highly attenuated human CMV-vectored HIV vaccine is now in cGMP manufacturing and slated for clinical testing in 2019. Plasmid launched live-attenuated vaccines are *Escherichia coli*-produced DNA vaccines that upon administration replicate in mammalian cells, assemble into virus particles, and infect and are amplified by surrounding cells. They can function as a live-attenuated yellow fever vaccine, as demonstrated by proof-of-concept studies in small animals and non-human primates. This approach has the potential to serve as a platform technology for other targets, including pathogens of epidemic potential such as Lassa fever virus.

Human challenge models

As described at GVIRF, controlled human infection models (CHIMs) have been used to study pathogenesis, assess correlates of protection, provide efficacy data for cholera and typhoid vaccine licensure and down-select among enterotoxogenic *E. coli* vaccine candidates. Development of CHIMs for some diseases has been challenging due to complexity in infectious agents and host-pathogen

interactions, variable infection rates and complex disease profiles. GVIRF participants called for: greater standardization of CHIMs; establishing guidelines for CHIM studies used to support licensure; focusing on end-user populations (for example through CHIM sites in endemic areas); and application of advanced immunology in CHIMs to identify correlates of protection.

Research and development for emerging infectious diseases

In response to the 2014 West African Ebola outbreak, the WHO *R&D Blueprint for Action to Prevent Epidemics* was launched in May 2016 to accelerate research and development for epidemic prevention and response *(11)*. As of 2018, the diseases prioritized under the *Blueprint* are Crimean-Congo haemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, Middle East respiratory syndrome, severe acute respiratory syndrome, Nipah and henipaviral diseases, Rift Valley fever, Zika virus disease, and "Disease X", which refers to an emerging pathogen yet to be identified that may cause epidemic human disease in the future *(12)*. Under the *Blueprint*, roadmaps and target product profiles are being developed; current versions of these documents are available on the WHO website *(13)*. Norms and standards tailored to the epidemic context are being formulated, including approaches to regulatory pathways and ethical issues, clinical trial design, data and sample sharing and capacity building. These roadmaps and guidelines should reduce the time between the start of an outbreak and the testing of candidate interventions.

Delivery

Implementation research

Implementation research, delivery innovations, national immunization programme strengthening and strong overall health systems are essential to ensure all children receive the vaccines they need. Addressing inequities in access to vaccines requires innovation to determine where these children are and why they are not being vaccinated, and to make products more robust and easier to deliver.

Adding to the promise and the challenge of immunization are new target populations such as adolescents and new vaccines with complex regimens that will be difficult to deliver, especially in low-resource settings. Implementation research will be required to inform policy decisions and to guide delivery, as demonstrated by the malaria vaccine pilot studies. Because these studies are large and expensive to conduct, a new paradigm is needed where implementation research is an integral part of vaccine development. This new paradigm is essential to realizing the full benefits of immunization.

Mission Indradhanush

India's Mission Indradhanush was launched in 2014 to improve immunization coverage in children and pregnant women. It ultimately reached 528 districts across 35 states and union territories, strengthening immunization through a multi-dimensional approach that combined capacity building, detailed planning, measurement and accountability, and use of ICT to find and reach the unreached. With political support at the highest levels, Mission Indradhanush helped increase the proportion of fully immunized infants in India from 65% in 2014 to 78% in 2017. Its successor, Intensified Mission Indradhanush, is aiming to fully immunize 90% of Indian infants in 2018.

Social media outreach

Innovative programmes are using social media to target underserved populations and address vaccine hesitancy. In Suzhou, China, a New Citizen Transaction Center is registering migratory children and a public service account on the WeChat social media app is being used to schedule vaccination appointments, send reminders and disseminate information. In the Ukraine, group chats with parents and health professionals are being organized to address concerns about vaccination. GVIRF participants observed that technology and social media have enormous potential to improve social mobilization and vaccine acceptance.

Maternal immunization

Immunization in pregnancy is a well-established approach to preventing disease in mothers and infants. WHO recommends influenza and tetanus vaccines for use in pregnancy; additional vaccines are recommended for use in specific situations, such as disease outbreaks. Vaccines are also in development for maternal immunization to protect infants from RSV and Group B Streptococcus. Programmes immunizing pregnant women against tetanus have shown that multiple delivery approaches may be needed to reach the most vulnerable populations, and that issues of service quality and vaccine hesitancy must be addressed. GVIRF participants observed that: operational research will be needed to efficiently deliver the new maternal immunization vaccines; introducing new vaccines for pregnant women will create opportunities to strengthen antenatal care; and adverse events following immunization, whether related or unrelated to the vaccine, raise concerns that must be addressed with strong monitoring and risk management.

System capacity

Developing-country vaccine manufacturers

Developing-country vaccine manufacturers are now supplying vaccines for approximately 84% of the world's birth cohort annually. Yet the low- and lower-middle-income countries they serve account respectively for only 8% and 4% of global vaccine revenues. Meanwhile, developing-country vaccine manufacturers are under intense pressure to supply quality product at the lowest possible price. For example, UNICEF is now procuring DTP–HepB–Hib vaccine at less than US$ 0.80 per dose, a price that may be unsustainable for some manufacturers *(14)*. GVIRF participants emphasized that access to affordable vaccines requires prices that are sustainable for manufacturers in the long term.

Mature developing-country vaccine manufacturers have gone beyond relying on partners for technology transfer to supporting in-house development of new products. To ensure sustained commercial viability, they require a robust business case for each product. Business risks include: long development timelines and regulatory complexities that extend time to market; lack of demand predictability, which leads to poor capacity utilization and high fixed costs; diverse procurement mechanisms; pressure for unsustainably low prices; and regional markets where it can be difficult to achieve economies of scale. Patent restrictions can also create barriers for developing-country vaccine manufacturers *(15)*. GVIRF Participants observed that national governments and regional bodies can contribute by strengthening national regulatory authorities, providing incentives and direct investments, fostering a supportive business environment, improving the intellectual property landscape, and building a highly-skilled workforce.

3) End-to-end integration

The second overarching theme of GVIRF reflected the ongoing shift from silo approaches to an integrated end-to-end perspective that considers how a new vaccine will be deployed as part of a comprehensive disease control strategy.

Evolving disease control strategies

Polio

Vaccines have been the mainstay of polio eradication, but the current vaccines have limitations as well as benefits. Oral poliovirus vaccines (OPV) contain live-attenuated viruses derived from the three types of wild poliovirus (WPV). These vaccines give individual protection against paralytic polio and block transmission of the virus. Rarely, the attenuated vaccine strains can give rise to circulating vaccine-derived polioviruses (cVDPV), which resemble WPV in transmissibility and virulence. Inactivated poliovirus vaccines (IPV) confer individual protection against all three types of poliovirus but do not block poliovirus transmission. As a result, in countries with a high risk of polio importation or transmission, OPV remains the primary tool for polio eradication *(16)*. To facilitate polio eradication, efforts are under way to develop improved IPVs that confer mucosal immunity and safer oral vaccines using genetically-stable approaches or non-infectious virus-like particles. If successful, these new products will address the persistent risk of vaccine-derived poliovirus.

Pneumococcus

Pneumococcal conjugate vaccines (PCVs) have been introduced in 134 countries, averting an estimated 250 000 pneumococcal deaths globally from 2000 to 2015 *(17)*. Limited serotype replacement has been observed: non-vaccine-type invasive pneumococcal disease has increased after PCV introduction, but increases are small compared to the sustained decline in vaccine-type disease *(18)*. GVIRF participants described two future directions in pneumococcal vaccination. The first optimizes the number of doses and their schedule to improve sustainability without sacrificing impact. Current data suggest that a two-dose primary series followed by a booster dose may provide better herd protection than the WHO-recommended three-dose primary series, and that a single primary immunization followed by a booster dose may be sufficient to maintain herd immunity. Additional studies are under way to evaluate alternative dosing regimens *(19–21)*. The second targets new vaccines that expand protection and prevent serotype replacement. Candidates in development include higher-valency PCVs and protein or whole-cell vaccines that could have broad efficacy against all serotypes *(22)*.

Rotavirus

There are now seven licensed rotavirus vaccines and they are in use in about half of all countries. Their efficacy among children aged under 5 years is inversely related to the under-five mortality rate: these vaccines reduced rotavirus acute gastroenteritis hospitalizations and emergency department visits by 71% in countries with low child mortality and by 46% in countries with high child mortality *(23)*. GVIRF participants emphasized the importance of understanding how the gut environment influences responses to rotavirus vaccines, in order to improve vaccine performance. Non-replicating injectable vaccines, which may have better performance in all settings, are in development as an alternative approach to improving efficacy in countries with high child mortality *(22)*.

Pandemic influenza

Coordinated global efforts are under way to improve pandemic influenza preparedness. The WHO *Pandemic Influenza Risk Management* guideline recommends that countries implement a risk-based and integrated approach to pandemic influenza preparedness *(24)*. More than half of countries, however, do not have publicly-available national preparedness plans, and many existing plans are outdated or incomplete. In the event of a pandemic there are multiple challenges to an effective response, including the significant delay between the start of the pandemic and the first availability of vaccine, and the limited global vaccine manufacturing capacity. To address delays in vaccine availability, universal influenza vaccines are in development as described above. To address the capacity shortage and ensure national and regional supply, several developing countries have been partnering with WHO to build domestic influenza vaccine manufacturing capacity; six have achieved approval or conducted clinical trials of pandemic influenza vaccines *(25)*.

New vaccines

Full public health value propositions

Given limited resources, competing priorities and alternative interventions for treatment or prevention, value propositions for new vaccines

are an increasingly important decision tool. Full public health value propositions are intended to help funders, manufacturers and countries set investment priorities by describing the role of a new vaccine in the context of an overall disease control strategy, providing an end-to-end review of evidence and presenting a comprehensive analysis of the value of a vaccine. Full public health value propositions go beyond the customary perspective of direct individual health benefits and capture the full economic and societal benefits of vaccination. They identify evidence gaps that must be addressed, such as operational research needs for products with complex delivery requirements *(26)*"ISSN" : "0264410X", "abstract" : "There is an enhanced focus on considering the full public health value (FPHV. Full public health value propositions are being developed for vaccine targets such as Group B Streptococcus, enterotoxogenic *E. coli*, and herpes simplex virus, among additional propositions being considered.

Respiratory syncytial virus

Three approaches are being pursued for protection of neonates and infants against RSV: maternal immunization during pregnancy; infant immunization shortly after birth; and passive immunization with mAbs. The most advanced maternal vaccine candidate is being evaluated in a Phase III efficacy trial with interim results expected in 2019 (NCT02624947). Infant immunization strategies are in earlier phase studies. Extended half-life mAbs for passive immunization are under development. As these products approach licensure, policy considerations such as the minimum acceptable efficacy, the effects of seasonality, the impact of concurrent conditions such as HIV infection on effectiveness of maternal immunization, and the delivery capacity of health systems must be addressed.

Antimicrobial resistance

Vaccines for frequently resistant pathogens can prevent infections, reduce antimicrobial use, promote antibiotic stewardship and limit the emergence and spread of antimicrobial resistance *(27–29)*. As presented at GVIRF, new vaccines targeting *Pseudomonas, Staphylococcus aureus,* and uropathogenic *E. coli* are in development to prevent human diseases that drive antibiotic consumption *(30–32)*. Participants observed that identifying and reaching the appropriate target populations for such vaccines may be challenging, especially given the low coverage achieved for well-established vaccines such as influenza and called on one another to: define and communicate the value of vaccines to combat antimicrobial resistance; identify populations who would benefit most; and consider affordability and accessibility in low- and middle-income countries.

Other diseases

Vaccines against human hookworm and hepatitis C virus are in development, and early stage clinical trials are currently under way. In parallel, value propositions that describe how the vaccines will be used in disease control strategies, and the costs and benefits of the proposed interventions are being developed, make the case for further clinical development and commercialization of these new vaccines.

4) Conclusions

Every two years, GVIRF takes stock of global research in vaccines and immunization. The 2018 GVIRF highlighted the power of vaccines to improve health and facilitate development, and showcased the energy and creativity of immunization stakeholders worldwide. However, challenges remain and innovation is urgently needed to improve access to vaccines and primary health care. GVIRF participants highlighted two factors as crucial to meeting this need: a focus on equity and sustainability throughout the immunization ecosystem, and an enabling political environment that prioritizes health and immunization.

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II

TRACKING RESOURCES INVESTED IN IMMUNIZATION: REPORT ON HEALTH ACCOUNTS ACTIVITIES

Background

Health accounts provide information on the magnitude of countries' total resources for health and the flow of those resources – from their source to the actual use of services[1]. Based on an international framework released in 2011 – the System of Health Accounts (SHA)[2] – health accounts, among other insights for decision-making, allow for the collection and analysis of disease expenditure amounts including those for priority programmes and intervention areas such as immunization.

The World Health Organization (WHO) is the leading agency providing in-country technical support and capacity-building activities to technicians from the ministry of health for the regular production and use of good-quality SHA-2011-based expenditure estimates. Over the past five years (by the end of 2017), those efforts have led to the release of at least one year of country-produced health-account estimates in 81 low- and middle-income countries – out of which nearly half are from Africa (38). Yet, only 36% of them had detailed immunization expenditures for publication in the Global Health Expenditure Database (GHED)[3], a database that WHO maintains in parallel to its support to the data production work. For more information, see http://apps.who.int/nha/database/Home/Index/en.

Unless otherwise specified all estimates and calculations are from 2015. Country "expenditure on immunization" encompasses monies spent on both routine- and campaign-related activities.

Results

In terms of representativeness, African countries are heavily represented accounting for 76% of the 29 country-immunization expenditures posted on GHED[4] – the seven non-African countries constituting the other 24% are Bhutan, Bosnia and Herzegovina, Cambodia, Lao People's Democratic Republic, Tajikistan, Tunisia[5] and Samoa. This only reflects the fact that SHA-2011 methodology's uptake has been greater in the African Region from the beginning. Thus, since mastering all the elements of the production process can take four to five years, low- and middle-income countries from other parts of the world are lagging a bit behind at the moment. In 2017 preliminary results for 29 countries were released, while further efforts are still being made to improve the data quality. As a result of the quality ascertainment process ongoing for a couple of years, countries in the database can end up with one to six years of immunization expenditure estimates – Gabon and Nigeria are the only two with complete data series across the 2010–2015 period.

It is worth noting that the expenditure estimates are presented by funding source only – namely from external origin and from public domestic sources. The total amount incurred for immunization in a given country-year is not made available as the part funded by private domestic sources (out-of-pocket mainly) is being questioned in terms of both underlying methods and relevance.

In summary, the median per capita spending on immunization from external origin is estimated at US$ 4.6 per capita for the population aged under 5 years whereas the value of the corresponding amount funded from public domestic sources' is US$ 2.3 only. Mauritania, Sierra Leone and the Democratic Republic of Congo, by decreasing order, are proportionally receiving the most – with up to US$ 14.2 spent on immunization programmes per child[6] originating from abroad[7]. On the other end, Uganda, Guinea-Bissau and Chad have not attracted – or are not reporting[8] – as much international funding for immunization, all laying below US$ 2 per capita spent in the population aged under 5 years.

Given the small number of countries currently reporting data, it was not possible to produce an analysis by country groups on level of income.

Next steps

Currently the remaining country-produced estimates are being refined and made publication-ready. This process will increase data quality and usefulness in better informing policy-makers and stakeholders at country and global levels.

In the future it is expected that health accounts data from additional countries will be received on

1 Meaning each expenditure line can be traced back to its origin (external, domestic public, or domestic private) as well as to its end use (curative services, prevention, or admin. and governance for example).
2 A system of Health Accounts 2011: revised edition. Paris: Organisation for Economic Co-operation and Development/Eurostat/World Health Organization: 2017 (https://doi.org/10.1787/9789264270985-en, accessed 19 September 2018).
3 The database, updated on a yearly basis (with the addition of T-2 estimates each December), contains data points from the year 2000 onwards for 190+ countries.
4 The total list of countries with immunization expenditure estimates available is as follows: Benin, Bhutan, Bosnia and Herzegovina, Botswana, Burkina Faso, Burundi, Cambodia, Chad, Congo, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Ghana, Guinea, Guinea-Bissau, Lao People's Democratic Republic, Malawi, Mauritania, Namibia, Niger, Nigeria, Samoa, Sao Tome and Principe, Seychelles, Sierra Leone, Tajikistan, Tunisia, United Republic of Tanzania and Uganda.
5 North African countries such as Tunisia are grouped in the Eastern Mediterranean Region in the WHO regional classification system.
6 In this chapter "per child" refers to children aged under 5 years.
7 All estimates and calculations are from 2015 or from the latest available year – namely 2014 for Mauritania, Namibia and Tunisia; 2013 for Botswana, Burundi, Sao Tome & Principe and Sierra Leone; and, 2011 for Chad and Guinea Bissau.
8 As it could be the case in Chad. Further refinement and analysis are under way for that particular country.

a yearly basis. This will allow for an analysis with greater granularity, showing patterns related to immunization programme financing.

One equally important task will be to compare the immunization-related data collected via WHO/SHA-2011 with that reported through the UNICEF-WHO Joint Reporting Form (JRF)[9] mechanism and analyse convergence of data and inconsistencies across datasets and improve overall data quality. To this end, strengthening (or establishing where it is yet to exist) concrete collaborative work between SHA technicians and the Expanded Programme on Immunization (EPI) managers at country level will be key. In the context of a strong focus on universal health coverage it is foreseeable that the WHO/SHA-2011 mechanism will be another useful tool to inform immunization policies and support programmes.

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[9] http://www.who.int/immunization/programmes_systems/financing/data_indicators/en/

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III

INDEPENDENT SUBMISSION FROM THE GAVI CSO CONSTITUENCY AND STEERING COMMITTEE

Gavi CSO Constituency
for Immunisation and Stronger Health Systems

Helping to reach Every Child with Immunisation and Health Services

Introduction

The 2016 Midterm Review of the Global Vaccine Action Plan (GVAP) by the Strategic Advisory Group of Experts on Immunization (SAGE) noted significant concern that at the midpoint of the GVAP (2012-2020), progress towards reaching goals to eradicate vaccine-preventable diseases (VPD) and increase access to vaccines is too slow – with the global average for immunization coverage growing at only 1% since 2010.[1] The report highlighted that only 16 countries have made measurable progress since 2010 including countries with the highest numbers of unvaccinated people – Democratic Republic of the Congo, Ethiopia and India.

Serious efforts on the part of all immunization partners will be needed to reach the GVAP goals by 2020 for all countries. To help guide this effort, the SAGE made nine recommendations with specific sub-recommendations attached to each. As part of recommendation five to, "Enhance accountability mechanisms to monitor implementation of Global and Regional Vaccine Action Plans," the SAGE specifically recommended that "Civil society organizations should describe how their work maps against different national immunization plans in their 2017 GVAP report, so that the geographic and programmatic scope of their work is more visible. Where possible, CSOs should also measure and share the impact of their work."

The Gavi CSO Constituency and Steering Committee welcomed the above SAGE recommendation and in response led the development of a "CSO reporting framework" with the input of WHO, UNICEF, Gavi, members of the SAGE GVAP reporting working group, and a wide range of immunization actors. This effort has culminated in the development of a set of tools to be used by CSOs at the country level to report their attributable contributions to their country's National Immunization Plan, and, by proxy, to the GVAP. In-country testing should take place in 2 pilot countries in 2018.

The purpose of this year's independent civil society report is to:

1. Highlight key findings from the 2017 Gavi CSO Constituency Survey
2. Provide a set of recommendations for CSO engagement in immunization programmes

In 2018, the survey was conducted in 22 focus countries. These include countries from three WHO regions:

1. Africa region (AFRO) – Benin, Burkina Faso, Cameroon, Chad, Côte d'Ivoire, DRC, Ethiopia, Ghana, Guinea, Kenya, Liberia, Madagascar, Malawi, Mali, Nigeria, Sierra Leone, Togo, Uganda and Zambia
2. Eastern Mediterranean (EMRO) – Pakistan
3. South East Asia (SEARO) – India
4. Region of the Americas (PAHO)- Haiti

Methodology

The Gavi CSO Constituency Coordinator and the Gavi CSO Steering Committee provided guidance and received the survey report from CRS.

For the 2018 survey, CRS improved the data quality and shortened the data collection timeline by (1) using an online data collection tool; and (2) hiring and supervising in-country enumerators. CRS trained in-country focal points via pre-recorded videos and webinars. The focal point in each country then oversaw the enumerator training and the collection and uploading of data via an online data collection tool.

Action	Responsible	Jan	Feb	March	April	May
Introduce survey process and rationale	CRS					
Conduct pilot test	CRS					
Communicate the survey process and share tools and dates	CRS					
Train focal points	CRS					

[1] 2016 Midterm Review of the Global Vaccine Action Plan: Strategic Advisory Group of Experts on Immunization - http://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/

Action	Responsible	Jan	Feb	March	April	May
Train enumerators	Survey focal points					
Data collection	Enumerators + survey focal points					
Online data entry	CRS					
Compile and analyse data	CRS					
Report back on results	CRS					

2017 Gavi CSO Constituency Survey

The Gavi Civil Society Organization (CSO) Constituency Platforms Project (Gavi CSO Project) supports the establishment of national civil society platforms in Gavi-priority countries around the world. These platforms advocate for improved immunization coverage and stronger health systems within their countries. Catholic Relief Services (CRS) manages the Gavi CSO Platforms Project, with oversight and technical support provided by the Gavi CSO Constituency Steering Committee's Oversight and Advisory Group.

Because information on the civil society contribution to immunization is helpful to the CSO platforms' advocacy and coordination efforts, in February-April 2018, CRS surveyed project-supported CSO networks in 22 countries, Benin, Burkina Faso, Cameroon, Chad, DRC, Ethiopia, Ghana, Guinea, Haiti, India, Ivory Coast (Côte d'Ivoire), Kenya, Liberia, Madagascar, Malawi, Mali, Nigeria, Pakistan, Sierra Leone, Togo, Uganda and Zambia, to demonstrate the contributions that CSOs made in 2017 towards the global immunization goals detailed in the Global Vaccine Action Plan (GVAP).

The survey questionnaire focused on:

1. The number of people CSOs immunized;
2. The number of people CSOs educated about vaccines; and
3. How CSOs are contributing to the Global Vaccine Action Plan (GVAP).

Summary of Key Results

A total of 1,463 CSOs in 22 countries responded, for a response rate of 99%. In 2017, they had the following achievements:

- CSOs reached 418,048 communities with immunization sensitization and mobilization messages.
- CSOs reached 83,747,025 communities with immunization sensitization and mobilization messages.
- CSOs administered at least one vaccine to 3,399,465 male children and 3,566,478 female children.
- CSOs administered at least one vaccine to 92,564 adult males and 1,326,801 adult females.
- 64% of the CSOs reported having come across children who had never been vaccinated.
- The most commonly reported reasons for children not being fully immunized were: lack of awareness of need for vaccination; lack of faith in immunization; rumors; caregiver busy; immunization services too far; child ill; other children never vaccinated.
- 35% of the CSO respondents have been conducting immunization activities for 1--5 years.
- 98% of the CSOs are registered with their government.
- Only 3% of the CSOs self-identify as religious organizations.

Overall Detailed Survey Results

For this year's CSO independent submission, several key results from the survey are summarized in the Tables below. It is important to note that the majority of CSOs self-identified primarily as community associations and nongovernmental organizations (NGOs) although the other choices for types of organizations, including academia, charity, professional association, advocacy group, foundation and religious organization, also applied. The survey defined a community association as "a nongovernmental association of participating members of a community, such as a neighborhood, village, condominium, cooperative, or group of homeowners or property owners in a delineated geographic area." An NGO was defined in the survey as a non-profit organization that is independent from states and international governmental organizations; usually funded by donations but some avoid formal funding altogether and are run primarily by volunteers. The majority of the CSOs self-identified as a Community Association, Charity or NGO.

Responses to survey questions were based on the perspectives and experiences of the individual completing the survey on behalf of his/her CSO.

Table 1: CSOs participating in the 2018 Gavi CSO Constituency Survey (in # and % as indicated)

Country	Active CSOs	Planned	Actual	Percent achievement
Benin	50	50	50	100%
Burkina Faso	38	38	34	89%
Cameroon	163	102	102	100%
Chad	70	70	70	100%
Cote d'Ivoire	Unknown	102	102	100%
DRC	98	62	62	100%
Ethiopia	24	24	20	83%
Ghana	253	105	101	96%
Guinea	330	100	100	100%
Haiti	23	23	23	100%
India	194	158	158	100%
Kenya	14	14	12	86%
Liberia	25	25	25	100%
Madagascar	50	50	50	100%
Malawi	31	31	31	100%
Mali	82	82	82	100%
Nigeria	41	41	40	98%
Pakistan**	81	107	107	100%
Sierra Leone	219	146	146	100%
Togo	17	17	17	100%
Uganda	168	103	103	100%
Zambia	30	30	26	87%
Total	**2001**	**1480**	**1463**	99%

** Pakistan interviewed 20 CSOs who were not platform members but who were active in immunization in Pakistan

Never-vaccinated children

More than eighty percent (80%) of the CSOs in Cameroon, DRC, Ethiopia, Haiti, Kenya, Liberia, Madagascar and Nigeria had encountered children who had never been vaccinated. Surprisingly given their low immunization rates, **Mali (29.3%)** and **Chad (31.4%)** had the fewest number of CSOs reporting encounters with never-vaccinated children.

When encountering a never-vaccinated child, 93 percent (93.1%) of respondents reported that they counselled the caregivers on the importance of immunization. Fifty-seven percent (57.2%) initiated an immunization catch up schedule.

Table 2: CSOs encountering children who had never been vaccinated, and their follow up actions (in %)

Country	% of CSOs that have encountered a never-vaccinated child	% of CSOs that have NOT encountered a never vaccinated child	Action taken by CSO		
			Initiated an immunization catch up schedule	Referred to health center	Counselled caregiver
Benin	34.0	66.0	15.2	81.8	78.8
Burkina Faso	29.4	70.6	29.2	75.0	91.7
Cameroon	8.8	91.2	53.8	91.4	93.5
Chad	68.6	31.4	36.4	68.2	86.4
Cote d'Ivoire	35.3	64.7	60.6	86.4	98.5
DRC	12.5	87.5	64.3	91.1	92.9
Ethiopia	20.0	80.0	68.8	68.8	93.8
Ghana	32.7	67.3	83.8	94.1	95.6
Guinea	24.0	76.0	23.7	53.9	92.1
Haiti	17.4	82.6	5.3	57.9	94.7
India	46.2	53.8	48.2	92.9	96.5
Kenya	8.3	91.7	36.4	72.7	72.7
Liberia	12.0	88.0	72.7	100.0	81.8
Madagascar	8.0	92.0	47.8	84.8	93.5
Malawi	41.9	58.1	44.4	50.0	72.2
Mali	70.7	29.3	70.8	79.2	95.8
Nigeria	15.0	85.0	82.4	97.1	97.1
Pakistan	38.3	61.7	62.1	93.9	95.5
Sierra Leone	47.3	52.7	92.2	94.8	93.5
Togo	23.5	76.5	46.2	100.0	100.0
Uganda	48.5	51.5	67.9	90.6	96.2
Zambia	26.9	73.1	78.9	94.7	94.7
Total	**36%**	**64%**	57%	85%	93%

Reasons for non-vaccination

Based on their experiences and interactions with communities, CSOs listed and ranked the reasons children are unvaccinated or incompletely immunized. These were due to a (1) **lack of**

information (Table 3a); and (2) **other obstacles** (Table 3b).

Table 3a: CSOs reporting children were never vaccinated due to lack of information (%)

Country	Unaware of need for vaccination	Place and/ or time for immunization unknown	Fear of side reactions	Wrong ideas/ perceptions about contraindications	Misunderstanding of the available information
Benin	57.6	39.4	84.8	60.6	60.6
Burkina Faso	70.8	29.2	70.8	75.0	79.2
Cameroon	81.7	51.6	86.0	87.1	80.6
Chad	63.6	27.3	81.8	86.4	86.4
Cote d'Ivoire	83.3	43.9	72.7	75.8	89.4
DRC	62.5	33.9	53.6	46.4	44.6
Ethiopia	75.0	68.8	62.5	68.8	68.8
Ghana	77.9	63.2	73.5	80.9	76.5
Guinea	60.5	7.9	85.5	84.2	75.0
Haiti	68.4	68.4	52.6	57.9	57.9
India	92.9	35.3	90.6	78.8	77.6
Kenya	100.0	81.8	90.9	100.0	90.9
Liberia	68.2	90.9	90.9	81.8	86.4
Madagascar	84.8	52.2	80.4	87.0	65.2
Malawi	55.6	44.4	55.6	66.7	77.8
Mali	37.5	33.3	33.3	37.5	50.0
Nigeria	55.9	47.1	76.5	79.4	50.0
Pakistan	98.5	84.8	84.8	90.9	84.8
Sierra Leone	64.9	68.8	90.9	96.1	77.9
Togo	69.2	38.5	76.9	92.3	76.9
Uganda	52.8	49.1	50.9	60.4	52.8
Zambia	63.2	36.8	68.4	73.7	73.7
Total	73%	49%	77%	78%	73%

Table 3b: CSOs reporting children were not vaccinated due to other obstacles (%)

Country	Place of immunization too far	Time of immunization inconvenient	Vaccinator absent	Vaccine Unavailable	Caregiver busy	Family problems, including illness of caregiver	Child ill, not brought	Child ill, brought but not given vaccine	Long waiting time
Benin	63.6	21.2	24.2	24.2	45.5	21.2	33.3	21.2	27.3
Burkina Faso	37.5	70.8	16.7	33.3	62.5	37.5	62.5	37.5	70.8
Cameroon	48.4	39.8	10.8	36.6	66.7	38.7	58.1	22.6	50.5
Chad	45.5	9.1	4.5	45.5	13.6	4.5	45.5	13.6	45.5
Cote d'Ivoire	65.2	47.0	12.1	43.9	74.2	47.0	62.1	31.8	62.1
DRC	32.1	26.8	25.0	35.7	53.6	37.5	37.5	25.0	25.0
Ethiopia	93.8	62.5	50.0	62.5	56.3	50.0	56.3	31.3	50.0
Ghana	64.7	66.2	35.3	47.1	52.9	45.6	51.5	26.5	48.5
Guinea	13.2	14.5	3.9	2.6	56.6	31.6	77.6	2.6	11.8
Haiti	84.2	52.6	68.4	78.9	84.2	73.7	52.6	36.8	57.9
India	60.0	18.8	21.2	20.0	51.8	70.6	77.6	57.6	17.6
Kenya	90.9	72.7	54.5	72.7	72.7	81.8	63.6	36.4	63.6
Liberia	86.4	81.8	77.3	68.2	86.4	77.3	68.2	45.5	95.5
Madagascar	73.9	63.0	45.7	21.7	67.4	52.2	80.4	58.7	56.5
Malawi	44.4	38.9	33.3	38.9	27.8	44.4	44.4	22.2	44.4
Mali	25.0	41.7	12.5	33.3	33.3	29.2	29.2	25.0	25.0
Nigeria	55.9	52.9	17.6	29.4	32.4	41.2	52.9	26.5	35.3
Pakistan	87.9	77.3	59.1	65.2	63.6	71.2	80.3	53.0	50.0
Sierra Leone	84.4	76.6	31.2	36.4	75.3	44.2	39.0	10.4	79.2
Togo	61.5	15.4	0.0	92.3	46.2	15.4	23.1	23.1	76.9
Uganda	67.9	30.2	20.8	34.0	52.8	64.2	54.7	37.7	37.7
Zambia	78.9	31.6	5.3	21.1	26.3	63.2	42.1	36.8	36.8
Total	60%	45%	26%	37%	58%	48%	58%	31%	45%

Reasons for children not being fully immunized

The previous section was concerned with children who had never been vaccinated. This section focuses on why children are not fully immunized. The reasons given in both sections were similar. In both, the survey listed reasons in three categories: 1) lack of information (Table 4); 2) lack of motivation (Table 5); and 3) other obstacles (Table 6).

Table 4: CSOs reporting children were not fully vaccinated due to lack of information (%)

Country	Unaware of need for vaccination	Unaware of need to return for 2nd or 3rd dose	Place and/ or time of immunization unknown	Wrong ideas/ perceptions about contraindications	Misunderstanding of the available information
Benin	58.0	44.0	32.0	64.0	56.0
Burkina Faso	76.5	44.1	38.2	79.4	91.2
Cameroon	80.4	68.6	39.2	83.3	84.3
Chad	35.7	31.4	14.3	62.9	45.7
Cote d'Ivoire	71.6	49.0	42.2	80.4	86.3
DRC	54.7	35.9	32.8	46.9	43.8
Ethiopia	65.0	60.0	50.0	55.0	55.0
Ghana	63.4	69.3	53.5	73.3	58.4
Guinea	53.0	54.0	14.0	89.0	64.0
Haiti	65.2	73.9	60.9	60.9	73.9
India	88.6	90.5	25.3	86.7	84.8
Kenya	83.3	83.3	33.3	100.0	83.3
Liberia	80.0	76.0	68.0	80.0	80.0
Madagascar	84.0	68.0	66.0	86.0	72.0
Malawi	64.5	45.2	41.9	58.1	54.8
Mali	14.6	24.4	23.2	34.1	41.5
Nigeria	47.5	42.5	32.5	85.0	77.5
Pakistan	86.0	75.7	75.7	89.7	87.9
Sierra Leone	37.0	51.4	41.8	93.2	55.5
Togo	76.5	58.8	41.2	70.6	76.5
Uganda	48.5	59.2	40.8	70.9	49.5
Zambia	42.3	57.7	19.2	65.4	61.5
Total	61%	58%	39%	76%	67%

Table 5: CSOs reporting children not fully vaccinated due to lack of motivation (%)

Country	No faith in immunization (cultural/religious reasons)	Personal grudges between caregiver and vaccinator	Postponed until another time	Rumors
Benin	78.0	22.0	28.0	74.0
Burkina Faso	73.5	17.6	44.1	82.4
Cameroon	90.2	39.2	52.0	90.2
Chad	30.0	2.9	12.9	52.9
Cote d'Ivoire	70.6	14.7	75.5	80.4
DRC	71.9	28.1	39.1	75.0
Ethiopia	20.0	25.0	35.0	50.0
Ghana	54.5	28.7	59.4	63.4
Guinea	83.0	29.0	31.0	91.0
Haiti	43.5	52.2	69.6	73.9
India	57.6	10.8	49.4	80.4
Kenya	100.0	16.7	50.0	91.7
Liberia	60.0	44.0	52.0	88.0
Madagascar	78.0	42.0	72.0	92.0
Malawi	45.2	16.1	22.6	38.7
Mali	48.8	24.4	24.4	72.0
Nigeria	70.0	15.0	50.0	80.0
Pakistan	79.4	48.6	72.9	87.9
Sierra Leone	56.2	30.1	73.3	58.9
Togo	70.6	23.5	47.1	76.5
Uganda	67.0	22.3	39.8	50.5
Zambia	84.6	23.1	53.8	69.2
Total	65%	26%	50%	74%

Table 6: CSOs reporting children were not fully vaccinated due to other obstacles (%)

Country	Place of immunization too far	Time of immunization inconvenient	Vaccinator Absent	Vaccine not available	Caregiver busy	Family problems, including illness of caregiver	Child ill, not brought	Child ill, brought but not given vaccine	Long waiting time
Benin	80.0	24.0	14.0	14.0	36.0	20.0	30.0	24.0	40.0
Burkina Faso	35.3	79.4	14.7	38.2	52.9	44.1	67.6	32.4	52.9
Cameroon	54.9	39.2	10.8	41.2	62.7	43.1	52.0	18.6	47.1
Chad	18.6	2.9	1.4	15.7	24.3	14.3	31.4	4.3	15.7
Cote d'Ivoire	65.7	48.0	16.7	31.4	67.6	48.0	62.7	34.3	56.9
DRC	37.5	21.9	20.3	29.7	43.8	31.3	34.4	23.4	31.3
Ethiopia	70.0	55.0	45.0	55.0	40.0	45.0	55.0	25.0	35.0
Ghana	69.3	67.3	29.7	48.5	62.4	50.5	44.6	26.7	53.5
Guinea	18.0	14.0	9.0	9.0	51.0	33.0	74.0	5.0	13.0
Haiti	91.3	56.5	65.2	82.6	82.6	87.0	65.2	43.5	69.6
India	44.3	43.0	22.8	34.2	69.0	80.4	88.6	63.3	22.8
Kenya	91.7	75.0	50.0	66.7	58.3	100.0	66.7	33.3	75.0
Liberia	64.0	76.0	32.0	60.0	80.0	76.0	64.0	52.0	80.0
Madagascar	82.0	66.0	50.0	32.0	76.0	52.0	82.0	68.0	62.0
Malawi	74.2	45.2	29.0	38.7	25.8	48.4	45.2	19.4	51.6
Mali	36.6	36.6	13.4	29.3	19.5	23.2	22.0	14.6	24.4
Nigeria	57.5	50.0	17.5	22.5	40.0	45.0	52.5	35.0	47.5
Pakistan	88.8	81.3	64.5	66.4	72.9	68.2	75.7	61.7	68.2
Sierra Leone	68.5	75.3	32.2	21.9	68.5	35.6	28.8	9.6	62.3
Togo	76.5	41.2	5.9	82.4	52.9	23.5	23.5	17.6	76.5
Uganda	68.9	47.6	25.2	41.7	54.4	68.0	59.2	39.8	36.9
Zambia	65.4	34.6	19.2	23.1	30.8	53.8	42.3	23.1	53.8
Total	58%	48%	25%	35%	56%	49%	55%	31%	44%

Service recipients

CSOs were also asked to report on the number of individuals and communities they reached with community sensitization and/or mobilization services for immunization in 2017 (Table 7).

CSOs were also asked to report on the number of children and adults they vaccinated with at least one vaccine in 2017 (Table 8). ***Note that CSOs were not able to capture the number of individuals who were sensitized/mobilized by CSOs but vaccinated by a non-CSO.***

Table 7: Number of communities and individuals reached by CSOs with sensitization or mobilization services in 2017

Country	Number of communities reached with community sensitization and/or mobilization for immunization	Number of individuals reached with community sensitization and/or mobilization for immunization
Benin	6,314	315,997
Burkina Faso	3,422	312,703
Cameroon	5,946	1,443,023
Chad	52,734	240,381
Cote d'Ivoire	30,578	8,528,082
DRC	2,812	29,157,636
Ethiopia	90,379	5,324,324
Ghana	5,429	444,113
Guinea	2,181	8,758,059
Haiti	228	15,985
India	113,552	9,909,001
Kenya	152	668,023
Liberia	6,547	25,952
Madagascar	7,567	2,415,698
Malawi	19,576	402,327
Mali	1,822	27,781
Nigeria	342	70,178
Pakistan	49,518	12,037,734
Sierra Leone	6,970	2,250,137
Togo	2,635	744,097
Uganda	9,140	548,435
Zambia	204	107,359
Total	418,048	83,747,025

Table 8: Number of individuals vaccinated by CSOs in 2017

Country	Number of individuals vaccinated by CSOs				TOTAL vaccinated
	Children		Adults		
	Male	Female	Male	Female	
Benin	27,818	34,706	913	11,129	74,566
Burkina Faso	7,084	7,243	1,648	4,013	19,988
Cameroon	54,616	55,483	13,263	22,663	146,025
Chad	7,953	6,528	292	3,203	17,976
Cote d'Ivoire	133,542	131,967	2,207	161,696	429,412
DRC	58,557	93,302	26,121	96,461	274,441
Ethiopia	2,048,031	2,143,793	18	201,554	4,393,396
Ghana	23,972	64,296	7,750	9,413	105,431
Guinea	11,355	16,268	500	1,162	29,285
Haiti	690	642	-	2,032	3,364
India	133,212	123,136	19,000	156,157	431,505
Kenya	28,143	30,925	103	1,976	61,147
Liberia	4,250	9,286	2,362	3,879	19,777
Madagascar	8,831	11,471	1,233	541	22,076
Malawi	3,759	6,555	1,760	1,630	13,704
Mali	-	-	-	-	
Nigeria	3,752	4,657	1,024	2,705	12,138
Pakistan	596,679	510,976	5,000	626,915	1,739,570
Sierra Leone	7,379	21,936	1,048	703	31,066
Togo	7,527	9,642	1,464	4,429	23,062
Uganda	229,886	280,418	6,401	13,913	530,618
Zambia	2,429	3,248	457	627	6,761
Total	3,399,465	3,566,478	92,564	1,326,801	8,385,308
Grand Total	6,965,943		1,419,365		

CSO activities

The survey asked CSOs a series of Yes/No questions about their involvement in specific, pre-defined activities that were organized around GVAP strategic objectives (SO) 1-4. For SO1, CSOs mostly carried out immunization-related information sharing; a lesser number of organizations participated in national-level discussions on immunization and health. For SO2, CSOs indicated that most of their activities were in community education on immunization followed by advocacy directed at local and national authorities. For SO3, CSOs mainly mobilized communities and raised awareness and interest in immunization through sensitization and education, and to a lesser extent they directly administered vaccines. Finally, for SO4, CSOs mostly tracked community members who had defaulted on their immunization schedule. Country-by-country details for each SO and related activities are provided in Tables 9-12 below.

Table 9: Strategic Objective 1: All countries commit to immunization as a priority (% CSOs responding yes)

Country	Participate in national-level discussions on immunization and health	Share immunization-related information with other CSOs	Joint planning with local, district or national level EPI
Benin	40.0	92.0	44.0
Burkina Faso	79.4	88.2	64.7
Cameroon	31.4	82.4	48.0
Chad	40.0	72.9	30.0
Cote d'Ivoire	48.0	75.5	58.8
DRC	68.8	93.8	62.5
Ethiopia	95.0	85.0	90.0
Ghana	62.4	88.1	77.2
Guinea	27.0	93.0	44.0
Haiti	39.1	100.0	26.1
India	23.4	93.0	55.1
Kenya	58.3	83.3	91.7
Liberia	92.0	96.0	88.0
Madagascar	56.0	64.0	52.0
Malawi	51.6	77.4	67.7
Mali	79.3	100.0	96.3
Nigeria	45.0	97.5	92.5
Pakistan	70.1	84.1	71.0
Sierra Leone	63.0	96.6	81.5
Togo	52.9	82.4	94.1
Uganda	57.3	93.2	92.2
Zambia	76.9	92.3	88.5
Total	52%	88%	66%

Table 10: Strategic Objective 2: Individuals and communities understand the values of vaccines and demand immunization as both their right and responsibility (% CSOs responding)

Country	Educate communities, households, and individuals on immunization	Advocate to local, district or national level leaders and policy makers	Conduct social research to improve immunization services
Benin	94.0	64.0	42.0
Burkina Faso	94.1	79.4	20.6
Cameroon	95.1	71.6	48.0
Chad	71.4	51.4	31.4
Cote d'Ivoire	92.2	57.8	34.3
DRC	95.3	81.3	40.6
Ethiopia	70.0	80.0	50.0
Ghana	90.1	85.1	46.5
Guinea	95.0	77.0	29.0
Haiti	87.0	47.8	34.8
India	98.1	53.8	24.1
Kenya	91.7	91.7	50.0
Liberia	100.0	92.0	32.0
Madagascar	92.0	86.0	72.0
Malawi	93.5	83.9	29.0
Mali	96.3	100.0	78.0
Nigeria	100.0	97.5	72.5
Pakistan	92.5	80.4	39.3
Sierra Leone	97.9	93.2	30.8
Togo	100.0	70.6	52.9
Uganda	95.1	91.3	47.6
Zambia	96.2	76.9	46.2
Total	94%	77%	41%

Table 11: Strategic Objective 3: The benefits of immunization are equitably extended to all people (% CSOs responding)

Country	Work with underserved and marginalized groups to increase their interest and ability to access vaccination	Address gender-related barriers to immunization	Mobilize communities to participate in vaccination campaigns or other immunization related events	Administer vaccines to underserved and marginalized populations (routine vaccination)	Administer vaccines to underserved and marginalized populations (vaccine campaigns)
Benin	78.0	58.0	70.0	18.0	16.0
Burkina Faso	88.2	91.2	94.1	14.7	17.6
Cameroon	76.5	68.6	83.3	11.8	12.7
Chad	52.9	68.6	67.1	17.1	17.1
Cote d'Ivoire	75.5	61.8	68.6	14.7	14.7
DRC	87.5	78.1	87.5	28.1	26.6
Ethiopia	80.0	65.0	55.0	20.0	20.0
Ghana	88.1	86.1	88.1	29.7	37.6
Guinea	89.0	92.0	87.0	2.0	19.0
Haiti	60.9	65.2	95.7	8.7	8.7
India	93.7	94.3	95.6	5.1	4.4
Kenya	100.0	58.3	83.3	41.7	41.7
Liberia	76.0	72.0	92.0	40.0	44.0
Madagascar	72.0	52.0	94.0	20.0	20.0
Malawi	77.4	74.2	90.3	16.1	22.6
Mali	96.3	100.0	98.8	9.8	8.5
Nigeria	92.5	82.5	97.5	32.5	32.5
Pakistan	82.2	82.2	94.4	49.5	57.9
Sierra Leone	95.9	72.6	95.2	5.5	5.5
Togo	88.2	100.0	100.0	41.2	41.2
Uganda	90.3	89.3	95.1	18.4	17.5
Zambia	84.6	84.6	88.5	26.9	23.1
Total	85%	79%	88%	18%	20%

Table 12: Strategic Objective 4: Strong immunization systems are an integral part of a well-functioning health system (% CSOs responding)

Country	Administer vaccines to populations that are NOT underserved or marginalized (routine vaccination)	Track and follow up with defaulters	Train health care workers or volunteers in immunization-related topics	Assist in transporting vaccines from center to administration site
Benin	14.0	42.0	42.0	12.0
Burkina Faso	14.7	58.8	55.9	11.8
Cameroon	11.8	91.2	81.4	13.7
Chad	8.6	30.0	35.7	2.9
Cote d'Ivoire	16.7	62.7	60.8	13.7
DRC	23.4	76.6	60.9	18.8
Ethiopia	20.0	50.0	85.0	60.0
Ghana	25.7	78.2	74.3	55.4
Guinea	4.0	76.0	36.0	59.0
Haiti	8.7	30.4	26.1	17.4
India	3.8	57.6	72.8	8.2
Kenya	33.3	50.0	83.3	41.7
Liberia	40.0	80.0	76.0	32.0
Madagascar	18.0	76.0	42.0	50.0
Malawi	12.9	54.8	41.9	45.2
Mali	8.5	93.9	64.6	91.5
Nigeria	30.0	90.0	87.5	37.5
Pakistan	39.3	65.4	74.8	40.2
Sierra Leone	5.5	58.9	13.0	11.6
Togo	47.1	94.1	88.2	17.6
Uganda	16.5	66.0	55.3	46.6
Zambia	19.2	57.7	50.0	61.5
Total	16%	67%	57%	32%

Participation in the national immunization plan and familiarity with the GVAP

The survey sought to establish how familiar CSOs are with the GVAP, to what extent they have participated in the development of national immunization plans, and how often they have been invited to meetings where the national immunization plan was presented or discussed.

- CSOs in Chad, Guinea and Haiti were least familiar with the GVAP.
- CSOs in Ethiopia and Togo were most familiar with the GVAP.
- CSOs in Guinea and Haiti were least involved in developing their national immunization plan.
- More than half the CSOs in Kenya, Liberia and Mali were involved in the development of their national immunization plan.
- More than 75 percent of CSO respondents in Burkina Faso, Ethiopia, Kenya, Liberia, Madagascar, Mali and Sierra Leone were invited to meetings where their national immunization plan was presented or discussed. - CSOs in Chad, India and Zambia had the lowest invitation rates.

Table 13: CSOs reporting familiarity with the GVAP, participating in national plan development, and invited to attend meetings where the national immunization plan was presented or shared (%)

Country	CSOs familiar with the GVAP	CSO participating in development of national immunization plan	CSOs invited to a meeting where the national immunization plan was discussed
Benin	44.0	16.0	40.0
Burkina Faso	61.8	41.2	82.4
Cameroon	30.4	19.6	25.5
Chad	15.7	25.7	20.0
Cote d'Ivoire	20.6	14.7	43.1
DRC	46.9	45.3	50.0
Ethiopia	85.0	55.0	75.0
Ghana	49.5	30.7	63.4
Guinea	22.0	13.0	44.0
Haiti	13.0	13.0	30.4
India	61.4	19.6	24.1
Kenya	58.3	58.3	91.7
Liberia	76.0	76.0	84.0
Madagascar	40.0	48.0	78.0
Malawi	35.5	25.8	51.6
Mali	30.5	96.3	93.9
Nigeria	75.0	22.5	40.0
Pakistan	55.1	34.6	45.8
Sierra Leone	69.2	41.1	77.4
Togo	94.1	17.6	35.3
Uganda	39.8	47.6	51.5
Zambia	73.1	42.3	23.1
Total	46%	34%	51%

Limitations

1. CRS had limited information on platform membership in Cameroon, Cote d'Ivoire, DRC and Guinea. This made it difficult to accurately calculate the sample size.
2. Responses, including quantitative data, were self-reported and not independently verified.
3. The survey did not reach every CSO active in immunization in the target countries, therefore the results lack an accurate denominator and are illustrative only.

Conclusion

The survey affirmed the wide geographic presence of CSOs in each country. The contributions of CSOs include advocacy for immunization services to government; education and awareness creation about immunization to the communities, mobilization of communities to utilize vaccination services and participation in immunization program activities to catalyze the achievement of the strategic objects of GVAP.

This survey also highlights the role of CSOs predominantly in demand promotion, social mobilisation, community engagement, reducing vaccine hesitancy, awareness raising and behaviour change communications. A large number of CSOs are working on the administration of vaccines as well in areas where government service delivery is weak.

Key Recommendations

CSOs should consider using these survey results to design behavior change messages that target the reasons for their communities' vaccine hesitancy.

CSO platforms should sensitize their members to the Global Vaccine Action Plan and other global action frameworks.

CSO platforms should improve on their efforts to sensitize their governments to the need to utilize CSOs' capacities to improve vaccine uptake in the communities.

The findings of the survey could be utilised as an evidence of CSOs contribution for immunization and CSOs could be engaged for low immunization coverage areas at the country level.

Actual field coverage surveys could be designed in areas where CSOs have actively contributed for demand promotion and social mobilisation to demonstrate CSOs contribution.

IV

INDEPENDENT SUBMISSIONS

American Red Cross - Independent Submissions from other Stakeholders

Cotonou, Benin - 2017 - © WHO / AFRO

In 2017 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) in four countries Burundi, Malawi, Indonesia, and Senegal, as well as a Periodic Intensification of Routine Immunization (PIRI) activity in Benin. These campaigns focused on mobilizing Red Cross volunteers to conduct house to house visits in targeted areas. The volunteers were recruited and mobilized from within each community to provide a built-in level of trust that enables them to better engage community members and increase demand through education and encouragement. The table below provides an overview of the activities conducted in each of the supported countries.

National Society Supported by American Red Cross	Intervention*	Number of Subnational Areas Targeted	Households Visited	Number of Volunteers Recruited	Targeted Population
Benin Red Cross Society	PIRI	2	177,590	500	209,758
Burundi Red Cross Society	MR SIA	3	153,489	4,600	585,000
Malawi Red Cross Society	MR SIA	6	601,385	2,600	3,287,832
Indonesia Red Cross	MR SIA	5	623,063	1,696	2,700,000
Senegal Red Cross	MR SIA	1	513,521	1,100	426,073
Total		**17**	**2,069,048**	**10,496**	**7,208,663**

**M = measles vaccine; MR = combined measles rubella vaccine; PIRI = Periodic Intensification of Routine Immunization*

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 a formal analysis with the U.S. Centers for Disease Control and Prevention to conduct an impact evaluation to better quantify these results.

Network for Education and Support in Immunisation (NESI)

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, particularly in low- and middle-income countries. Through partnerships with WHO, Gavi, academic institutions, Ministries of Health and other interested parties, NESI focuses on capacity building, education and training, and institutional strengthening, in order to complete its mission.

During 2017, NESI contributed to two of the six Strategic Objectives of the Global Vaccine Action Plan.

SO1: Country ownership – *Strengthen national capacity to formulate evidence-based policies.*

Two regional forums with peer-to-peer exchange of information, best practices and tools related to new and under-utilised vaccine introduction were organised:

- Co-organiser and presenter at stakeholders meeting "Strengthening capacity on new vaccine introduction in the Middle East: varicella vaccination", Amman, Jordan (January 2017). Organised in collaboration with the University of Jordan and EMPHNET/GHD.
- Co-organiser and presenter at workshop "The role of the NITAGs in strengthening routine immunisation and new vaccine introduction: varicella vaccine as a case study", Amman, Jordan (May 2017). Organised in collaboration with the University of Jordan and EMPHNET/GHD.

SO4: Strong immunisation systems – *Strengthen capacity of managers and frontline workers.*

NESI's pre- and in-service training programmes are tailored to the needs of the immunisation programmes in the respective partner countries, with country ownership as guiding principle.

In-service training:

In-service courses are key to building national vaccinology expertise by: (1) strengthening the capacity of academics in vaccinology and to guide NITAGs and policy-makers to make evidence-based recommendations and decisions on vaccines and immunisation; (2) strengthening the capacity of EPI managers, EPI staff and community health workers in efficient management of immunisation programmes and maintaining public trust through effective communication with individuals and communities.

- Co-organiser and co-facilitator in "TropEd Advanced Vaccinology Course", Berlin, Germany (January 2017), as partner of the Institute of Tropical Medicine and International Health.
- Co-organiser and co-facilitator in "Regional capacity building workshop on EPI/IMCI interactive training and resource tool", Kigali, Rwanda (May-June 2017), as partner of WHO/AFRO.
- Development of training modules on "Pneumococcal disease and PCV new multi-dose vial presentation", in collaboration with WHO/HQ. These training modules can be used by any country switching from the PCV mono- or two-dose vial to the four-dose vial presentation. http://www.nesi.be/content/pneumococcal-vaccine-0
- Validation of training modules, developed by the EBODAC consortium, for mobile training and support service for community health workers in Sierra Leone.
- Supported the development of a training DVD "Formation sur la vaccination pour les professionnels de santé" in Morocco, developed by the Societé Marocaine d'Infectiologie Pédiatrique et de Vaccinologie (SOMIPEV) and Université Cadi Ayyad.

Pre-service training:

Pre-service health training institutions are crucial in delivering medical and nursing staff deployable in immunisation programmes. Clinical and public health training that incorporates the learning objectives of EPI will enable students to develop a firm basis of EPI core knowledge and skills.

Country support given to Indonesia, Kenya and Morocco to strengthen EPI training at medical faculties and nursing schools.

Supported "National EPI prototype curriculum induction workshop" at Kenya Medical Training College, Mombasa, Kenya (November 2017).

Save the Children (SC) contribution to GVAP implementation – 2017/2018

Contribution to GVAP goal/ objective	Intervention/activity	Country examples	Other comments
Goals: 1 SOs: 2	The CORE Group Polio Project (CGPP) is a multi-country initiative, supported by USAID and BMGF. SC CGPP staff are supported by in-country CGPP secretariats, which are supported by the global secretariat, hosted by World Vision.	SC is currently active in CGPP in Nigeria and Ethiopia: Nigeria: The project currently supports 22 primary health care facilities in four LGAs of Katsina state, which achieved 91% OPV3 and Penta3 coverage in March 2018. Ethiopia: SC is supporting CGPP work in five Woredas in Somali Region. The project focuses on maintaining high levels of surveillance to detect potential importations or outbreaks, high levels of routine and supplementary vaccination coverage to protect the country from importations, and a strong outbreak response plan to implement in case of an importation.	
Goals: 3 SOs: 2, 3, & 4	TA for micro-planning & community mobilization activities to increase demand.	Mali: The USAID-funded Services de Santé à Grand Impact (SSGI) consortium are working together to scale up increased and sustained use of high impact health services and healthy behaviors. During the 12-month period of October 2016 through September 2017, 363,223 infants received Penta 3 by 12 months of age, 99% of the target. SSGI supports vaccination activities in districts that have the lowest immunization rates. Technical assistance is being given to strengthen micro-planning for EPI.	
Goals: 3 & 4 SOs: 5 & 6	Use of an SMS-based, open-source, web-accessible logistics management information system to reduce stock-outs of immunization supplies.	Malawi: Since 2014, with funding from the Pfizer Foundation, SC has been supporting the MOH to improve coverage of immunization and uptake of family planning services through implementation of an Integrated Family Planning and Immunization Project. Pilot implementation of EPI cStock in two districts demonstrated significant improvement in the stock status of essential EPI supplies, and no reported stock-outs of vaccines, as well as timely reporting of EPI supplies and products. cStock is an SMS-based, open-source, web-accessible logistics management information system for community-level health products developed by John Snow International (JSI) in collaboration with the Malawi MOH.	

Contribution to GVAP goal/ objective	Intervention/activity	Country examples	Other comments
Goals: 3 SOs: 2, 3, & 4	Support local jurisdictions to improve immunization coverage.	Kenya: The USAID-supported Afya County and National Support Program started working with the Kenyan MOH and four focus counties of Kitui, Migori, Kakamega, and Kisumu in late 2017 to support the delivery of quality, integrated services in family planning, RMNCAH, nutrition, and WASH. SC is leading the project's child health work, which includes support to improve immunization coverage. Immunization activities at the household level will include health education, defaulter tracing, and referral. At the community level, outreach to hard-to-reach areas will be supported, including efforts to identify and immunize unvaccinated children. At the sub-county and county levels, the project will support EPI managers to ensure availability of vaccines and other supplies, strengthening of the cold chain, and ensuring data-driven activity planning and budgeting.	

GVAP goals: (1) Achieve a world free of polio; (2) Meet global and regional elimination targets; (3) Meet vaccination coverage targets in every region, country and community; (4) Develop and introduce new and improved vaccines and technologies; (5) Exceed the Millennium. GVAP strategic objectives: (1) Ensuring country ownership (2) Demand for immunisation (3) The benefits of immunisation are equitably extended to all people (4) Strong immunisation systems are an integral part of a well-functioning health system (5) Stock-outs and access to sustained supply of vaccines of assured quality (6) country, regional and global research and development innovations maximise the benefits of immunisation (7) Access to sustainable financing and supply for immunisation.

The Task Force for Global Health Global Vaccine Action Plan (GVAP) Survey Project – Phase II Intermediate Report

Background: In 2016, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) determined that the pace of global progress must increase if all of the GVAP targets are to be achieved by 2020. With support from the U.S. Centers for Disease Control and Prevention (CDC), The Task Force for Global Health (TFGH) developed a two-phase project to learn more from global, regional, and national immunization stakeholders about how to achieve greater progress toward the GVAP goals. Phase I involved surveying global stakeholders; results were summarized in 2017. Development of Phase II surveys received input from Gavi, the Vaccine Alliance, the United Nations Children's Fund (UNICEF), and the WHO. This report summarizes intermediate results of the Phase II surveys.

Methodology: The Phase II survey was initially designed for Expanded Programme on Immunization (EPI) managers from 18 countries (n=18). Countries were selected based on differences in DPT3 coverage 2010-2016 and a population size >4 million. 23 countries listed in the SAGE midterm report were classified as 'improving' based on 35% increase in DPT3 coverage–of these, eight were selected (Azerbaijan, Costa Rica, the Democratic Republic of Congo, Ethiopia, India, Philippines, the United Republic of Tanzania, and Zambia). 21 countries were classified as 'declining' (35% decrease) and of these, eight were selected (Angola, Brazil, Guatemala, Kazakhstan, Panama, Pakistan, Nigeria, and Ukraine). In addition, because of the large number of unvaccinated children in each, Afghanistan (+2%) was categorized as an improving country and Indonesia (-2%) as a declining country. The survey was then modified for WHO Regional Advisors (n=6), WHO country representatives (n=18), and UNICEF country representatives or Health Chiefs (n=18). Surveys included closed-ended (e.g., multiple choice, matrix) and open-ended questions and were carried out by telephone, email, or Survey Monkey.

Results: As of 30 June 2018, 13/18 country EPI managers (72%), 4/6 Regional Advisors (67%), and 13/36 WHO and UNICEF country representatives (36%) have responded. The surveys remain open until August 1st and a significant number of additional responses are expected. Full survey and interview questions are shown in Appendices I-III. An overview of the results obtained thus far from an initial analysis of closed-ended questions is shared below.

Usefulness of SAGE-recommended activities: All 30 respondents were asked to indicate how useful each of the 22 activities (based on recommendations in the SAGE midterm or 2017 assessment report) are or would be for achieving greater progress toward the GVAP goals, using a scale from 1 (not useful) to 5 (very useful). Based on weighted averages, the most useful activities (in rank order) from responses thus far are:

1. Getting Ministers of Health and Finance and other political leaders to become stronger advocates of immunization (notably, 83% of respondents indicated this activity as "very useful")
2. Improved monitoring of vaccination coverage
3. Upgrading surveillance systems (e.g., disease detection, data reporting)

Perceived utility of activities was generally similar between improving and declining countries and by job role. Almost all respondents indicated each listed activity as somewhat useful (4) or very useful (5). Of 12 technical assistance activities that international partner agencies could provide to country immunization programs, the perceived most useful are:

1. How to strengthen surveillance and reporting systems and data quality
2. How to monitor vaccine supply and delivery (e.g., cold chain evaluation)
3. How to better educate EPI professionals (e.g., a high-level vaccinology course)

Challenges faced by country immunization programs: All 30 respondents were asked to indicate the severity of 26 managerial, operational, and technical challenges that country immunization programs may have faced in recent years in trying to achieve the GVAP goals, using a scale from 1 (not a challenge) to 5 (major challenge). Overall, the three most severe challenges indicated are:

1. Being able to effectively reach mobile and/or underserved populations with vaccination
2. Getting the needed level of financial support from domestic private partners for program implementation
3. Other surveillance and reporting system issues (e.g., lack of good diagnostics, issues with specimen shipping, lack of lab supplies)

Wide distributions were observed for many respondent answers, which may cause weighted averages to be misleading and mask substantial differences among countries. These distributions are understandable given the diversity across the six WHO regions and 18 selected countries and will be analyzed in the final report. Responses were generally similar when stratified by country category and respondent job role, with a few exceptions. Challenges for which there was a 31 point difference (on a 5-point scale) between respondents from declining and improving countries (greater magnitude of differences listed first) include:

- *Greater challenge indicated among respondents from improving countries*— 1) Getting the needed level of financial support from domestic private partners for vaccine procurement, 2) Getting the needed level of financial support from domestic private partners for program implementation, and 3) Getting the needed level of financial support from the national government for program implementation
- *Greater challenge indicated among respondents from declining countries*— 1) Vaccine shortages and stockouts, not including global shortages and 2) Vaccine supply shortages and stockouts (including diluents, syringes, safety boxes, registries)

Challenges for which there was a 31 point difference between 1) EPI managers and 2) Regional Advisors and WHO/UNICEF country representatives include:

- *Greater challenge indicated between Regional Advisors and WHO/UNICEF country representatives compared to EPI managers*— 1) Getting the needed level of political will and commitment for program funding, 2) Being able to show the value and outcome of immunization program activities, 3) Being able to effectively reach mobile and/or underserved populations with vaccination activities, and 4) Being able to quickly and effectively respond to vaccine-preventable disease cases and outbreaks

Priorities of country immunization programs: All EPI managers indicated that the GVAP "accelerated the implementation of [their] immunization activities" (n=13). Seven WHO/UNICEF country representatives indicated likewise but five indicated that the GVAP "had no influence on the direction or pace of [their] immunization activities" (n=13). Country EPI managers and WHO/UNICEF country representatives were asked to indicate their top immunization program priorities (based on the GVAP and GVAP-related goals), using a scale from 1 (not a priority) to 5 (major program priority). So far, the top three program priorities are:

1. Eliminating rubella or maintaining rubella elimination
2. Eliminating measles or maintaining measles elimination (notably, receiving the highest percentage of "major priority (i.e., score of 5)" votes [80% of respondents])
3. Eliminating polio or maintaining polio-free status and ensuring virus containment

Almost all respondents indicated nine listed program priorities, developed from the GVAP indicators, as a priority (4) or a major priority (5). Perceived importance of program activities was generally similar between improving and declining countries and by job role.

Conclusion: There was general concordance between respondents from improving and declining countries and by job role, with apparent differences noted above. Further analysis will include additional responses and open-ended questions, including critical concerns in planning the new GVAP strategy.

For more information, contact:

World Health Organization
Department of Immunization, Vaccines and Biologicals
1211 Geneva 27
Switzerland

E-mail: vaccines@who.int
Web: www.who.int/immunization/global_vaccine_action_plan/en/