Status Report on Progress Towards Measles and Rubella Elimination

SAGE Working Group on Measles and Rubella (17 October 2013)

Contents

I. Introduction

The updated WHO position papers on use of measles vaccines (2009) and rubella vaccines (2011) both made significant policy advances. Since 2011, 9 countries have introduced rubella vaccine in their national immunization programme and 13 countries are planning introduction in 2014 or 2015. As the world moves towards universal use of combined measles-rubella (MR) and measles-mumps-rubella (MMR) vaccines, there is need to integrate the existing recommendations on use of measles and rubella vaccines and address policy gaps that have been raised by countries. In addition, with the changing epidemiology of measles and rubella, there is a need to provide more specific guidance on appropriate target age range for supplementary immunization activities (SIAs) using MR vaccine or single-antigen measles (M) vaccine. This report provides an update on progress towards global control and regional elimination targets, the evidence to support draft policy recommendations on the use of MR vaccine for both doses in the routine immunization schedule, criteria for when to expand the target age range for SIAs using M and MR vaccines, draft recommendations for vaccination of health workers, and a prioritized list of research topics to address barriers to measles and rubella elimination.

SAGE is being asked to review this report, provide guidance on how to get back on track to achieving global and regional targets, decide whether the available evidence supports more specific recommendations on both the use of MR and M vaccines and on vaccination of health care workers, and discuss the prioritized list of research topics.

II. Current global and regional targets

Global targets

Millennium Development Goal 4 aims to reduce deaths among children overall by two thirds by 2015 compared with the level in 1990. Worldwide, the mortality rate for children under five dropped by 41% - from 87 deaths per 1,000 live births in 1990 to 51 in 2011.[1] Accelerated measles control activities have contributed an estimated 23% of the overall reduction in <5 year child mortality between 1990 and 2008.[2] Despite these enormous accomplishments, if current trends continue, the 2015 MDG4 target will not be met and 19 countries[3] are experiencing no decline, or an increase in <5 year child mortality.[4]

[1] The Millennium Development Goals Report 2013, accessed on 9 October 2013 at: http://www.un.org/millenniumgoals/pdf/report-2013/mdg-report-2013-english.pdf

[2] Van den Ent, M, et al. Measles mortality reduction contributes substantially to reduction in all-cause mortality among children less than 5 years of age, 1990-2008. J Infect Dis 2011,204:S18-S23

[3] Afghanistan, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, the Democratic Republic of the Congo (DRC), Equatorial Guinea, Gabon, Guinea-Bissau, Iraq, Kenya , Lesotho, Mali, Mauritania, Papua New Guinea, Somalia, Swaziland

[4] The Second Report of the independent Expert Review Group (iERG) on Information and Accountability for Women's and Children's Health, accessed on 9 October 2013 at http://www.who.int/woman_child_accountability/ierg/news/ierg_2013_report_launch/en/index3.html

In May 2010, Member States at the World Health Assembly (WHA) established the following measles control targets to be achieved by 2015 as milestones towards the future eradication of measles:

- achieve ≥90% coverage with the first dose of measles-containing vaccine nationally and ≥80% vaccination coverage in every district or equivalent administrative unit
- reduce annual measles incidence to less than five cases per million and maintain that level
- reduce measles mortality by 95% or more in comparison with 2000 estimates.

At the WHA in May 2012, the Global Vaccine Action Plan (GVAP) of the Decade of Vaccines was endorsed. One of the four high level goals in GVAP is meeting global and regional elimination targets and the target for measles and rubella is to achieve elimination in at least 5 WHO Regions by 2020. These GVAP measles and rubella elimination targets are closely aligned with the targets in the Global Measles and Rubella Strategic Plan, 2012-2020 which was endorsed by SAGE at their November 2012 meeting. The Global Measles and Rubella Strategic Plan includes a five-pronged strategy to: 1) achieve and maintain high levels of population immunity by achieving ≥95% vaccination coverage in all districts with two doses of measles- and rubella-containing vaccines; 2) monitor disease using effective surveillance, and evaluate programmatic efforts; 3) develop outbreak preparedness and respond rapidly to outbreaks; 4) communicate and engage to build public confidence and demand for immunization; and 5) perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

Regional targets

On 13 September 2013, the 11 Member States of the South East Asian Region (SEAR) of WHO endorsed a resolution to eliminate measles and accelerate control of rubella/CRS by 2020. With this decision, all six WHO regions now have measles elimination targets. The Region of the Americas (AMR) achieved its target in 2002. The target dates for the other Regions are Western Pacific Region (WPR) (2012), European (EUR) and Eastern Mediterranean Regions (EMR) (2015) and the African (AFR) and South East Asian Regions (2020).

Four of the six WHO regions have set control or elimination targets for rubella. The Americas targeted rubella and congenital rubella syndrome (CRS) elimination by 2010 and achieved this in 2009, one year ahead of schedule. The European Region aims to eliminate rubella by 2015. The Western Pacific and South East Asian Regions aim to have significantly accelerated rubella control and CRS prevention by 2015 and 2020, respectively. The African and Eastern Mediterranean Regions have yet to establish rubella control or elimination goals.

While the GVAP goals for measles and rubella elimination match the WHO Regional targets for 2015, that is measles elimination in 4 Regions (AMR, EUR, EMR and WPR) and rubella elimination in 2 Regions (AMR and EUR), there is a lack of specificity with respect to the 2020 GVAP goals. Four Regions still need to establish target dates for rubella elimination and it is not explicit as to which Region is not included in the 2020 target date for elimination of measles and rubella.

III. Progress Towards Global Targets

- Good progress towards the global 2015 targets has been made with coverage with the first dose of measles-containing vaccine (MCV1) increasing from 73% in 2000 to 84% in 2012. However MCV1 coverage has remained at 84% for the past 4 years and 34% of Member States are yet to reach at least 90% MCV1 coverage. 74% of Member States have a second dose of measles-containing vaccine (MCV2) offered through routine services reaching 56% coverage in target-aged children in 2012. SIAs reached 112 million children in 2012.
- Since 2000, after setbacks in 2010 and 2011, reported measles incidence decreased by 77% to 33 cases per million population in 2012. 63% of Member States have achieved the 2015 global incidence target of measles incidence <5 per million population. From 2000–2011, estimated measles deaths decreased by 71% globally.
- 69% of Member States provide at least one dose of rubella-containing vaccine (RCV) in their national immunization programme and reported rubella cases have decreased by 83% since 2000.
- In November 2012, SAGE concluded that despite this progress, based on current trends and programme performance, the 2015 global targets as well as regional elimination targets in 4 out of 6 WHO Regions will *not* be achieved on time.

Immunization Activities

During 2000–2009, estimated global MCV1 coverage increased from 73% to 84% and has leveled off at 84% from 2009 to 2012. By 2012, 3 of the 6 WHO regions (AMR, EUR, and WPR) had achieved ≥90% estimated MCV1 coverage (Table).

The proportion of all Member States with ≥90% MCV1 coverage increased from 43% in 2000 to 66% in 2012. Since 2010, notable progress was seen in the Western Pacific, the American and European Regions. However, both African and the Eastern Mediterranean Regions have shown a decline in the proportion of Member States with ≥90% MCV1 coverage from 2010 to 2012 (see Figure below)

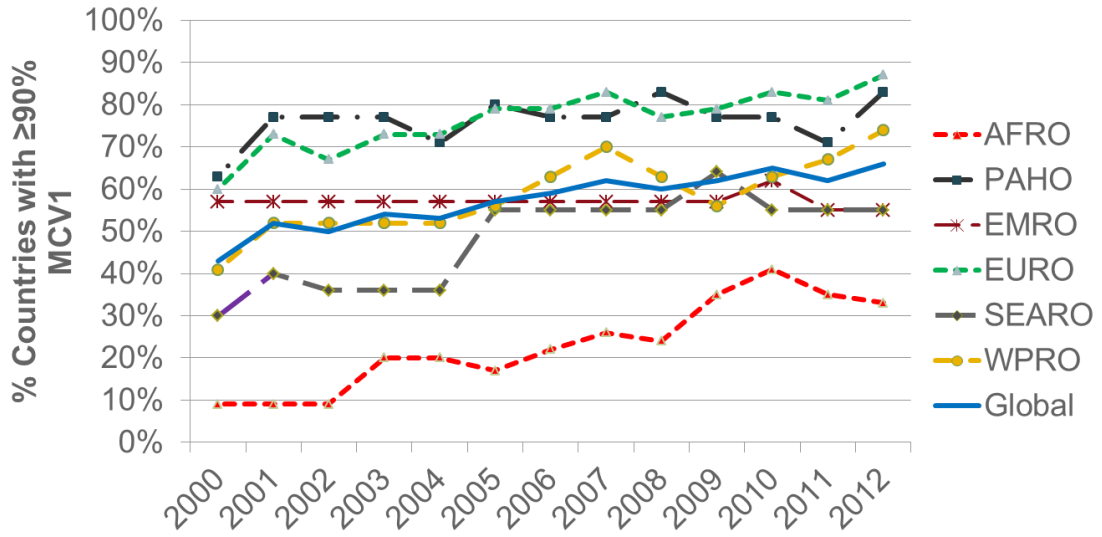


Figure: Proportion of countries with ≥ 90% MCV1 coverage by WHO Region and Globally, 2000-2012

In 2012 based on country administrative data, only (58 countries) 37% of all Member States achieved the target of exceeding 80% MCV1 coverage in every district showing a slow but steady increase over the past 10 years. Progress can be seen for Western Pacific, the South East Asia and European Regions with only modest improvements in the African and American Regions. However, the Eastern Mediterranean Region has been declining since 2009.

Of the estimated 21 million children who never received MCV1 in 2012, 13.5 million (64%) were in just 6 Member States: India (6.4 million), Nigeria (3.8 million), Ethiopia (1 million), Indonesia (0.9 million) Pakistan (0.7 million) and the Democratic Republic of the Congo (DRC) (0.7 million).

By 2012 MCV2 was offered through routine services in 147 (75%) Member States, ranging from 12 (26%) of 46 countries in the African Region to 53 (100%) of the countries in the European Region.

By 2012 coverage with MCV2 in target-aged children, based on administrative records, was reported to WHO and UNICEF by 137 (92%) Member States with coverage of 56%, up from 13% in 2000.

During 2000–2012, over one billion children received a measles vaccination through SIAs. During 2012, based on reports by Member States to WHO, 32 measles SIAs reached >112 million children. Reported coverage was >95% for 20 (63%) of SIAs with 14 (44%) Member States conducting coverage surveys to validate coverage. Of the 32 SIAs, 7 were MR SIAs and 26 have integrated at least one other child health intervention (e.g. OPV, bed nets, de worming and Vitamin A).

By 2012, 132 (68%) Member States were providing at least one dose of RCV, up from 99 (52%) in 2000. Though rubella coverage is almost identical to that of measles, as all Member States provide rubella vaccine combined with measles or measles and mumps vaccines, regional and global coverage is much lower as not all Member States use the vaccine.

The proportion of Member States having introduced rubella vaccine by 2012 ranged from 7% in the African Region to 100% of Member States in the American and European Regions.

Disease Surveillance

The number of Member States annually reporting measles surveillance data to WHO and UNICEF increased from 169 (88%) in 2000 to 187 (93%) in 2012 and for rubella from 102 (53%) in 2000 to 174 (90%) in 2012. Effective measles and rubella surveillance includes establishing case-based surveillance with laboratory testing of persons with suspected measles, rubella or the syndrome of acute rash and fever to confirm cases and outbreaks and to identify measles and rubella virus genotypes. By 2012, 183 (94%) Member States had implemented case-based surveillance, up from 120 (62%) in 2004. In addition, the number of Member States supported with standardized quality-controlled measles and rubella testing by the WHO Measles and Rubella Laboratory Network had increased to 184 (95%) from 71 (37%) in 2000. Though 128 (66%) of Member States reported data on congenital rubella syndrome (CRS) in 2012, up from 75 (39%) Member States in 2000, few cases of CRS are reported, as described below.

During 2000–2012, the number of global reported measles cases reached its lowest levels ever decreasing by 75% from 853,480 to 227,335 cases and measles incidence decreased 77% from 146 to 33 cases per million population, with all WHO regions reporting decreases in case numbers and incidence (see Figure and Table).

From 2000-2008, the number of global reported measles cases decreased; however, from 2008 to 2009, overall global reported measles cases remained stable, with increases in the African Region (AFR) from 37,012 to 83,479 and in the EMR from 12,120 to 36,605 balanced by a decrease in the WPR from 147,987 to 66,609.

From 2009 to 2010, global reported measles cases increased to 342,107. Decreases in WPR to 49,460, in EMR to 10,072, and in the SEAR from 84,356 to 52,529 were offset by increases in AFR to 199,174 and in the EUR from 7,499 to 30,625.

From 2010 to 2011, global reported measles cases increased to 354,882. Further decreases in WPR to 21,050 were offset by increases in the other regions: EMR to 35,923, SEAR to 65,161, AFR to 194,364 and EUR to 37,073 (Figure).

From 2011 to 2012 the global number of cases of measles decreased to 227,335 with a decrease in all regions but EMR. Globally, the percentage of Member States with reported measles incidence <5 cases per million population increased from 38% in 2000 to 63% in 2012.

Table. Estimates of coverage with the first dose of measles-containing vaccine administered through routine immunization services among children aged 1 year, reported measles cases and incidence by WHO region, 2000 & 2012. Estimated measles deaths globally and by WHO Region for 2000 & 2011.

	2000					2012						2011
WHO region	**% coverage with the first dose of measles-containing vaccine [a]**	**Number of reported measles cases [b]**	**Measles incidence (cases per million population) [c d]**	**% Member States with incidence <5 per million [d]**	**Estimated Measles Deaths (95% CI)**	**% coverage with the first dose of measles-containing vaccine [a]**	**Number of reported measles cases [b]**	**% decline from 2000**	**Measles incidence (cases per million population) [c d]**	**% decline from 2000**	**% Member States with incidence <5 per million [d]**	**Estimated Measles Deaths (95% CI) and [% decrease since 2000]**
African	53	520,102	841	8	338,500 (216,300-736,100)	73	106,052	80	124.94	85	39	55,200 (22,600-338,400) [84%]
Americas	93	1,755	2	89	<100	94	88	95	0.09	96	100	<100
Eastern Mediterranean	72	38,592	90	17	59,600 (31,600-100,500)	83	36,456	6	59.53	34	41	30,200 (19,000-55,800) [49%]
European	91	37,421	50	48	400 (140-2,400)	94	27,030	28	36.92	26	74	140 (16-1,800)[62%]
South-East Asia	65	78,558	51	0	137,100 (94,800-205,300)	78	46,945	40	25.61	50	36	70,700 (51,800-100,400)[48%]
South-East Asia (excluding India)	77	39,723	80	0	48,800 (23,700-97,300)	88	28,277	29	47.39	41	40	14,500 (8,000-30,000) [70%]
India	59	38,835	37	0	88,300 (71,100-108,000)	74	18,668	52	15.1	59	0	56,200 (43,800-70,300)[36%]
Western Pacific	85	177,052	105	30	12,800 (4,200-64,600)	97	10,764	94	5.86	94	70	1,300 (180-43,900)[90%]
Total	**73**	**853,480**	**146**	**38**	**548,300 (347,000-1,108,900)**	**84**	**227,335**	**75**	**33.33**	**77**	**63**	**157,700 (93,600-540,300)[71%]**

a Coverage data: WHO/UNICEF estimates of national immunization coverage. Geneva, World Health Organization, 2013 (update of 13 July 2013).
b Reported case data: Measles reported cases. Geneva, World Health Organization, 2012 (update of 13 July 2013) Americas data for 2012 from Measles/rubella/congenital rubella syndrome surveillance data final classification, 2012. (update 25 September 2013) (http://ais.paho.org/phip/viz/im_vaccinepreventablediseases.asp, accessed 8 October 2013).Kenya data for 2013 from WHO / AFRO"
c Population data: United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Prospects: The 2012 Revision, CD-ROM Edition
d Any Member State not reporting data on measles cases for that year were removed from the denominator

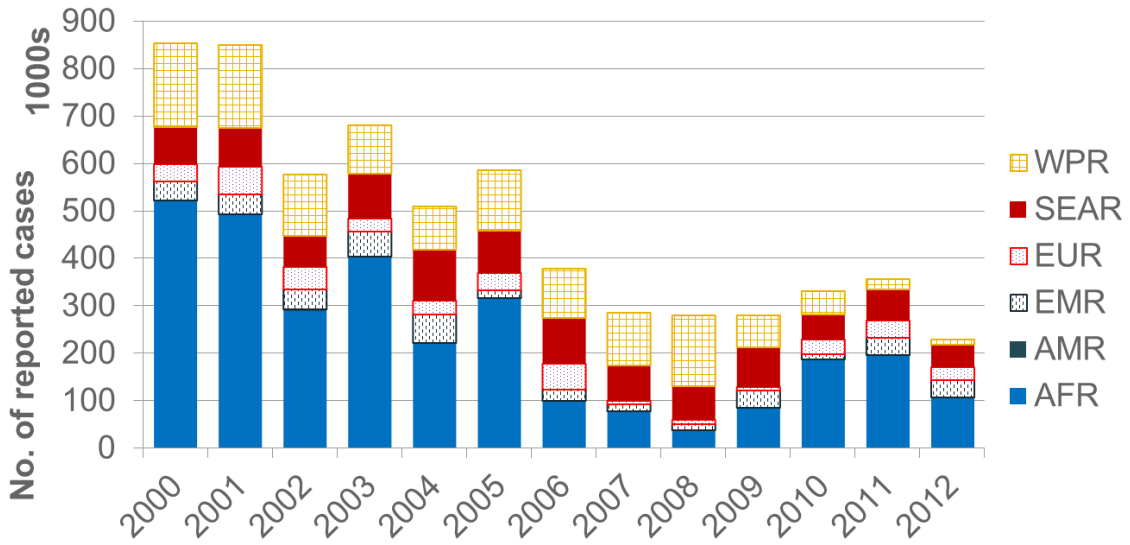


Figure: Reported measles cases by WHO Region, 2000-2012

In 2012, a number of Member States experienced large measles outbreaks which in some cases have been ongoing since 2011 or before. These include: DRC (134,042 cases in 2011 and 73,794 in 2012), Nigeria (8,491 cases in 2010; 18,843 in 2011; and 19,062 in 2012), India (18,668 in 2012), Pakistan (14, 984 in 2012), Ukraine (12, 744 in 2012); Somalia (17,298 cases in 2011 and 9,983 in 2012), Indonesia (9,429 in 2012), China (6,183 in 2012), Sudan (8,523 in 2012), Angola (4,442 in 2012), Ethiopia (4,235 cases in 2010; 3,255 in 2011 and 4,347 in 2012) and Romania (4,271 in 2012). The outbreaks were primarily due to low MCV1 coverage or due to suboptimal or delayed SIAs. In areas of high reported coverage, outbreak investigations found that susceptible individuals had accumulated over several years among adolescents and adults who had missed vaccination, thus high reported national routine or SIA coverage had masked subnational immunity gaps.

During 2000–2012, global reported rubella cases decreased 83% from 670,894 to 93,990. However, these numbers should be interpreted with caution because rubella is grossly under-reported particularly in Member States not using rubella vaccine. The greatest decrease in reported rubella cases was a 95% decrease in the European Region, from 804,567 to 30,509, and a 99.9% decrease in the Americas, from 39,228 in 2000 to only 5 cases in 2012. In other regions the number of cases increased during this period in parallel with the increase in the number of Member States reporting rubella cases. Compared to rubella fewer Member States report CRS cases, though the number increased from 75 (39%) in 2000 to 128 (66%) in 2012. The number of reported CRS case is very low, with 297 reported CRS cases in 2012 which is a reflection of poor or no CRS surveillance and low reporting.

Disease Burden Estimates

During 2000–2011, estimated measles deaths decreased by 71% from 548 300 to 157 700, and all Regions plus India had substantial reductions in estimated measles mortality ranging from 36% to 90%.

In 2011, estimated global measles mortality increased from the 2010 estimate and 99% of the measles mortality burden was in AFR, EMR, and SEAR. In India, the 36% decrease in estimated measles mortality during 2001–2011 was mainly due to the National Measles Catch-up Programme to provide MCV2, beginning in 2010 with MCV2 introduction in routine services in states with reported MCV1 coverage ≥80%, and with SIAs followed by MCV2 introduction in routine services in states with reported MCV1 coverage <80%.

While surveillance for rubella has improved over the past decade, only a small proportion of CRS cases are reported. Disease modelling studies suggest that the burden of CRS has been stable from 1996 to 2008, dropping slightly from 120,342 estimated cases in 1996 to 111,888 in 2008.

Draft Recommendations

- For elimination, Member States need to achieve ≥95% coverage nationally and in every district with 2 doses of MCV either through routine services and/or SIAs. The elimination effort should continue to be used as a mechanism for strengthening routine coverage in every district.
- In order to align regional goals with the GVAP goal of achieving measles and rubella elimination in at least five WHO regions by 2020, encourage Regions that have not yet established rubella elimination goals (AFR, EMR, SEAR, WPR) to do so using the unique opportunity offered by the Global Alliance for Vaccines and Immunization (GAVI) support.
- Regional TAGs to review country plans for measles and rubella elimination, including planned dates for introduction of RCV for countries not yet using rubella vaccine.

IV. Progress Towards Regional Targets

African Region

- Countries in the African Region have established the goal to eliminate measles by 2020.
- As of 2012, only 3 countries were using rubella vaccine in their childhood immunization programme and the Region has not yet established a rubella control or elimination goal.
- Between the years 2001 and 2012, the African Region improved its MCV1 coverage from 56% to 73%.
- In 2012, 20,935 cases of measles were confirmed by lab and epidemiological linkage (incidence rate of 27 per million); As of August 2013, 35,558 confirmed measles cases have been reported (incidence rate of 41 per million)
- As of end 2012, 15 countries out of 46 (32%) are on track to meet the measles elimination target. On the other hand, 16 countries (35%) are clearly at risk of failing to reach the 2020 elimination goal, unless programmatic measures are taken to ensure that the implementation of the strategies in strengthened.
- Weak immunization systems particularly in some large countries (Nigeria, DRC, Ethiopia) remain the major challenge to achieving elimination targets.

The African Region of the WHO is comprised of 46 Member States with a total population estimated at 850 million in 2012. The African Region adopted the measles mortality reduction goal since 2001, and has been implementing the WHO/UNICEF recommended strategies ever since. In September 2011, the 60th Regional Committee of the WHO adopted a goal of measles elimination for the African Region by the year 2020, which includes the following targets:

- Achieve 90% coverage with the first dose of measles vaccine nationally (WHO/UNICEF estimates) AND exceed 80% vaccination coverage in every district or equivalent administrative unit in all countries.
- Achieve at least 95% coverage with measles vaccines during SIAs in at least 80% of districts.
- Achieve a measles incidence of less than one confirmed measles case reported per million population per year (excluding imported cases).
- Achieve the surveillance performance targets

WHO/AFRO does not yet have a goal for CRS/rubella elimination. However, countries are being encouraged to determine the local burden of disease and to introduce rubella vaccine according to the recommendations provided in the most recent WHO rubella vaccine position paper.

Progress

Routine Immunization: Between 2001 and 2012, the African Region has improved its MCV1 coverage from 56% to 73% (according to the WHO/UNICEF estimates), with an average improvement of 1.5 – 2

percentage points per year. (Figure) In 2012, nine of the 46 member states achieved measles vaccination coverage of 95% or more[5], while 15 had coverage of 90% or more. On the other hand, 5 countries[6] had coverage of less than 60%, down from 19 countries in 2000.

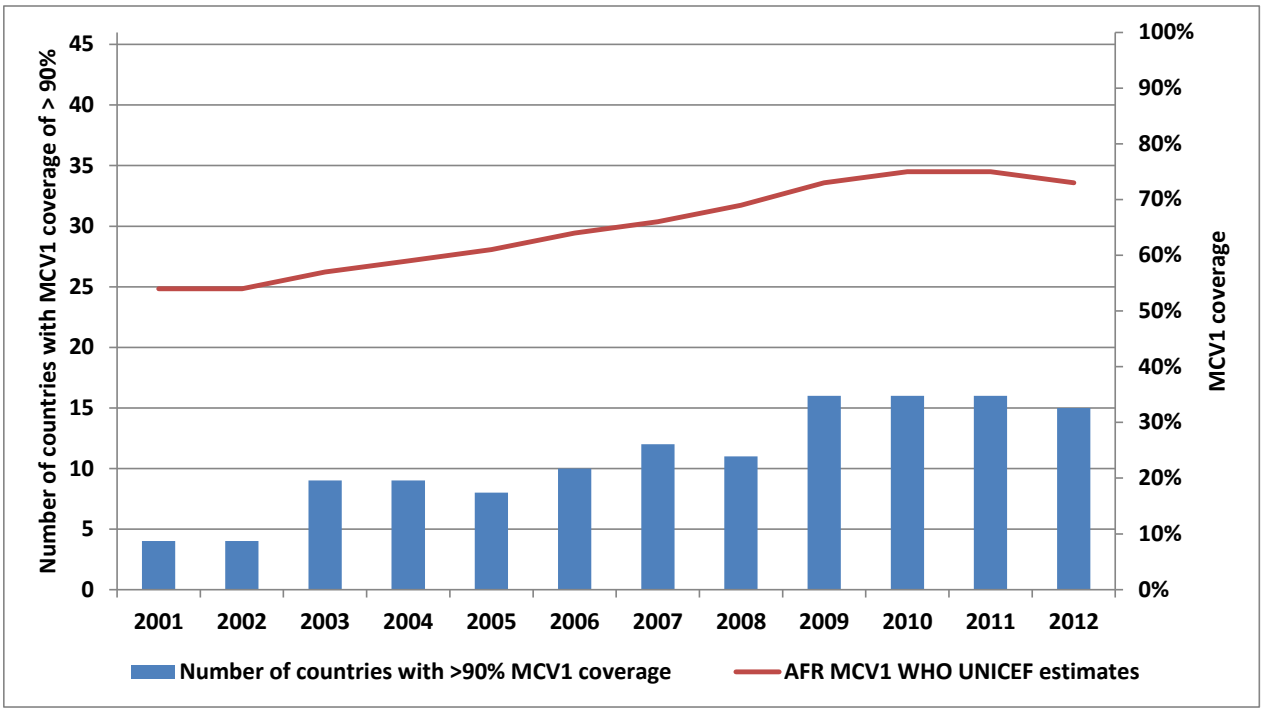


Figure. Regional MCV1 coverage (WHO/UNICEF estimates) and countries with >90% coverage. 2001 – 2012.

As of October 2013, 6 countries[7] have received GAVI approval and have introduced/ or are in the process of introducing MCV2. In 2014, four more eligible countries[8] are expected to apply for support from the GAVI to introduce MCV2 in the second year of life. As of August 2013, MCV2 is provided as part of the routine immunisation doses in a total of 13 countries.[9]

As of 2012, 3 countries in the African Region (Cape Verde, Mauritius and Seychelles) have introduced RCV in their national childhood immunization programme. In addition, 3 countries (Ghana, Rwanda, and Senegal) have been approved to receive funding from GAVI to introduce RCV in 2013/2014. Furthermore Burkina Faso and the United Republic of Tanzania have submitted an application to GAVI to introduce RCV in 2014/2015.

[5] Algeria, Angola, Cap vert, Eritrea, Gambia, Mauritius, Rwanda, Seychelles, Tanzania.
[6] Central African Republic, Eq Guinea, , Guinea, , Mali, Nigeria
[7] Burundi, Zambia, Eritrea, Ghana, the Gambia, Sao Tome and Principe
[8] Malawi, Mozambique, Senegal, Sierra Leone.
[9] Algeria, Botswana, Burundi, Cape Verde, Ghana, Lesotho, Mauritius, Seychelles, South Africa, Swaziland, Eritrea, the Gambia, Zambia.

Supplemental Immunization Activities (SIAs): Between 2001 and May 2013, a total of 596.2 million children were vaccinated through SIAs in 43 Member States.[10] Out of the 167 SIAs conducted over that period, 110 SIAs have attained administrative coverage of 95% or more, while 33 SIAs had reported coverage of less than 90%. From 2010 to October 2013, in 11 of the 40 countries which conducted follow-up measles SIAs, and for which we have detailed district level administrative coverage data, at least 90% of the districts achieved administrative coverage levels of 95% or more. Both Ghana and Rwanda have conducted MR SIAs in 2013, while Cape Verde and Senegal are expected to do so by the end of 2013.

Measles case-based surveillance: As of October 2013, 43 countries in the Region have established case-based surveillance for measles[11], supported with a network of 44 national measles serological laboratories, of which three also serve as regional reference laboratories[12].

In 2012, 55,717 suspected cases were reported from the countries in the Region, of which 91% benefited from appropriate investigation, and 20,935 cases of measles were confirmed by lab and epidemiological linkage. Twenty-seven countries have met the target of 80% or more districts reporting, with Regional average of 84%. At regional level, the non-measles febrile rash illness rate is 3.7 per 100,000, with 29 of 43 countries having met the target of at least 2 per 100,000 population. The Regional incidence of confirmed measles is 4.2 per 100,000 population in 2011 and 2.7 in 2012.

In 2013, between January and end-July a total of 58,657 suspected cases were reported of which 35,558 were confirmed by laboratory and epidemiological linkage. At regional level, the non-measles febrile rash illness rate is 2.9 per 100,000, and 77% of the districts have already reported at least one suspected case of measles with a blood specimen. The Regional incidence of confirmed measles is 4.1 per 100,000 population as of August 2013. (Table)

[10] All countries in the African Region except Algeria, Mauritius and Seychelles.
[11] These 43 countries include all Member States in the African Region except Mauritius, Sao Tome & Principe and Seychelles.
[12] The three Regional Reference Laboratories are located in Johannesburg (South Africa), Kampala (Uganda), and Abidjan (Cote d'Ivoire).

Table. Key Measles Surveillance Performance Indicators, African Region 2007 – end July 2013.

Performance indicators	2010	2011	2012	2013[13]
Number of reporting countries (out of 46)	42	43	43	43
Number of suspected measles cases reported	163,575	74,896	55,717	58,657
Number of confirmed measles cases	127,422	32,323	20,935	35,558
Percentage of confirmed measles cases (%)	78%	43%	38%	60.6%
% of cases investigated appropriately including with the collection of blood samples (target >80%)	96%	82%	91%	78%
Non-measles febrile rash illness (target >2/ 100,000 population)	3.7	4.4	3.7	2.9
% districts reporting at least 1 case with blood sample (target >80%)	84%	81%	84%	77%
Incidence of confirmed measles per 100,000 population	16.5	4.2	2.7	4.1

Challenges

The MCV1 coverage across the Region, which has been increasing steadily between 2002 and 2010, has shown a levelling off in the last three years. Some of the countries with large populations still have major infrastructure and systemic challenges to raise and maintain high coverage levels. The countries with the largest number of children who did not receive first dose measles vaccine include Nigeria, Ethiopia and DRC.

Large scale measles outbreaks have continued in DRC, due to the gaps in national and subnational level routine immunization coverage, as well as the delays in conducting follow-up measles SIAs in 2010, (linked to delays in mobilizing resources for scheduled follow-up measles SIAs). The situation is compounded by the increasing shift in epidemiological susceptibility involving older children, and thus requiring a widening of the target age group for follow-up and outbreak response immunization activities.

There is a need to foster stronger country ownership and leadership in the implementation of strategies towards the attainment of the measles elimination targets.

Summary

Countries in the African Region continue to implement strategies to meet the specific programmatic targets for Regional measles elimination to be met by end 2020. As of end 2012, fifteen countries[14] are on track to meet these targets. On the other hand, 16 of the 46 countries have missed most of the targets, and are at risk of failing to reach the 2020 elimination goal, unless programmatic measures are taken to ensure that the implementation of the strategies in strengthened.

[13] Data for January – end July 2013.

[14] Algeria, Botswana, Cape Verde, Eritrea, the Gambia, Ghana, Mauritius, Mozambique, Rwanda, Sao Tome and Principe, Seychelles, Swaziland, Tanzania and Zimbabwe

American Region

- Member States have approved a plan of action for maintaining the elimination of measles, rubella and CRS in the Region of the Americas
- Continued circulation of the measles and rubella in other regions of the world has a profound economic impact on the Americas in responding to outbreaks.
- The public health implications of mass gatherings are becoming more pronounced; as such events draw ever-larger international crowds. This raises the possibility of the importation of measles and rubella viruses from other regions of the world.
- Technical Advisory Group (TAG) recommended administration of the second dose of MMR vaccine (MMR2) at 15-18 months with a note that it can be given simultaneously with other vaccines.
- Follow up campaigns are still maintained to guarantee high population immunity against measles besides maintaining high routine immunization coverage.
- Recent outbreaks also suggest that spatial heterogeneity in coverage should be a particular focus of programme activities.
- Advocacy strategies have been used for keeping the measles and rubella elimination in the political agenda. International Expert Committee (IEC) Members for the verification process have held a key role as advocates for maintaining the elimination.
- Major on-going challenges include funding constraints due to competing health priorities in the Member States, and among donor agencies.
- The Americas is at the final stage in the process to verify the region free of endemic measles, rubella and CRS.

Background

Since 2002, the Region of the Americas has achieved and maintained elimination of measles and the last case of endemic transmission of rubella was reported in 2009. However, continued circulation of the measles virus in other regions of the world has had an impact on the epidemiology of measles in the region.

All of the reported measles cases (N=146) in 2012 and 2013 (N=318) have been linked to imported viruses. In 2012, the most common genotype was B3, mainly due to several secondary cases reported from the outbreak in Ecuador. In 2013, the most common circulating genotype has been D8, which has been mostly related to outbreaks in USA and Brazil. There were 166 cases of measles reported in the United States by the 34th epidemiological week. Also, Brazil has confirmed 114 cases by the week 38: vast majority from an outbreak from Pernambuco (85%) (see Figure).

In 2012, 16 people were reported to have rubella. In 2013, as of October 3, 7 rubella cases have been reported; majority linked to a rubella outbreak in Japan. While rubella remains endemic elsewhere in the

world, imported CRS will continue to be a public health concern in the Americas. In 2012, 3 cases of CRS were detected in the United States in infants whose mothers were infected during their pregnancy in Africa. CRS cases have not been reported on this year.

Strategies for Maintaining the Regional Elimination of Measles and Rubella

Political commitment

Due to virus importation and consequent risk for reintroduction of viruses in the Americas, at the Pan American Sanitary Conference in 2012, the Member States approved a plan of action for maintaining the elimination of measles, rubella and CRS in the Region of the Americas (resolution CSP28.R14. annexed). According to the Plan of Action countries are called upon to strengthen active surveillance of measles, rubella and CRS and to ensure measures for responding in a timely manner to imported outbreaks.

Surveillance

All countries have a sensitive and timely case based measles and rubella/CRS surveillance system, but the quality of active epidemiological surveillance is not always homogenous at the sub-national and local levels. There are also some gaps in the surveillance of CRS; where they exist, countries use alternative and complementary lines of evidence such as conducting retrospective studies. Integrated epidemiological surveillance of measles/rubella met nearly all of the performance indicators for 2012, over 80%, and high performance has been continued in 2013. Virologic surveillance has been sufficient to document the interruption of transmission of measles and rubella for verification of elimination and detect virus importations.

PAHO has developed and validated the research protocol and instruments for external assessments of the surveillance systems and implemented first evaluations in 2013. Also for the purpose of analysing the performance and challenges of Measles and Rubella Laboratory Network, a meeting was held in May 2013 with the participation of experts from regional reference laboratories for measles and rubella for the Region of the Americas as well as PAHO immunization professionals.

Outbreak response

Over-all countries have responded well to reported cases of measles and rubella, carrying out outbreak response activities such as searching for cases, tracing contacts, and evaluating risk. PAHO has also enhanced outbreak investigation and response at local, national, and regional levels by developing a standardized guideline for post-elimination setting; outbreak investigation workshop to familiarize this guideline at the regional level is taking place is December 2013. The costs associated with control of outbreaks can be substantial, and rapid containment of the first cases is crucial. In Ecuador, the public health response to the outbreak in 2011-2012 was estimated to cost over eight million dollars. The government is currently conducting an economic study, to understand better the amount of indirect costs associated with containing the outbreak.

Mass gatherings

The public health implications of mass gatherings are becoming more pronounced; as such events draw ever-larger international crowds. This raises the possibility of the importation of measles and rubella viruses from other regions of the world, which could lead to outbreaks, and at a high cost in terms of health, placing the maintenance of the elimination of these diseases at risk. PAHO has cooperated with

Member States in hosting mass gatherings, and released health alerts on measles and rubella. In this year, the Region of the Americas was the venue of two large-scale international events, including the 28th World Youth Day 2013 in Rio de Janeiro Brazil and the 9th World Games 2013 in Cali, Colombia. As part of preparation, countries carried out supplementary immunization activities and intensified surveillance both before and after events. In the coming years, the Americas host the 2014 FIFA World Cup and the 31st Summer Olympic Games in 2016, both in Brazil. As always, PAHO stands ready to support countries seeking technical advice as part of preparedness for mass gatherings.

Vaccination and coverage monitoring

Most of the countries in the region report a very high immunization coverage (>95%). During 2012, countries and territories reported higher coverage for the first dose (MMR1) of 94%, recommended at one year of age, however, for MMR2 it is 77%. With the goal of achieving the highest MMR2 coverage possible, the TAG recommended administration of the MMR2 vaccine at 15-18 months with a note that it can be given simultaneously with other vaccines, such as the first DPT booster. However, follow-up campaigns are still maintained to guarantee high population immunity against measles in addition to maintaining high routine immunization coverage. The countries analyse vaccination coverage by age cohorts to target population groups with concentrations of unvaccinated individuals. Last year four countries implemented national follow-up campaigns: Bolivia, Haiti, Honduras and Nicaragua. Recent outbreaks also suggest that spatial heterogeneity in coverage should also be a focus of concern. The countries have conducted rapid monitoring of vaccinated in high risk areas and implement mop-up campaigns or intensified vaccination activities in areas with lower vaccination coverage. As per SAGE and TAG recommendation, PAHO is initiating research on efficacy on administrating MMR vaccine and yellow fever vaccine together.

Advocacy and Communications

Communication approaches have been variously used for promoting routine immunization, and campaigns through social communications. Vaccination Week was held in April 2013 to raise population awareness and to keep the topic on the forefront of social and political agendas; the next one is planned to take place in 2014. A large scale promotion campaign for FIFA is planned in 2014 to disseminate messages on the importance of being vaccinated against measles and rubella.

Strategies for advocacy have been also used for keeping the measles and rubella elimination in the political agenda. An important goal of this advocacy and fundraising work is to secure continuity of technical cooperation for the Member States in order to maintain the achieved results. International Expert Committee Members for the verification process have held a key role as advocates for maintaining the elimination. At the regional level PAHO is currently developing an advocacy book showing the impact of the different elimination strategies in the Americas. Testimonies are included from people who worked in member states, as well as from those involved in elimination efforts at the regional level.

Resource mobilization

Major on-going challenges include funding constraints; due competing health priorities in the Member States, and among donor agencies.

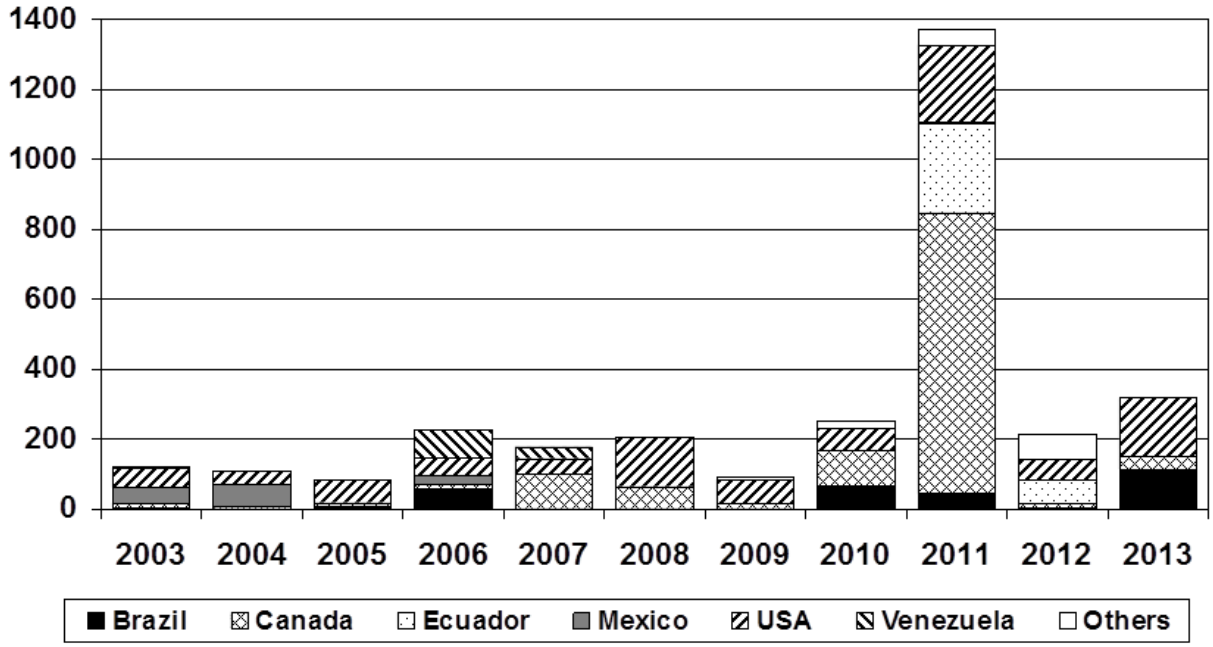
Verification of the elimination of measles, rubella and CRS

The American Region is at the final stage in the process to verify the region free of endemic measles, rubella and CRS. In May 2013, the fourth meeting of the IEC was held jointly with the 23 national commissions and a sub-regional commission from the English Speaking Caribbean in order to:

1. follow-up on progress made on the documentation and verification of elimination, know the results of IEC members' country visits and the status of the national documents presented by the countries,
2. identify obstacles and challenges to maintaining the elimination of measles, rubella and CRS in the Region, and
3. discuss the implementation of the Regional Plan of Action for maintaining the elimination of measles, rubella and CRS and the work plan for 2013-2014.

The recommendations from the meeting, endorsed by TAG, include general and specific recommendations for countries and the PAHO Secretariat. According to the recommendations the final national elimination reports should be submitted to the IEC by the end of the year. The countries should also implement their national plan of actions to maintain the elimination including follow-up campaigns. IEC conducted field visits to Haiti, Colombia, Argentina, Peru, Ecuador and Brazil in 2012-2013. IEC members will continue making visits to countries where maintaining elimination remains a significant challenge in 2014. Moreover, the IEC is planning to present the progress report on the verification process for the PAHO's Executive Committee in 2014 and held a regional meeting with the National Commissions in April 2014.

Figure: Distribution of Confirmed Measles Cases Following the Interruption of Endemic Transmission, the Americas, 2003-2013*



*** Data as of epidemiological week 39/2013**

Eastern Mediterranean Region

- EMR has made significant progress towards measles elimination both in terms of improving MCV1 coverage and decreasing numbers of reported cases from 2000 to 2010.
- Since 2010 the Region has gone through many challenges including political changes, conflicts, floods, and famine. These have led to a decrease in the regional MCV1 coverage and increase in outbreaks and reported measles cases. Outbreaks occurred in Afghanistan, Pakistan, Somalia, Sudan and Yemen, Syria and neighboring countries.
- Although there is no regional rubella elimination target, 13 countries have adopted a rubella elimination target and are making good progress towards achieving that target. Most of the regional rubella burden is among GAVI eligible countries that have not yet introduced RCV.
- Both routine coverage data and SIA quality are key challenges to be addressed.

Introduction

In 1997, the 22 countries in the Eastern Mediterranean Region (EMR) resolved to eliminate measles from their region by 2010 (EM/RC44/R.6). Despite significant progress, in terms of morbidity and mortality reduction in all countries, the region did not achieve measles elimination by the target date of 2010. Accordingly, in 2011, the Regional Committee of the Eastern Mediterranean resolved to revise the target date of measles elimination to 2015 (EM/RC58/R.5)

Several EMR countries are suffering from complex emergencies, internal conflict and financial constraints which constitute major challenges facing measles elimination. Endemicity of poliovirus in Afghanistan and Pakistan and early 2013 re-emergency of polio cases in Somalia add to these challenges.

Countries of the EMR are at different stages of measles endemicity and have variable capacity of measles elimination. EMR countries are categorized in 3 groups, based on incidence of measles in 2011:

Countries **at elimination** and ready for validating elimination (reporting 0 cases for ≥2 years or more in presence of a nationwide measles case-based surveillance and high measles coverage for both MCV1 and MCV2): Bahrain, Jordan, Syria, Palestine. However in 2012 crisis started in Syria that has disrupted the proper implementation of routine immunization and measles cases appear late 2012 after two consecutive years with no laboratory confirmed case. Then measles cases appear neighboring countries hosting Syria refugee one of them is Jordan which also had reported zero cases for ≥2 years. Bahrain and Palestine maintained zero reporting of confirmed case.

Countries **close to Elimination**: (incidence < 5 cases/1,000,000 with a nationwide measles case-based surveillance and high measles coverage for both MCV1 and MCV2): Egypt, Iran, Oman, Tunisia, maintained their status except Iraq and Lebanon which have experienced measles outbreaks since early 2013 to date.

Countries with **high burden of disease**: Afghanistan, Djibouti, Kuwait, Libya, Morocco, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, South Sudan, United Arab Emirates and Yemen. These countries still present the highest number of cases in the EMR, but there are on-going activities such as SIAs and implementation of RED and technical supports to advice how to close the immunity gaps.

Measles and Rubella Epidemiology

Measles

The implementation of elimination strategies in Member States has led to a rapid decrease in measles and rubella incidence in the region. In 2012 six countries (26%) have reported measles incidence of <1 case per million persons in the presence of a sensitive and well-functioning nationwide surveillance system: Bahrain, Iraq, Jordan, Oman, Palestine and Syria. In spite of this progress, there has been a resurgence of measles cases in several countries from late 2009 which has continued to 2013. The total confirmed measles cases reported in 2012 and January-July 2013 are 23,451 and 11,312 cases respectively, 79% of these cases are reported from Afghanistan, Pakistan, Sudan and Yemen. Pakistan and Sudan alone accounts for 70% of cases in 2012 and 74% in 2013, despite implementing of follow up SIAs in 2010-2011.

This resurgence has occurred in some countries that have been reporting high routine and SIAs vaccination coverage however, a substantial proportion of the measles cases reported during these outbreaks were unvaccinated, which raises the concern about the quality of the reported routine coverage data as well as the quality of implemented SIAs.

Table. Countries Reporting High Number of Confirmed Measles Cases, 2009- 2013 (July)

Countries	2009	2010	2011	2012	Jul-13
Afghanistan	2158	1528	1357	2797	315
Pakistan	267	1008	2675	8046	5994
Sudan	27	568	5581	8461	2338
Yemen	77	352	2411	2159	298
Total	2529	3456	12024	21463	8945

Rubella

Currently, 16 of the 22 countries in EMR are using rubella vaccine in their EPI program with high coverage ≥90% coverage of RCV1 and as of 2012 15 countries using a 2 dose of MMR and one country using MR schedule. Thirteen countries (60 %) have established a national target for rubella/CRS elimination. Ten countries now are implementing CRS surveillance as well. In addition, rubella case-based surveillance is integrated with measles surveillance in all countries in the Region. In 2012, 1606 rubella confirmed cases were reported by the EMR countries. Tunisia used to provide rubella vaccine for girls only, a strategy that created an immunity gap among males resulting in a huge rubella outbreak in 2011 and 2012 with reported cases of 1072 and 155, respectively. This has been reverted in 2013 by conducting MR campaign and introducing rubella vaccine in the routine immunization.

The new GAVI window for supporting MR catch up campaign is an excellent opportunity to intensify measles/rubella control and elimination activities. In January 2012, the EMRO organized a Regional

consultation on Rubella and CRS to discuss the regional situation and the possibility of establishing regional rubella and CRS control or elimination target.

Table. Countries Reporting High Number of Confirmed Rubella Cases (with the exception of Tunisia, these countries have not yet introduced rubella vaccine), 2009 to 2013 (July)

Countries	2009	2010	2011	2012	Jul-13
Afghanistan	34	45	87	89	7
Pakistan	84	206	211	178	495
Sudan	343	302	237	173	238
Yemen	173	154	153	134	423
Tunisia	4	155	1072	483	8
Total	634	707	688	574	1163

The above four countries excluding Tunisia as well as two more countries (Djibouti and Somalia) are all eligible for GAVI support to introduce rubella vaccine. So far only Yemen has applied to GAVI for MR introduction campaign and was approved with condition on implementation of effective vaccine management which was implemented in during September 2013.

Progress Towards the Current Goal

Achieving high population immunity

Based WHO/UNICEF estimates, routine MCV1 coverage improved during the past decade from 72% in 2000 to 84% in 2011. However, estimates for 2012 indicated a decrease in MCV1 regional coverage to 83% due, mainly, to the drop in MCV1 coverage in Pakistan and the slight decrease in Morocco, Syria, and Yemen. 12 countries maintained reporting of 95% or more for MCV1 in 2011 and 2012. In addition, the coverage of routine immunization has impressively increased in priority countries. For example, MCV1 coverage estimate was 64% in South Sudan in 2012.

Despite the progress in the Region, countries including Afghanistan, Pakistan, Somalia, Sudan and Yemen have experienced several outbreaks in late 2010 through 2013. These outbreaks occurred due to delay in implementation of the follow-up SIAs, a deteriorating security situation, and/or inadequate funds.

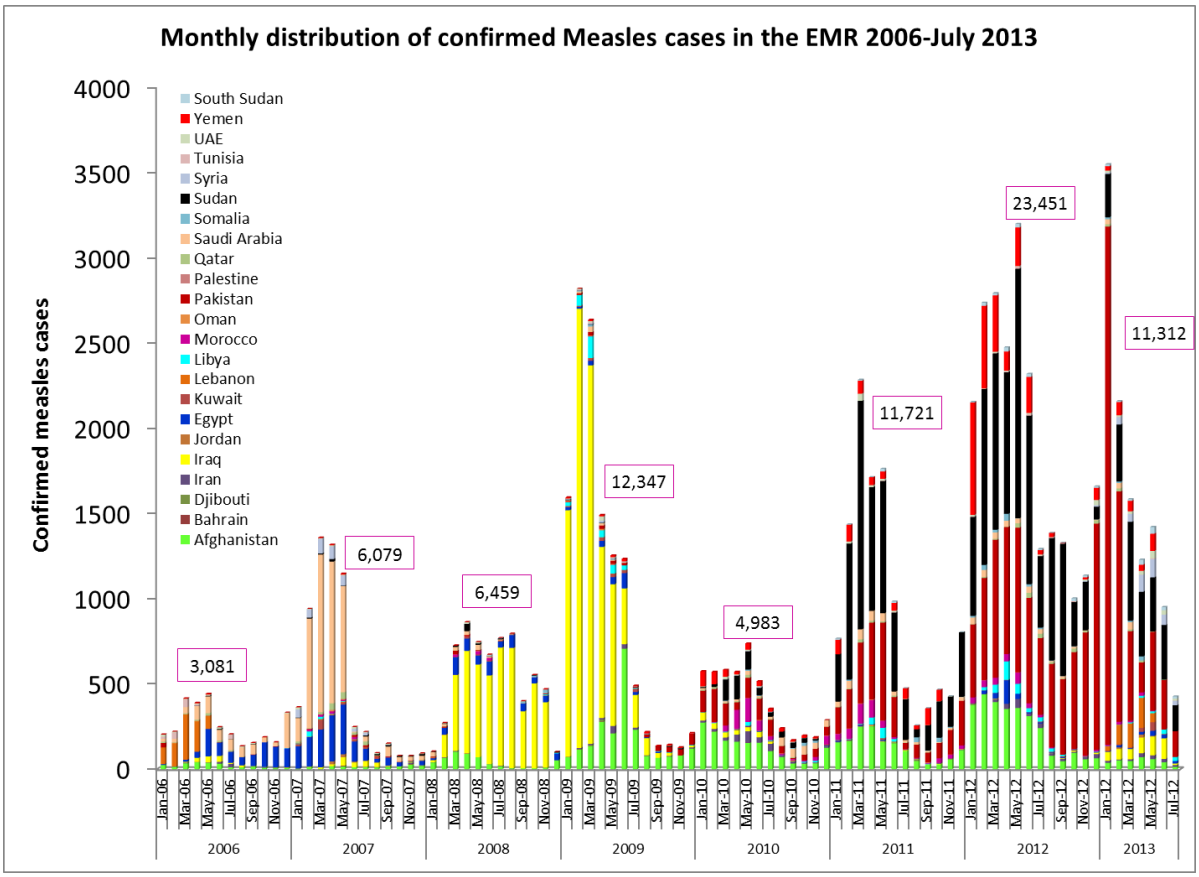
As of 2012, twenty one member states are implementing a 2nd dose of measles vaccine through routine services. Eleven of these countries have reached the 95% coverage with 2 doses of MCV at national level based on national reporting in 2011 and 2012.

Follow-up measles campaigns are being conducted in countries that have not reached the target 95% coverage with 2 doses of measles vaccine. During 2012 up to September 2013, around 55 million children have been vaccinated through measles supplementary immunization activities (SIAs) in Afghanistan, Djibouti, Pakistan, Somalia, S. Sudan and Yemen. A new initiative for the implementation of synchronized MCV campaigns in Syria and Jordan will be conducted in November 2013.

Case-based and laboratory surveillance

All EMR countries have moved to measles case-base surveillance with laboratory confirmation, 21 (95%) of these countries are implementing nationwide, and two countries Somalia and South Sudan are

performing surveillance in identified sentinel sites. In 2009, 13,892 samples were tested in the EMR Lab Net for measles IgM; this increased to 15,074 serum samples tested in 2012. Countries report monthly to EMRO measles cases and surveillance indicators. There is a significant improvement in the performance of measles case-based surveillance in most of the countries in the region, as reflected by the status of measles surveillance performance indicators.



Also much progress has been made towards collecting genotype information from measles cases, 21 (91%) EMR countries have characterized circulating measles virus as a result of the increased capacity of the laboratory network. From 2000-2009 the major genotypes detected were D4 (47%) and B3 (38%), but since 2011 to date genotype B3 is increasingly being detected accounting for 81% of the reported genotypes in 2012, other genotypes detected were D5, D8, D9 and H1.

Enabling Factors

- Commitment of EMR countries towards measles elimination renewed, RC58/R.5
- Partners' support to low income countries (e.g., The Measles and Rubella Initiative)
- Accumulating experience from other disease elimination/eradication efforts and successful implementation of measles catch–up and follow up campaigns.
- Current activities and initiatives to strengthen health systems and routine immunization in priority countries which resulted in improved reported vaccination coverage and measles surveillance being expanded and strengthened.

- GAVI windows of support for MCV2 introduction, RCV and measles SIAs in priority countries.

Challenges

The Region is still facing challenges to reach the measles elimination goal. From 2010 to date the Region is going through many challenges: political changes, conflicts, floods, famine as well as shortage of funds from partners. Routine vaccination coverage in many countries in the Region didn't reach at least 95% coverage with both MCV1 and MCV2 in all districts, the level that supports reaching measles elimination. Therefore, maintaining very high levels of population immunity throughout the population is a significant challenge in this context.

Measles epidemiological and molecular surveillance is not up to the standard that supports validating measles elimination, even in most of the countries with established nationwide surveillance. Some countries of the region are experiencing measles outbreaks even among the age groups that have been vaccinated during SIAs with reported high coverage. Pockets of susceptible populations still exist in some countries in the form of hard to reach populations in low income countries and in countries with big expatriate populations. All this has had an adverse effect on measles elimination activities and increased risk of outbreaks, as seen in Afghanistan, Pakistan Somalia, Sudan and Yemen. Funding for follow up campaigns and competing priorities are continuing challenges for these countries.

Addressing the challenges

- Renewed commitment by member states (EM/RC58/R.5)
- Strengthening capacities at country level in regard to micro-planning and use of innovative approaches to reach unreached and hard to reach populations (e.g. RED/ CHD)
- Technical support to priority countries in surveillance and outbreak investigation
- Efficient use of available funding and encourage countries to maximize benefits from all GAVI windows of support especially new vaccine introduction, MR campaign, outbreak response and HSS
- Increasing the coordination/communication between Member States and EMRO with development partners in the region

European Region

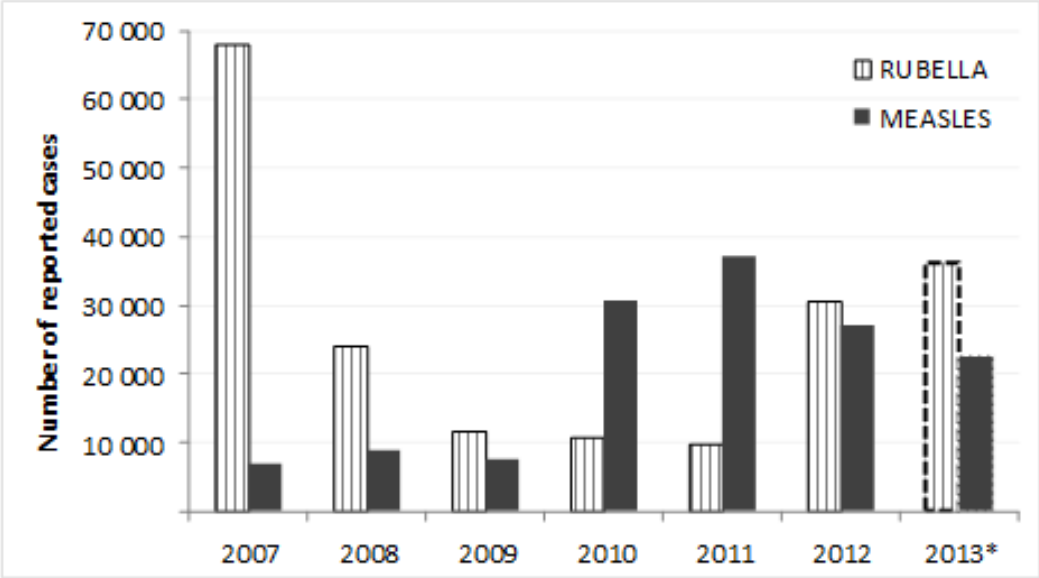
- Measles and rubella outbreaks are still occurring in the Region and are not always responded to with timely and appropriate control measures.
- The *Measles and Rubella Elimination 2015 - Package for Accelerated Action* has been launched in order to guide WHO Europe and Member States to reach the goal by 2015.
- Renewed political commitment and urgent need to close immunity gaps in the population are the main priorities for Member States.

Progress towards the current goals

Following an all-time low in the number of reported measles cases in 2007 with just 6936 cases, the period 2008-2012 has seen an increased level of measles transmission with over 110,000 cases. The majority of cases were reported from countries that experienced large-scale outbreaks including Bulgaria,

France and Ukraine. Most cases occurred in the general population although outbreaks were also reported related to susceptible subpopulations (ethnic minorities, religious and philosophical groups).

Figure. Number of reported measles and rubella cases in the WHO European Region, 2007 through first eight months of 2013.



Data source: 2007-2012 data: WHO/UNICEF Joint Reporting Form.
*Data for the first eight months of 2013: Monthly measles and rubella reports to WHO Regional Office

For 2013, a large number of cases similar to that reported for 2012, is expected. For the first eight months of 2013, 24 023 measles cases have been reported. Large outbreaks have occurred in Georgia and Turkey with 7423 cases and 7018 cases, respectively. Other countries such as Germany and the United Kingdom have also experienced resurgences. In 2013, outbreaks have also affected susceptible subpopulations such as the orthodox protestant community in the Netherlands and the Orthodox Jewish Community in the UK (London). Unlike 2012, when no measles-related deaths were reported, six deaths (age range 4 months-31 years) were reported to date for the first eight months 2013.

For 2012 and the first eight months of 2013, the majority of cases were among unimmunized individuals and were mostly reported in infants and children. However, older age-groups were also affected. During these consecutive time periods, 26% and 34% of the total cases, respectively, occurred among adults aged 20 years and older. The observed age pattern of cases reflects the persistent gaps in population immunity. Such gaps can be explained by historical immunization programme weaknesses, late introduction of vaccine and gaps in service delivery. Nevertheless, taking into consideration that MCV has been routinely used for more than 20 years the majority of cases could have been prevented.

The number of reported rubella cases decreased from 804 567 in 1999, to 9672 cases in 2011. However, in 2012 a few countries reported high incidence and outbreaks. During that year, out of 30 509 cases of rubella, 88% were reported from Romania and Poland with 20 812 cases and 6263 cases, respectively. The outbreak in Romania in 2011-2012 with over 24 000 cases resulted in 55 confirmed CRS cases, nine

of whom were fatal. As for 2012, a large number of rubella cases is expected for 2013, as 36,871 rubella cases, almost all from Poland, have been reported for the first eight months of 2013. The annual reported number of reported measles and rubella cases since 2007 is shown in the figure above.

Successes and Challenges

The epidemiology of measles and rubella in recent years mirrors differences of population immunity between Member States in the European Region. Some countries do not face significant increase of incidence after the importation of measles or rubella viruses. However, with the large number of measles and rubella cases reported in 2012, and so far in 2013, it is becoming increasingly apparent that the routine childhood immunization programmes and activities may not be sufficient to reach the 2015 target without renewed political commitment, accelerated action and innovative ways of reaching susceptible populations. Closing immunity gaps in the population whilst maintaining high routine vaccination coverage with two doses of MMR vaccine presents challenges for immunization programmes to increase overall population immunity. In July 2013, Armenia, Azerbaijan and Georgia agreed on comprehensive efforts for the coming year to close immunity gaps in the population and prevent further spread of the disease within and across their borders. The major activities should be completed by mid–2014.

Rubella surveillance is still a challenge in the WHO European Region. Until 2012, four countries (Belgium, Denmark, France and Germany) did not have national surveillance for rubella. There is also a need for improving the laboratory capacity for rubella surveillance. Different surveillance systems for congenital rubella syndrome, congenital rubella infection and/or rubella in pregnancy, exist in the Member States. The Regional office receives annual reports on the case count; however, the available information is not sufficient and adequate for detailed analyses. Under-reporting is likely, as rubella still persists in a few Member States and only 276 CRS cases were reported in the European Region during 2000–2012.

Actions taken

To support the documentation of the elimination effort, a verification process is on-going. The Regional Verification Commission for Measles and Rubella Elimination (established in January 2012) serves as the foundation for this effort, which is further guided by a *Framework for the verification process in the WHO European Region.*[15] The Regional Office has also assisted Member States in establishing national verification committees (NVC). To date, 38 of the 53 Member States in the Region have established a NVC. Four sub-regional meetings of the RVC with NVCs and representatives of national health systems were held in late 2012 and 2013. A standardized assessment for verifying the interruption of endemic measles and rubella virus transmission will be based on detailed information on a number of components. These include: measles and rubella epidemiology, virological surveillance, analysis of vaccinated population cohorts, the quality of surveillance and the sustainability of the National Immunization Programme.

To meet the 2015 target, the Regional Office recognizes the need for greater political commitment and accelerated actions by Member States as well as scaled up support from WHO and other partners. A

[15] World Health Organization 2012. Eliminating measles and rubella. Framework for the verification process in the WHO European Region. www.euro.who.int/__data/assets/pdf_file/0005/156776/e96153-Eng-final-version.pdf

Package for accelerated action 2013–2015[16] has been developed through a consultative process and endorsed by the European Technical Advisory Group of Experts on Immunization (ETAGE). It identifies priority areas in which the Regional Office will strengthen technical support to Member States as they seek to eliminate measles and rubella, and sets indicators and milestones by which progress resulting from the efforts of all stakeholders can be measured.

Alongside traditionally tried and tested methods to boost demand for vaccines and provide equitable access, the Package considers innovative ways to change current approaches, acknowledging that "business as usual" may not be sufficient to reach the elimination target. The Package for accelerated action groups recommended activities in the following six categories:

- Vaccination and immunization system strengthening
- Surveillance
- Outbreak prevention and response
- Communications, information and advocacy
- Resource mobilization and partnerships
- Verification of measles and rubella elimination.

Renewed attention, and commitment and innovative tools are required to overcome the many challenges of maintaining strong immunization programmes. For this reason a *Guide to Tailoring Immunization Programmes (TIP)* [17] was developed to provide proven methods and tools to assist national immunization programmes design targeted strategies that increase uptake of infant and childhood vaccinations. The Guide provides tools to identify susceptible populations to identify the barriers to vaccination and implement evidence-based interventions. The Guide is intended for use by healthcare professionals, public health authorities and decision makers. After successful pilot-testing in Bulgaria in 2012, the Guide was launched in April 2013 as part of the Package for accelerated action and is to be rolled out in several countries across the Region. Sweden has already implemented it to improve vaccination coverage among an ethnic minority group, immigrants and an anthroposophic community.

Vaccination concerns among a significant minority of healthcare workers results in lack of strong provider recommendation for vaccination during patient encounters. To address these concerns there are also plans to adapt TIP to specific healthcare worker networks each year as part of the Package, and to engage the academic and practicing network of paediatricians at the national level to enhance support for measles and rubella elimination activities.

The Regional Office has also developed a manual to assist immunization programme managers to respond to communications issues caused by real or perceived vaccine-related events (VRE). The manual *Vaccine*

[16] World Health Organization 2013. Measles and rubella elimination 2015. Package for accelerated action: 2013–2015. www.euro.who.int/__data/assets/pdf_file/0020/215480/PACKAGE-FOR-ACCELERATED-ACTION-20132015.pdf

[17] World Health Organization 2013.The Guide to Tailoring Immunization Programmes. Increasing coverage of infant and child vaccination in the WHO European Region www.euro.who.int/__data/assets/pdf_file/0003/187347/The-Guide-to-Tailoring-Immunization-Programmes-TIP.pdf

safety events: managing the communications response[18] provides practical, informative strategies and tools to help plan and manage a communications response following a VRE in a local community, at a national level, or beyond. The aim of the manual is to increase public trust and confidence in vaccines, and to minimize the negative impact of VREs.

Summary

The occurrence of widespread outbreaks or indigenous transmission of measles in a few countries persisted in 2013. While most countries of the Region have controlled rubella, a small number still reported a high incidence and outbreaks. Sub-optimal rates of vaccination coverage and immunity gaps in the population remain at the core of the problem of continued measles or rubella transmission in the Region. Moreover, outbreaks of measles and rubella have also repeatedly occurred among certain subpopulations underlying their persistent vulnerability to these diseases.

Political and public complacency about the value of immunization and the lack of perceived threat of vaccine preventable diseases has contributed to suboptimal vaccination coverage. This, together with persisting immunity gaps in the population calls for a renewed political commitment, improved risk communication by health authorities and accelerated action by Member States and partners to eliminate measles and rubella in the WHO European Region. The process of verifying the elimination of measles and rubella in the Region that began in 2011 will provide an opportunity for each country to evaluate the sensitivity of measles and rubella surveillance and identify areas where more efforts are needed to achieve the goal of eliminating these diseases

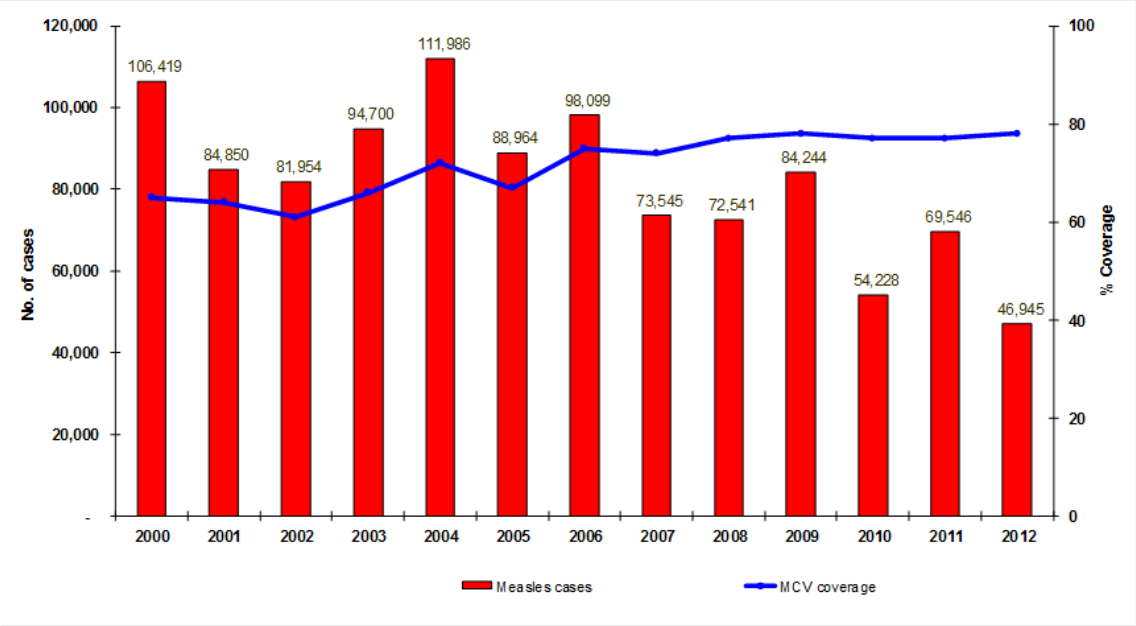
South-East Asia Region

- In September 2013, all Member States unanimously adopted the resolution to eliminate measles and control rubella/CRS by 2020.
- Regional routine MCV1 coverage has significantly increased from 65% in 2000 to 78% in 2012; however, MCV1 coverage remains below 80% in both India and Indonesia.
- All countries provide two doses of MCV with India completing a measles catch-up SIAs targeting 139 million children.
- Six out of 11 countries have introduced nationwide RCV into their national immunization program with one wide age range MR SIA conducted in Nepal in 2013.
- Funding remains a key challenge to achieving the regional measles and rubella targets in addition to the introduction of RCV in a few large countries and scaling up the use of MCV2.

[18] World Health Organization 2013.Vaccine Safety Events: managing the communications response. A Guide for Ministry of Health EPI Managers and Health Promotion Units. www.euro.who.int/__data/assets/pdf_file/0007/187171/Vaccine-Safety-Events-managing-the-communications-response-final.pdf

In the South East Asia Region (SEAR), MCV1 coverage has increased from 65% in 2000 to 78% in 2012 along with a decline in total number of reported measles cases in this same period (See Figure). In SEAR, only five countries remain to introduce rubella into their national immunization programmes (NIP). They are DPR Korea, Myanmar, Indonesia and Timor-Leste; in India four states (Delhi, Goa, Pondicherry and Sikkim) have already introduced MMR in their routine immunization, and the Government of India is currently discussing the roll out of rubella nationwide. Only Nepal and Timor-Leste remain to add a second dose of measles into their NIP.

Figure: Reported Measles Cases* and MCV1 Coverage+, SEAR, 2000–2012



* source: WHO/UNICEF JRF; + WHO/UNICEF coverage estimates, 2013

A total of 17,402 suspected cases of measles were reported from the countries of SEA Region in 2013, as of September 30th; of these 2,934 were laboratory confirmed measles and epidemiologically linked cases, and 3,219 laboratory confirmed and epidemiologically-linked rubella cases. There were a total of 189 measles outbreaks reported resulting in the report of 5,182 suspected cases of measles. A total of 1165 laboratory & epidemiology linked confirmed cases of measles and 2,717 cases of rubella were reported from these outbreaks.

The total measles catch up campaign target for India was 139 million (spanning 2010-2013), out of which 33.4 million were vaccinated during 2013. Further, India had initiated WHO-NPSP assisted laboratory based measles surveillance on the AFP surveillance platform in two southern states in 2005, which now has been expanded to 15 states covering 90% of the country population with laboratory strength of 11 across the country. As part of this surveillance expansion plan, in 2013, three more states (Maharashtra, Odisha and Uttar Pradesh) have been added to this measles surveillance network, with a plan to expand further to cover 24 states and 95% of the county population by the end of 2013.

In Nepal, the third phase of the MR campaign started on 14 December 2012 and finished on 14 January 2013 in 35 districts. The target was 5,580,281 and coverage was reported at 5,638,149 (100%). One dose of OPV was integrated during the MR campaign. Bangladesh had planned a massive SIA for November 2013 targeting children from 1 to 15 years of age for a total target of 52 million. Unfortunately, due to unavoidable circumstances, the SIA is now postponed to February 2014.

In February 2013, a Regional Consultation on the Feasibility of Measles Elimination and Rubella/CRS Control was held in Kathmandu, Nepal, where participants from all countries of the Region met. Supported by international technical partners as well as the WHO's Headquarters and the SEA Regional Office, the countries agreed that measles elimination and rubella control was both programmatically and technically feasible and recommended 2020 as the target year. This issue was further discussed at the meeting of the SEA Immunization Technical Advisory Group (SEA-ITAG) in April 2013 which also reaffirmed the feasibility of measles elimination and rubella/CRS control by the year 2020. Finally, in early July, at the High Level Preparatory Meeting for the 66th Regional Committee of SEA Region, the proposal to set 2020 as the target year was accepted and a draft resolution prepared accordingly. At the 66th SEA RC meeting, the Member States unanimously adopted the proposed resolution to eliminate measles and control rubella/CRS by 2020 in the SEA Region.

In September 2013, at the 66th Meeting of the SEA Regional Committee, a resolution was passed setting 2020 as the target year for the Region to eliminate measles and control rubella/CRS. There were several events that led up to the passage of this important resolution for the SEA Region.

Immediately following the passage of the RC resolution, SEARO organized from 23-27 September 2013 a Regional Surveillance Standards Workshop on measles and rubella/CRS. The workshop was to achieve consensus on the indicators to monitor progress towards the 2020 goal and agreement on the quality indicators for measles and rubella/CRS surveillance in the Region.

SEA Region countries are committed to the elimination of measles and rubella/CRS control by 2020. However, there are many challenges to the achievement of the measles elimination and rubella/CRS control goals for this Region. Some of these are:

- A preliminary estimate projects the cost to be in excess of US $ 800 million for the SEAR to achieve the measles and rubella goals. Major efforts will be needed to mobilize the required resources;
- Expansion of the laboratory network will be needed in almost all countries to strengthen the quality of measles/rubella surveillance;
- Several large population countries still need to introduce rubella vaccine and scale up second dose of measles vaccine;
- Countries will need both additional financial resources as well technical support to move from the current outbreak surveillance to that of a case-based surveillance for measles and rubella.

Western Pacific Region

- All countries in the Region have made tremendous efforts to achieve and sustain measles elimination with significant decrease in measles incidence since 2008 and a high regional MCV1 coverage of 98%.
- The Measles Regional Verification Commission is now established and will monitor progress towards measles elimination annually.
- There has been a measles resurgence in 2013 in China. Endemic transmission continues only in China, Malaysia and the Philippines.
- In 2013, the Regional TAG recommended the region establish a rubella elimination target. Rubella vaccine is provided in all but four WPR countries and areas.
- Intensified efforts are needed to identify and close gaps in population immunity by conducting high-quality SIAs in countries with sustained measles virus transmission and improve routine MCV1 and MCV2 coverage

Background

The Western Pacific Region consists of 37 Member States (including 27 countries and 10 areas). For surveillance and verification purposes, the 21 Pacific islands are considered as one epidemiological block. In 2003, the Regional Committee for the Western Pacific (RC) resolved to eliminate measles. A target year of 2012 was established in 2005, and reaffirmed in 2010. In 2012, the Regional Committee urged member states to interrupt all residual endemic measles virus transmission as rapidly as possible. These RC resolutions emphasize accelerating rubella control and CRS prevention by combining them with measles elimination activities. In June 2013, the Technical Advisory Group on Immunization and Vaccine Preventable Diseases in the Western Pacific Region recommended that the Region establish a rubella elimination goal.

Regional update

Annual data on MCV coverage are reported from 36 of the 37 WPR countries and areas to WHO and UNICEF through the joint reporting form (JRF); overall, MCV1 coverage in WPR was 98% in 2012. In 2012, 15 (42%) countries and areas achieved $\geq$95% MCV1 coverage; MCV1 was administered at 8 months in one (3%), at age 9 months in six (17%), at age 10 months in one (3%), at age 12 months in 24 (67%), and at age >12 months in four (11%).

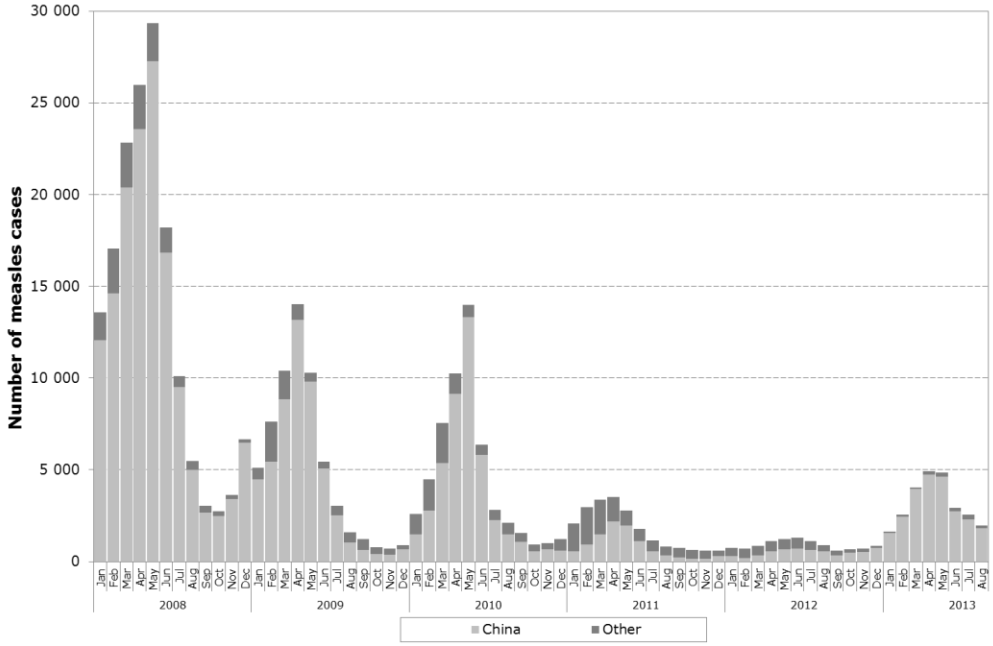
Thirty-three countries and areas provide routine MCV2, with 11 (31%) reporting $\geq$95% MCV2 coverage in 2012. Among the 33 countries and areas reporting MCV2 coverage in 2012, the scheduled age of MCV2 administration ranged from 12 months to 7 years. In 2012, more than 1.1 million children were targeted for vaccination in measles SIAs in Papua New Guinea and MR SIAs in Mongolia and Solomon Islands.

Measles case-based surveillance is conducted in all 37 WPR countries and areas. As of August 2013, nine (64%) of 14 countries and areas met the target of ≥2 suspected cases discarded as non-measles per 100,000 population; 96% of suspected cases were adequately investigated; 92% of suspected cases had adequate specimens collected for laboratory testing; and 96% of blood specimens received by the laboratory had results available within 7 days.

Progress to achieve elimination

By end of 2012, measles incidence reached an historic low, decreasing to 5.9 cases per million population. In 2013, only three countries in the Region report on-going endemic transmission: China (incidence 28.1 per million), Malaysia (8.1 per million), and the Philippines (7.2 per million). The only other countries reporting measles incidence rates above 5 per million population are Lao People's Democratic Republic (18.0 per million) and Macao (5.9 per million). In 2013, the predominant measles virus genotype detected in WPR is H1, with a few cases reported as B3, D8, D9, and G3.

Figure: Measles cases by month of onset, Western Pacific Region, 2008-2013



The WPR Guidelines on Verification of Measles Elimination were finalized in March 2013; progress toward measles elimination in WPR will be monitored by the Regional Verification Commission through annual progress reports from each country or area and from the Pacific islands countries and areas reporting as one epidemiologic block. The first annual progress reports from National Verification Committees were due on 1 October 2013.

Rubella-containing vaccine is not provided in four WPR countries and areas; three of these countries (Cambodia, Papua New Guinea, and Viet Nam) are eligible for financial support offered by the GAVI Alliance to conduct a wide-age-range SIA using combined measles-rubella vaccine followed by the introduction of rubella vaccine in their national routine immunization programs. In addition to contributing to rubella elimination, these SIAs provide a unique opportunity to boost population immunity to measles and contribute momentum to achieve and sustain measles elimination in WPR.

Challenges and opportunities

To achieve measles elimination in the Western Pacific Region, intensified efforts are needed to identify and close gaps in population immunity and by conducting high-quality SIAs in countries with sustained measles virus transmission (e.g., China, Malaysia, and the Philippines). Although China represents 75% of the regional population, in 2013, 96% of all confirmed measles cases were reported from China. In response to the relative measles resurgence, China hosted a National and International Consultation on Measles Elimination and EPI Strengthening in June 2013. Recommendations from the consultation included that provincial (or smaller) SIAs were needed to fill immunity gap; population coverage surveys should be considered among young children at national and subnational levels; to develop stronger immunization practice standards to reduce missed opportunities; and to reduce nosocomial transmission of measles by reducing admissions, isolating cases, and vaccinating health workers

Additional efforts are needed to strengthen routine immunization services in countries and areas with <95% coverage with the routine MCV1 or MCV2, to introduce a MCV2 dose in the four remaining countries and areas that do not yet have a routine 2-dose MCV schedule, and to use SIAs to close immunity gaps among measles-susceptible populations in countries and areas that have ongoing measles virus transmission.

High-quality case-based measles surveillance is critical to the verification process. Despite overall improvement in measles surveillance performance, gaps persist, as reflected by the low proportion of second-level administrative units with one or more non-measles discarded case per 100,000 population. Additionally, incomplete investigations of suspected measles cases in some countries challenge efforts to rapidly identify and respond to outbreaks and to measure and document progress towards elimination. The sensitivity of the measles surveillance system in other countries with discarded non-measles reporting rates of <2 per 100,000 population might be insufficient to rapidly detect and respond to outbreaks or to meet verification criteria.

Important progress has been made towards accelerating rubella control in recent years, including an increased number of countries using combination measles-rubella vaccine and an increased number of countries integrating measles and rubella surveillance. As a way forward, countries are encouraged to integrate measles and rubella elimination activities whenever possible; build rubella case-based surveillance, ideally integrating with measles surveillance; and gain understanding of rubella epidemiology and population immunity profiles to help develop effective and feasible immunization strategies to achieve rubella elimination.

V. Use of Rubella Vaccine in the Routine Vaccination Schedule

- Recommendations in the current rubella position paper are either unclear or weak with regards to the timing of administration of the 1st dose of RCV and to the choice of RCV formulation when two doses of measles containing vaccine are used by countries. This lack of clarity has led to suboptimal timing and usage of RCV in some countries.
- This section highlights the current practices and provides the rationale for the following draft recommendations:
  - For countries introducing or using rubella vaccine, it is strongly recommended that this be given in combination with the first dose of MCV (as MR or MMR).
  - In countries using RCV and a two-dose schedule of MCV, both doses should be the same formulation of MR or MMR. That is the same vaccine should be used for both doses.

Current policy guidance

The current position paper on rubella (http://www.who.int/wer/2011/wer8629.pdf) recommends that countries take the opportunity offered by accelerated measles control and elimination activities to introduce RCVs. In addition, it states that

> *"The first dose of an RCV can be delivered at 9 months or 12 months, depending on the level of measles virus transmission.*
>
> *"However, when combined with measles vaccination, it may be easier to implement a second dose of RCVs using the same combined MR vaccine or MMR vaccine for both doses"*

However, the position paper does not provide clear guidance as to the optimal timing for the administration of the RCV and it does not clearly explain the statement on the practicality of using the same formulation of RCV for both routine doses.

This section describes two issues that have arisen from unclear or weak policy guidance regarding the use of RCV as part of national routine immunization programmes. It proposes strengthening the recommendations and provides the rationale for them.

The timing of administration of the 1st dose of rubella containing vaccine

By 2012, 132 of 194 (68%) WHO member states have introduced RCV either as MR or MMR through their national immunization programmes. Of these, 117 (60%) have RCV included in both routinely administered doses of measles-containing vaccine (MCV). However, 9 member states with two routine doses of MCV have only one dose of RCV in their schedule -- 8 countries (Cape Verde, Iraq, Jordan, Lebanon, Maldives, Philippines, Saudi Arabia, and Tunisia) include the RCV only with MCV2 and the 9th country (Bangladesh) includes RCV with MCV1 but not with MCV2. Sixty two countries are yet to introduce a RCV (see table).

Table: The vaccine formulation and number of member states using measles and rubella containing vaccines in their routine national programmes

Vaccine used for first dose	Vaccine used for second dose	Number of countries
M	none	42
M	M	20
M	MR or MMR	8
MR or MMR	none	6
MR or MMR	M	1
MR or MMR	MR or MMR	117
Total		194

The problem

Given that global MCV1 coverage is considerably higher than MCV2 coverage (84% vs 36% for 2 year old cohorts in 2012), countries providing RCV with MCV2 rather than with MCV1 miss the opportunity of the higher coverage achieved with MCV1. In addition, as the second dose is given to older children than the first dose, this will delay the protection of children against rubella in some countries until children are 7 years of age. For example, for the 8 countries that have RCV only with MCV2, both the Philippines and Lebanon can gain 47% and 10% points in coverage by including the RCV with MCV1. In addition, children in Tunisia can be protected against rubella by 12 months of age rather than at age 6 years.

Therefore, there is a need to provide stronger recommendations on the timing of the first dose of RCV for the 8 countries that have already introduced RCV and give it with MCV2 only as well as for the 62 countries that are yet to introduce RCV.

Recommendation

- For countries introducing or using rubella vaccine, it is strongly recommended that this be given in combination with the first dose of MCV (as MR or MMR).

Using the same vaccine formulation for both routine doses

In 2012, of the 194 WHO member States, 146 administer a second dose of MCV through their routine national immunization programmes with 48 countries yet to introduce the routine second dose of MCV. Among the 146 countries using two routine doses of MCV, 117 include RCV with both doses, 9 use only 1 dose of RCV and the remaining 20 countries do not include RCV at all.

The problem

As stated above the current recommendation is not strongly in favour of using the same measles- and rubella-containing vaccine formulation for both doses. In addition, it does not mention that when the formulation contains mumps vaccine (MMR), then at least two doses must be given.

There are clear programmatic disadvantages of not including RCV with both MCV1 and MCV2. These include:

1. Complexities in vaccine procurement, logistics, recording, and reporting. There are inherent problems associated with ordering, procurement and downstream supply of different vaccine

formulations (e.g., M and MR or MMR) as well as recording and reporting which vaccine has been administered to an individual child. There is also the potential for programmatic error, for example administering M when MR or MMR is indicated in the schedule.

2. Higher wastage. With different vaccine formulations aimed at different target age groups, there is the potential for increased wastage resulting from unused vaccine in an opened vial at the end of the vaccination session. The actual wastage depends on the session size (i.e., the number of children attending and requiring a specific vaccine formulation), session frequency, and the nature of the vaccination post (fixed site, school-based immunization, vs. an outreach session).
3. Lower coverage. Providing RCV only once may lead to lower coverage levels than if it is provided at two different opportunities. Using RCV for both routine doses with result in more children being protected against rubella.

In addition to the disadvantages above, there are a number of programmatic considerations that need to be taken into consideration:

Cost

The cost of single-antigen measles vaccine at UNICEF 2013 procurement prices (for a 10-dose vial) is between 21.5 to 42.5 US cents per dose compared to 52.4 US cents per dose for MR vaccine.[19] Hence, the cost increase will be between 10 to 30 US cents per dose. However, there will be no added administration costs as one preparation will be replaced by another. In addition, due to larger volumes, the price of MR vaccine is very likely to come down from its current levels.

Safety

The safety of RCV in pregnant women has been established[20]; hence it can be used not only in routine immunization of children but also in mass immunization campaign settings targeting adolescents and adults without safety concerns[21].

Global vaccine supply

Currently there are 3 manufacturers supplying measles vaccine in 10-dose vials to UNICEF (P.T. Bio Farma, Sanofi Pasteur and Serum Institute of India Ltd). MR in 10-dose vials is supplied to UNICEF by Serum Institute of India Ltd and it is expected that their capacity for the manufacture of MR vaccine will increase directly in proportion to the decrease in demand for measles only vaccine. Recommendations to countries to use two RCV doses instead of one would have some additional supply requirements. For example, if all the 20 countries (no RCV) added 1 additional dose of RCV; and the 8+1 countries (1 RCV dose) made the switch to 2 doses of RCV, the requirement for MR vaccine (assuming a 15% wastage) is just over 59 million doses. This quantity of MR is already available with ease, e.g. the MR campaign in Bangladesh targeting <15 year olds will require approx. 60 million doses of MR vaccine. This has been fully met in addition to other needs from across the world. Hence a global shortage, at least in the

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[19] http://www.unicef.org/supply/files/Measles.pdf; http://www.unicef.org/supply/files/MR.pdf

[20] Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001-2008**.** Castillo-Solórzano C; Reef SE; Morice A; Vascones N; Chevez AE; Castalia-Soares R; Torres C; Vizzotti C; Ruiz Matus C.
J Infect Dis; 204 Suppl 2: S713-7, 2011 Sep.

[21] Congenital rubella syndrome after rubella vaccination in 1-4 weeks periconceptional period.
Nasiri R; Yoseffi J; Khajedaloe M; Sarafraz Yazdi M; Delgoshaei F. Indian J Pediatr; 76(3): 279-82, 2009 Mar.

medium term, is not expected and can be entirely avoided by prior planning of the phasing in of MR and phasing out of measles only vaccine.

Cold chain capacity

Since measles only vaccine will be replaced by MR vaccine, for the same presentation (1 dose or 10 dose vials) there will be no additional demand on cold chain capacity and existing cold chain capacities in countries will be adequate to deal with the change in formulation.

Based on the disadvantages and considerations listed above, there is need for a stronger recommendation to use the same formulation of measles- and rubella-containing vaccine for both routine doses in the childhood immunization schedule.

Recommendation

- In countries using RCV and a two-dose schedule of MCV, both doses should be the same formulation of MR or MMR. In other words, the same vaccine should be used for both doses.

VI. Target Age Range for Measles Follow-up SIAs and for Measles - Rubella Catch- up SIAs

- Country experience and preliminary results from mathematical modelling were reviewed to address the question: *What criteria should be used to guide countries on when to expand the target age range for follow-up measles (M) SIAs beyond 5 years and catch-up measles-rubella (MR) SIAs beyond 15 years?*
- Measles and rubella elimination has been achieved and maintained in countries using a range of different vaccine delivery approaches (2 routine doses only, 2 routine doses and a single catch-up SIA, 2 routine doses and regular SIAs, and 1 routine dose and regular SIAs). These countries have all achieved and maintained elimination by reaching and sustaining vaccination coverage ≥95% in routine services and/or SIAs for all cohorts born since the introduction of vaccination and in all or nearly all districts.
- Factors affecting the magnitude and duration of impact from M, or MR SIAs, include the pre-existing population immunity (from routine vaccination, previous SIAs, and natural infection), the target age range for the SIA, the coverage achieved in the SIA, and the interval between SIAs. The final impact of M or MR SIAs is determined by how well the choice of target age range and the coverage achieved fill existing gaps in population immunity.
- Poor quality coverage and surveillance data hamper the ability to accurately assess age-specific susceptibility to measles and rubella and hence identify the appropriate target age and interval between SIAs. Where better quality coverage and surveillance (including serosurveillance) data are available, this provides more valuable local evidence to guide programme planning than mathematical modelling that is currently available. The priority should be on improving this data in every country.
- The following sections on M and MR SIAs provide the rationale for the following draft recommendations:

  o No magic formula exists to determine the appropriate target age range for M or MR SIAs. Current rules of thumb are pragmatic and not based on specific evidence.

  o The analysis of immunity should be triangulated with measles and (if applicable) rubella surveillance data. Age groups with high incidence rates should correspond to age cohorts with lower levels of immunity. Data from high-quality serological surveys should also be used when available.

  o The target age range of M SIAs should be extended beyond 5 years based on a comprehensive review of the country situation, focusing on the age pattern of susceptibility to measles based on routine and SIA coverage results, the age-specific incidence of measles, the age distribution of measles cases, available seroprevalence data, population characteristics, and the programme capacity to achieve high (>95%) coverage.

  o Catch-up MR SIAs should be extended beyond 15 years either to accelerate the progress toward established rubella/CRS elimination goals or to fill gaps in population immunity based on similar epidemiologic and programmatic considerations as for M SIAs. Additional information to consider for

MR SIAs include levels of rubella immunity among women of child bearing age, epidemiology of rubella and CRS, and population characteristics – e.g., age-specific fertility rates and age of mothers of CRS affected infants or to accelerate progress towards established rubella/CRS elimination goals.

o Consideration should be given to the trade-offs between strengthening routine delivery versus conducting poor quality wide age range SIAs especially in countries where systems are weak.

Target age range for M follow-up SIAs

Current Practice and description of the issue

The current Measles Position Paper recommends all programmes provide two doses of measles vaccine and achieve high coverage in order to raise population immunity to ≥95% and prevent epidemics. Delivery of the second dose may occur at a scheduled age through routine services or periodically through mass campaigns depending on which strategy achieves the higher coverage. Countries may add a second dose to the routine immunization schedule when first dose coverage is ≥80% at the national level for three consecutive years as determined by the most accurate means available (for example, a well conducted population-based survey or WHO/UNICEF estimates). SIAs should start with a wide age-range catch-up SIA targeting children 9 months to 14 years of age, followed by regular follow-up SIAs targeting children born since the last SIA, generally 9 to 59 months of age. Follow-up SIAs should occur every 2-4 years so that an SIA is conducted before the number of susceptible pre-school age children reaches the size of a birth cohort.

In AFR countries accelerated measles control in the 1990s by testing ideas that SIAs targeting the age groups at highest risk of adverse outcomes from measles (those <5 years of age) or SIAs targeting urban areas would reduce measles incidence and deaths. At the time the limited data on the age distribution of cases suggested that 25-50% of cases were older than 5 years. These SIAs had limited impact on both cases and deaths, as reviewed by Otten in 2003[22]. In response countries were urged and supported financially to conduct SIAs targeting children up to 15 years of age. For follow-up SIAs the regional TAG recommended in 2005 the following guidelines that have been informally adopted by other regions:

- "After measles SIAs that achieve relatively homogeneous coverage rates of >90%
    - If routine measles coverage ≥80% - an interval of 4 years is recommended targeting children 9-59 months of age.
    - If routine measles coverage >60%-79% - an interval of 3 years is recommended targeting children aged 9-47 months.
    - If routine measles coverage <60% - an interval of 2 years is recommended targeting children 9-35 months of age
- After measles SIAs that achieve relatively homogeneous coverage rates <90%
    - If routine measles coverage ≥80% - an interval of 3 years is recommended.
    - If routine measles coverage <80% - an interval of 2 years is recommended."

[22] Otten MW Jr, Okwo-Bele JM, Kezaala R, Biellik R, Eggers R, Nshimirimana D. Impact of alternative approaches to accelerated measles control: experience in the African region, 1996-2002. J Infect Dis. 2003 May 15;187 Suppl 1:S36-43.

Countries have generally followed these guidelines for follow-up SIAs, except that most have targeted children 9-59 months of age regardless of the interval between SIAs. Countries that have followed the above recommendations include several countries in AFRO conducting SIAs in a 3 year cycle that targeted children 9-47 months of age (Central African Republic, Comoros, Eritrea, Madagascar, Niger, Swaziland, Togo, Uganda, and Zambia). Two countries in WPR also followed these guidelines: the Philippines in 2007 targeted children 9-47 months of age in an SIA held 3 years after the previous one and in 2010 Papua New Guinea also targeted children 6-35 months of age in an SIA held two years after the previous one.

Countries have also used a "90% rule" for the target age range of a catch-up or follow-up SIA. Under this rule of thumb, the SIA should target an age range that includes 90% of the age distribution of reported cases. Though this rule of thumb has worked well in many situations, it can be misleading in some situations, for example where overall incidence is low. Work is underway to use dynamic models of disease transmission to better define the rule. Catch-up SIAs in large countries in Asia (Bangladesh, China, India, and Pakistan) targeted from 9 months to 10 or 12 years based on the age range of reported cases. For example, in Bangladesh 86% of reported cases in 2003 were under 10 years of age, prompting the choice of 9 months to 9 years for the catch-up SIA in 2005-2006. Catch-up SIAs in other countries (e.g. Egypt, Kyrgyzstan, Republic of Korea, Sri Lanka) chose target age ranges targeting older children and adolescents based on the age distribution of cases and/or serosurveys, e.g., from 8 to 16 years in the Republic of Korea. These countries generally had strong routine programs and assured high levels of immunity in younger (<5 years) age cohorts with routine vaccination rather than SIAs.

Countries have also widened the target age range of follow-up SIAs in response to large outbreaks where the age distribution of cases is shifted to older age groups. The WHO guidelines on response to measles outbreaks in mortality reduction settings[23] recommend the age groups to be vaccinated be chosen to fill susceptibility gaps based on the routine vaccination coverage and coverage during SIAs in each birth cohort, age-specific incidence rates, and the age distribution of cases to determine the age group to target.. In these situations a review of routine and SIA coverage data usually reveals a period of low coverage corresponding to the age cohorts affected by the outbreak (see country examples below).

In 2012 GAVI decided to offer funding for measles follow-up SIAs in six large countries (Afghanistan, Chad, DRC, Ethiopia, Nigeria and Pakistan) based on the assumption that these SIAs would target children 9-59 months of age. Four countries expressed an interest in applying and on review of the age distribution of recent cases, only Nigeria requested support for a 9-59 month target age range, with DRC and Pakistan requesting support for 9 months to 9 years of age SIAs and Ethiopia requesting support for an SIA targeting 9 months – 14 years of age.

To provide clearer recommendations to countries and partners on when the target age range for measles SIAs should be expanded beyond 5 years, the Measles-Rubella Working Group of SAGE was asked to review country experience and modelling evidence. The country experience presented below is being used to refine questions to be answered through mathematical models of disease transmission.

[23] Response to measles outbreaks in measles mortality reduction settings. WHO/IVB/09.03 Geneva: World Health Organization. P 20.

Evidence and rationale for recommendations:

The following case studies provide evidence that uniform high coverage with MCV (>95%) must be reached and sustained in order to achieve elimination and that the timing and target age range for measles SIAs should fill any remaining gaps in population immunity.

Republic of Korea:

The target age range of the 2001 MR SIA was based on results of a serosurvey done during a large outbreak. The age distribution of measles cases matched age cohorts with low immunity from the serosurvey. With 96% SIA coverage and >92% coverage with 2 doses in routine, elimination has likely been achieved.

After achieving high coverage with one dose of MMR vaccine and experiencing <1 reported case per million population for 5 years, the Republic of Korea had a large measles outbreak in late 2000 and early 2001. The age distribution of cases was bimodal, with a peak in children aged <2 years of age and in school-age children 6 – 16 years of age. A serological survey of 18,402 school children (7-18 years of age) in late 2000 found that seronegativity was high (>5%) for all age cohorts, ranging from 5.3% at 17 years to 15.4% at 10 years of age. This age group corresponded to children born before the last major outbreak in 1994 and before the introduction of a second dose of measles in routine in 1997. The immunization programme instituted a school entry requirement for 2 doses of MMR vaccine that would ensure children 7 years and younger had high immunity and held an MR SIA targeting children 8-16 years of age in March 2001, achieving 96% coverage based on doses administered. After this SIA routine coverage with 2 doses has remained >92%. Incidence has been <1 per million population and only small, self-limited outbreaks occurred, most linked to importations and / or nosocomial transmission.

Albania:

The target age range of the MR SIA covered the age distribution of recent measles and rubella cases. With 98% coverage in the SIA and >93% coverage with 2 doses in routine, elimination has likely been achieved.

Albania reported large numbers of cases in the late 1990s after emerging from a period of isolation. In 1999 the country developed a measles-rubella elimination plan in order to meet regional elimination goals. From 1996 – 2000, 25-35% of cases were aged <5 years while 74% were 5-14 years of age. In the absence of rubella vaccination, rubella was also common in Albania, affecting primarily children <15 years in outbreaks every 5-6 years, including in one in 2000. The country chose to target children 9 months to 14 years of age with MR vaccine in 2000, reaching 98% coverage based on doses administered. MR vaccine was later provided through routine services to women 16-35y in 2001 and men 17-24y in 2003. After these activities routine coverage with 2 doses of MR vaccine (at 1 and 5 years of age) has remained >93%. Incidence of both measles and rubella has since been <5 per million population, except for 2006-7 when the country had outbreak of 90 reported cases linked to importations in disadvantaged, chiefly Roma, communities in 2006-7.

Kyrgyzstan:

The age distribution of the MR SIA covered the older half of the age distribution of recent measles and rubella cases and 2-dose routine covered the younger age groups. With 99% coverage in the SIA and >90% coverage with both routine doses, elimination has likely been achieved.

Kyrgyzstan reported large numbers of cases from 1997-1999 despite high coverage with one dose of measles vaccine. In 1997-1999, the outbreak started with 78% of reported cases 7-25y of age and 19% <7y of age and finished with 55% of cases 7-29y of age and 42% <7y. After implementing laboratory confirmation of suspected measles and rubella cases in 2000, the next year the country had a rubella outbreak with 2,017 reported cases: 40% aged <7y, 59% aged 7-25y, 1% >25y. In 1999 the country developed a measles-rubella elimination plan in order to meet regional elimination goals, with the country choosing to target children 7 to 25 years of age with an SIA using MR vaccine in 2001 and to target children <7 years of age through routine immunization. The SIA reached 99% coverage based on doses administered and 94% by coverage survey in the capital Bishkek. Since 2002, coverage of both routine doses (at 1 and 6 years of age) has been >90%. Measles and rubella incidence has been <5 per million population except for measles outbreaks in 2005-7 (120 reported cases) and 2011 (222 reported cases). The 2011 outbreak was linked to an importation from Uzbekistan and affected primarily children born since the 2001 SIA.

Ghana:

The age distribution of the initial measles catch-up SIA in 2001-2002 covered the age distribution of measles cases. Though coverage with the catch-up was >95%, coverage of the first follow-up SIA and routine (one dose) were both <90%. Routine improved afterwards to >90%, and second follow-up also attained >90% coverage by survey. Incidence since 2002 has been <20 confirmed cases per million population and no measles deaths have been recorded.

To control large yearly outbreaks of measles, Ghana analyzed the age distribution of cases in 3 districts and found 66% of cases <5 years and 30% between 5 – 14 years of age. Based on these results the country held an SIA targeting children from 9 months to 14 years of age in late 2001 (Central Region) and 2002 (remaining regions), achieving 99% coverage based on administered doses. Routine first dose coverage varied between 78-85% from 2001-2006 and between 86-95% thereafter, and the country held SIAs in 2006 and 2010 targeting children 9 – 59 months of age. SIA coverage was 79% in 2006, based on administrated doses, and 94% in 2010, based on a post-SIA coverage survey. Though reporting through the WHO-UNICEF Joint Reporting Form (JRF) suggests between 100-1,500 cases have been reported each year since the SIA, laboratory confirmed, case-based data from the MOH indicate that 14-394 confirmed cases were reported yearly since the SIA, giving an incidence of 0.62-19 per million population.

Kenya:

Initial SIAs targeting children <5 years of age did not control measles, with 37% of cases >5 years. Incidence dropped after an SIA targeting children <15 years of age. Routine coverage (1 dose) was <80% through 2006. Delayed first follow-up SIA allowed a large outbreak to occur. Though routine has improved to >85% since the 2006, SIAs have not targeted the growing proportion of cases aged >5 years. Incidence has remained high except for the year immediately after SIAs in 2009 and 2012.

Kenya experienced regular measles outbreaks in the 1990s-2000s despite reaching 80% coverage with one dose of measles vaccine (per coverage survey results) and conducting subnational SIAs targeting children 9 to 59 months in 1994, 1999 and 2000. As shown in the table below, from 1997-2001, 58% of the 53,508 reported cases were <5 years of age, with 25% aged 6-10 years and 12% aged 11-15 years. Based on these results the country held an SIA targeting children from 9 months to 14 years of age in 2002, achieving 98% coverage based on administered doses. Up until 2005, although first dose measles vaccination coverage was 70-80%, measles incidence was <5 reported cases per million population. A follow-up SIA initially planned for 2005 was delayed until 2006 in order to distribute long-lasting insecticide treated bednets during the SIA. In late 2005 measles cases began to increase, with 153 cases reported in 2005 and 1,847 cases reported in 2006. To control the outbreak the follow-up SIA was done in two phases both involving children 9-59 months of age, first targeting outbreak-affect districts in May 2006 and the second targeting the rest of the country in July, with >100% coverage based on doses administered. Though routine coverage increased to 80% in 2007 and 90% in 2008, measles incidence remained 30 – 50 reported cases per million population until the next follow-up SIA in 2009.

Although 24% of 3,609 cases reported from 2006-2009 were 6-15 years and 14% were ≥16 years, the 2009 SIA targeted children 9 – 59 months of age. After this SIA, achieving 82% coverage based on doses administered, and with routine coverage at 86-93% since 2008, incidence dropped to 2 reported cases per million population in 2010 but increased to >50 per million population in 2011. In 2011, 34% of 2,523 reported cases were aged 6-15 years and 22% were ≥16 years. No data was reported to the JRF in 2012 but >50 confirmed cases per million population were reported through the case-based surveillance system. In 2012 another SIA was done, with plans to target children 9 month to 9 years based on the age distribution of cases, but funds were available only to cover children 9 – 59 months. This SIA achieved 90% coverage based on a post-SIA survey and by 10 September 2013 only 177 confirmed cases have been reported.

Table. Age distribution of cases and SIAs, Kenya, 1997-2012.

	1997-2001	**2002**	**2005/6**	**2006-2009**	**2009**	**2011**	**2012**
SIA target		9m-14y	9-59m		9-59m		9-59m
SIA coverage		98%	>100%		82%		90%
Age distribution of cases							
<5 years	58%			61%		38%	
5-9 years	25%			19%		22%	
10-15 years	12%			5%		12%	
≥16 years	5%			14%		22%	

Malawi

After catch-up and follow-up SIAs targeting the recommended age range and generally achieving >95% administrative coverage, together with >80% routine coverage except for 2000-2004 (<80%), incidence was low for >10 years. A large outbreak occurred in 2010 and was not controlled by outbreak response targeting <5 years or <15 years covering only one district at a time. Though 28% of cases were ≥15 years, nationwide SIA targeting children aged 6 months – 14 years reaching >95% appeared to stop the outbreak. In years since incidence has been ≤2 confirmed cases per million.

Malawi was among the 7 southern African countries that decided to eliminate measles through high routine coverage plus catch-up and follow-up SIAs. In 1997 a catch-up SIA targeted children 9 months to

14 years of age, achieving 89% coverage based on administered doses, was conducted. Follow-up SIAs targeting children 9 – 59 months of age were implemented in 2002 and 2005, each achieving >100% coverage based on doses delivered. Routine coverage was >80% since then except for a dip to 70-80% from 2000-2004. Measles incidence was <100 reported cases per million population through 2005 then dropped to ≤10 per million population until a large outbreak in 2010. This outbreak spread throughout the country with 131,725 reported cases. Outbreak response campaigns targeting children 9-59 months of age early in the outbreak did not stop it from spreading. The age distribution of cases showed that 42% were <5 years of age, 30% were 5-14 years of age, and 28% were older than 15 years. These age cohorts were born during the years of low coverage (2000-2004) or were targeted by the initial catch-up SIA. Age-specific attack rates were highest in <3 years of age, roughly 1% in 3-20 years, and <1% for >20 years. District-level campaigns targeting children 6 months – 14 years or age lead to drops incidence in the target districts, but incidence continued to increase in adjacent districts. A nationwide SIA targeting children 6 months – 14 years of age was done in August achieving >100% coverage by dose administered, with incidence dropping to ≤2 reported cases per million in 2011 and 2012.

Zambia

Initial SIAs targeting children <5 years of age did not control measles, with 20-29% of cases >5 years of age. Incidence dropped after an SIA targeting children <15 years of age together with routine coverage (1 dose) >80% and a follow-up SIA coverage with 88% coverage by survey. In 2010 a large outbreak developed with many cases >5 years that continued into 2011 despite a follow-up SIA in 2010 targeting children 9 months to 4 years. Incidence decreased to low levels after an outbreak response in 4 districts in 2011 targeting <15 years and a nationwide SIA in 2012 also targeting <15 years of age.

Zambia attempted to control large yearly outbreaks of measles with SIAs targeting children from 9-59 months of age, first in urban areas in 1999 and in 50% of districts in 2000, with little change in measles incidence. The age distribution of cases is available from selected health facilities in Lusaka from 1996-2000 and an outbreak in Western Province in 2002. As shown in the table below, in Lusaka, 76% of cases were <5 years and 20% were 5-14 years of age, while in Western Province 30% of cases were <5 years, 29% were 5-14 years and 44% were >14 years of age. An SIA targeting children 6 months to 14 years of age was done in the Southern Province in late 2002 and in the rest of the country in June 2003, with coverage reaching >100% in each phase based on doses administered. With routine first dose coverage varying between 84 – 96% and a follow-up SIA in 2007 achieving 88% coverage based on a post-SIA survey, measles incidence averaged 23 reported cases per million population until 2010. In 2010 and 2011 the country had a large measles outbreak with >28,000 reported cases, with highest incidence in the east and north of the country near Malawi and DRC. The age distribution of cases from 2010 showed 55% were aged <5 years, 14% were 5-9 years of age, and 7% were 10-14 years. A follow-up SIA was held in 2010 that followed the AFRO TAG guidelines, targeting children 9-47 months of age and achieving 88% coverage by post-SIA survey. In 2011 the outbreak continued with a decrease in the proportion of cases <5 years to 46% and an increase in cases 5-9 years to 17% and 10-14 years to 9%. In 2011 outbreak response campaigns were held in highly-affected districts of Luapula and Northern Provinces (4 districts in each) targeting children 9 months to 14 years of age, with coverage per district ranging from 73-100% based on doses administered. In 2012 a nationwide SIA targeting children 6 months to 14 years achieved 96% coverage based on a post-SIA survey and that year 561 cases were reported and in the first half of 2013 only 1 confirmed case was reported.

Table. Age distribution of cases and SIAs, Zambia, 1996-2012.

	Lusaka Dist 1996-2000	W Prov 2002	2003	2007	2010	2010	2011	2012
SIA target			9m-14y	9-59m		9-47m		6m-14y
SIA coverage			>100%	>100%		88%		90%
Age distribution of cases								
<5 years	75%	31%			55%		46%	
5-9 years	13%	15%			14%		17%	
10-14 years	7%	14%			7%		9%	
≥15 years	4%	40%			25%		25%	

Viet Nam

Catch-up SIAs targeted children aged 9 months to 9 years, matching the age range of measles in the South but not in the North, where cases tended to be older. Incidence dropped after the SIAs with routine coverage with 1 dose generally >90%. District-level outbreak responses over the next 6 years did not prevent the accumulation of susceptible children and young adults. In 2008-2010 a large outbreak affected primarily adults not covered by the catch-up SIA and children born since the catch-up SIA, with low incidence in age groups covered by the SIA. Since a follow-up SIA targeting children <5 years in 2010, with 96% coverage, incidence has remained low.

Despite several years of high first dose coverage in the 1990s Viet Nam continued to report several thousand measles cases each year. The age distribution of cases in the late 1990s differed between South and North, with 70% of cases <10 years and 26% 10-14 years in the South and 51% <10 years and 41% 10-14 years in the North (see Table below). SIAs targeted children 9 months – 9 years of age in 1999-2002 (North) and in 2003 (South), achieving 99% coverage by doses administered. First dose coverage remained >90% except for a dip to 83% during a vaccine stock-out in 2007. Outbreaks in 2004-2006 mostly affected children missed by the SIA living in mountainous provinces in the far northwest. In response high-risk districts were targeted for SIAs in 2004 and 2007-2008, with >95% coverage based on doses administered. In addition a second dose of measles vaccine was introduced in 2006 at 6 years of age, reaching >95% coverage by 2008. In 2009 a measles outbreak started in young adults in the North then spread to the South, involving >7,700 cases. In both the North and South most cases were in 17-30 year olds, age groups not covered by the SIA in 2002-2003, and children <8 years, born since the SIA, though in the South more cases were <7 years while in the North more cases were ≥17 years. In 2010 a follow-up SIA was done targeting children 12-59 months of age and the age for MCV2 was lowered to 18 months of age. In 2011 and 2012 incidence has been <10 reported cases per million population.

Table. Age distribution of cases and SIAs, Viet Nam, 2001-2012.

	1990s North	1990s South	1999-2002 North	2003 South	2008-10 North	2008-10 South	2010
SIA target			9m-9y	9m-9y			9-59m
SIA coverage			99%	99%			96%
Age distribution of cases							
<5 years	13%	25%		<7 years	31%	54%	
5-9 years	38%	45%		8-16 years	8%	8%	
10-14 years	41%	26%		17-27 years	52%	32%	
≥15 years	8%	3%		>27 years	9%	6%	

Discussion

The experience of these 8 countries confirms that measles incidence can be reduced to very low levels with high coverage with two doses of MCV in routine, plus SIAs to fill immunity gaps determined by analyses of cases from recent outbreaks, the history of routine coverage, and in the Republic of Korea a well-timed and well-executed serological survey. Ghana and Malawi also reduced measles to low levels through repeated SIAs and >80% coverage with one dose of MCV in routine. The large outbreaks in Malawi and Zambia revealed gaps in coverage not appreciated during previous years of low incidence. The wide-age range SIAs done in response have reduced measles incidence to low levels, even though 10-30% of cases were aged >15 years. In Kenya, Malawi, Zambia and Viet Nam large outbreaks also revealed susceptibility gaps created by the choice of SIA target age range and poor coverage in some geographic areas. In Kenya and Viet Nam the delayed follow-up SIAs further increased these susceptibility gaps. It is likely that incidence will rebound in Kenya as coverage in both routine and the most recent SIA remains <95%. The age distribution of the outbreaks Viet Nam showed that the initial SIA was effective in lowering incidence in the age cohorts targeted, leaving high incidence in younger and older age cohorts. Adults aged 17-27 years were more affected by the outbreak in 2008-2010. These age cohorts also represented 30-40% of cases reported before the catch-up SIA. It is possible that targeting older age cohorts in the catch-up SIA and / or conducting nationwide follow-up SIAs would have prevented the 2008-2010 outbreak in Viet Nam.

Estimating susceptibility and immunity gaps in the population

Ideally, the target age range of SIAs would be based on the immunity profile of the population showing the estimated levels of seropositivity by age cohort. Nigel Gay in the 1990s[24] developed cutoffs for seronegativity based on age stratified notifications of measles in England and Wales before vaccination, pre-vaccination serological data from Denmark, and mathematical models of disease transmission (see table below). An immunity profile could be calculated from data on routine and SIA coverage for the past 15-20 years, as in the Measles Strategic Planning (MSP) Tool[25]. Data on routine coverage are usually based on the WHO-UNICEF estimates that rely on doses administered and coverage survey data.

[24] Gay, NJ in: Measles: A strategic framework for the elimination of measles in the European Region; Copenhagen: WHO EURO, 1999, pp 20-2

[25] Simons E, Mort M, Dabbagh A, Strebel P, Wolfson L. Strategic planning for measles control: using data to inform optimal vaccination strategies. J Infect Dis. 2011 Jul;204 Suppl 1:S28-34.

Table. Age-specific susceptibility targets.

Age group	Maximum proportion susceptible
1-4 years	15%
5-9 years	10%
10-14 years	5%
15+ years	5% in each cohort

Coverage achieved by SIAs is typically estimated through three methods. Data on administered doses, divided by the estimated target population, is the most readily available estimate. It comes from data already collected during the campaign, can be calculated at almost all levels of the health system, and is available quickly after an SIA. However, the estimates are often inaccurate and exceed 100% because of inaccurate estimates of the target population, vaccination of children outside the target age range, and inaccurate recording of doses administered. Rapid convenience assessments are sometimes done "systematically" and are used to determine SIA coverage. However, these assessments do not use a probability sample of the population and thus do not produce statistically valid estimates of vaccination coverage. Post-campaign coverage surveys have been done using EPI cluster survey, LQAS, and population-based methods (DHS). However, these surveys often rely on maternal recall as SIA doses are often not recorded or the documentation is lost (cards) or obscured (finger markings).

For many SIAs coverage surveys were not done and some countries have seen large outbreaks after SIAs with high administrative coverage. The MSP tool and disease models relying on SIA coverage data often predict that most cases were born since the last SIA when in fact a high proportion of reported cases are from older age cohorts. Though often resource- and time-demanding, in some cases a well-time serological survey could be helpful to clarify the susceptibility profile when other sources of data are incomplete and / or contradictory.

Draft Recommendations:

- Ensure high coverage (≥95%) during measles SIAs
- Verify coverage for all measles SIAs through statistically valid and generally accepted methodology
- Encourage recording of doses given during SIAs (by age group, number of zero-dose children vaccinated)
- Measles follow-up SIAs should be extended to target children >5 years of age based on a comprehensive review of the country situation, focusing on the age pattern of susceptibility to measles based on routine and SIA coverage results, the age-specific incidence of measles, the age distribution of measles cases, available seroprevalence data, population characteristics, and programme capacity to achieve high (≥95%) coverage.
- Extending the age range of measles SIAs should be considered when
    - A review of the susceptibility pattern shows age cohorts >5 years of age have high estimated susceptibility
    - A review of surveillance data shows age cohorts >5 years of age have high incidence or make up a significant proportion of the age distribution of reported cases in recent outbreaks
    - A well-conducted serological survey shows susceptibility rates >5% in age cohorts >5 years of age

- Consideration should be given to the trade-offs between strengthening routine delivery versus conducting poor quality wide age range SIAs especially in countries where systems are weak.

Target age range for MR catch SIAs

Current Practice and description of the issue

The current practice of rubella vaccine introduction has changed with the publication of the 2011 WHO rubella vaccine position paper. The updated position paper, recommended countries take advantage of the measles platform of two doses of measles vaccine to introduce MR or MMR vaccine. These measles vaccine delivery strategies provide an opportunity for synergy and a platform for advancing rubella and CRS elimination. The updated position paper also supported a paradigm shift in vaccination strategy for introduction of rubella-containing vaccines. The 2000 position paper placed an emphasis on direct protection of women of child bearing age (WCBA). While the revised position paper includes "efforts to vaccinate WCBA" as one of the strategies it places primary reliance on rapidly reducing and finally interrupting transmission of rubella through vaccination of children through an initial wide age range MR SIA, use of combined MR (or MMR) vaccine in the routine childhood immunization schedule, and regular follow-up MR SIAs as necessary. To avoid the potential of an increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater with at least 1 dose of an RCV delivered through routine services or regular SIAs, or both.

As of 2013, two WHO regions (AMR, EUR), have established rubella elimination goals by 2010 and 2015, respectively. In 2003, the region of the Americas established rubella/CRS elimination goal by 2010. To accelerate progress towards the goal, the PAHO TAG recommended that countries conduct wide age range MR SIAs with the age group to be targeted should be based on the country's epidemiology. The upper age limit should be determined from known patterns of fertility and expected susceptibility. In addition, both sexes should be targeted. All countries, except countries with long standing programs[26] conducted wide age campaigns in adult males and females extending up to 39 years in most countries.

The EUR rubella elimination goal is by 2015. By 2009, all countries in EUR had introduced RCV. In 2013, WHO EURO published "Measles and rubella elimination 2015. Package for accelerated action: 2013-2015"[27]. One of their key strategies is to "provide measles and rubella vaccination opportunities, including supplementary immunization activities (SIA), to all population groups at risk for and susceptible to measles and/or rubella."[28] In EUR great progress has been made toward the rubella elimination goal; however, there are still countries experiencing rubella outbreaks and immunity gaps, particularly in the adult population

[26] Aruba, former Netherland Antilles, Canada, French department, Panama, United States and Uruguay
[27] Available at http://www.euro.who.int/__data/assets/pdf_file/0020/215480/PACKAGE-FOR-ACCELERATED-ACTION-20132015.pdf (accessed 16 October 2013).
[28] Susceptible population groups should be defined by evaluating existing epidemiological data on measles and rubella cases, assessing historical vaccine-coverage data or, in some circumstances, conducting seroprevalence surveys

Both the GVAP and the Measles and Rubella Initiative strategic plan: 2012-2020 include two elimination milestones:

- by 2015, Rubella/congenital rubella syndrome eliminated in at least two WHO regions
- by 2020, measles and rubella eliminated in at least five WHO regions.

As of October 2013, only 2 WHO regions have rubella elimination goals, 1 WHO region (WPR) has an accelerated rubella control and CRS prevention goal[29], and 1 WHO region (SEAR) has a rubella control and CRS prevention goal by 2020. Two WHO regions (EMR, AFR) have no regional rubella control/elimination or CRS prevention/elimination goal.

As of October 2013, 135 (70%) countries have introduced RCV into their programs. There are 59 remaining countries, of which 2 additional countries (i.e., Cambodia, Senegal) will introduce RCV into their program in 2013. In order to achieve the GVAP goal, three additional regions will need to adopt an elimination goal for 2020. Almost all the 59 countries that have not introduced RCV are in the 3 regions without elimination goals. Of those 59 countries, 48 countries are GAVI eligible. The current GAVI support is for MR campaigns up to 14 years 11 months of age. However, to achieve the rubella elimination goal which is 7 years away, countries may need to expand the age range to older individuals.

For regions and countries with established elimination goals and countries planning to introduce RCV, the current practice is to review the epidemiology, particularly looking at the age distribution of the cases. To determine the upper age limit, review of the expected susceptibility which may be determined from age distribution of cases or through seroprevalence studies, particularly focusing on the susceptibility of women of childbearing age which may include reviewing the maternal age of CRS cases and age specific fertility rates. In some countries where age distribution of measles cases include adults (>15 years of age), the upper age of the SIA may be driven by the measles epidemiology (e.g., Iran, Kyrgyzstan).

Weakness of current data and reasons for this, and need for coverage and serosurveys

In many of the countries, rubella cases are being identified through the measles case-based surveillance system. Even though both diseases classically have fever and rash, the fever is usually milder than measles and in up to 50% of rubella cases may present without a rash or be subclinical, so rubella cases will be underreported. In many countries, rubella outbreaks are not investigated so documenting the age distribution of cases may be challenging. For countries without adequate surveillance data, additional studies (e,g, seroprevalence) or investigations may need to be conducted.

Evidence and rationale for recommendations for MR SIAs:

Both modelling and epidemiology data was presented to the SAGE in 2011 documented the significant impact of introductory SIAs, particularly when targeting up to 14 years 11 months for all countries when the coverage was at least 80%. The WHO SAGE Measles-rubella Working Group was asked to address the following question: "*Under what circumstances should MR catch-up campaigns be expanded to include cohorts >15 years of age?*"

[29] Accelerated rubella control is defined as < 1 case/100,000 population and CRS prevention is defined as <1CRS case per 100,000 live births.

The Working Group identified 2 situations in which the target age range for MR SIAs should be extended beyond 15 years:

1) To accelerate achievement of established rubella/CRS elimination goals; and
2) To fill immunity gaps identified through a thorough analysis of their country data for both measles and rubella.

1. To accelerate achieving the goal

Examples of accelerating achieving the established goal come from AMR. In 2003, a regional goal to eliminate rubella/CRS was established. In 2003, 3 countries had not introduced RCV and 7 countries had introduced RCV within the previous 5 years. Between 2003 and 2008, 14 countries conducted adult mass campaigns after introduction of RCV into their programs. The typical upper age range for these campaigns was 29 to 39 years of age including both males and females. However, 3 countries (i.e., Brazil, Chile, and Argentina) had conducted adult female only campaigns. After those SIAs, rubella virus transmission and outbreaks mainly occurred among adolescent and adult males. All three countries conducted subsequent SIAs targeting adolescent and adult males[30]. Transmission was interrupted in those countries. The countries in AMR are in the process of documenting the elimination of measles, rubella and CRS.

2. To fill immunity gaps to measles and/or rubella in older age-groups

As of September 2013, all 6 WHO regions have measles elimination goals. However, in many countries, the age distribution of cases has shifted to older adolescents and young adults. Presented to the SAGE WG were two country examples of where the introduction of RCV was integrated with measles epidemiology: Kyrgyzstan (presented above) and Iran.

Iran

In Iran, measles vaccination had been introduced 1967; however, between 1967 and 1983, measles vaccination was not routine offered in the public sector thus resulting in coverage <50%. In 1984, measles was offered to all infants and coverage increased rapidly to >90% in the early 1990s and between 1992 and 1996, coverage was >95%. In 1996, a subnational campaign targeting children aged 9 months to 15 years resulting in coverage up to 99%. The epidemiology of measles dramatically changed with the introduction of measles vaccine. Before 1967 (pre-vaccine introduction), the incidence of measles ranged from 581 to 1938 cases per 100,000 population. By 1984, the incidence had dropped to 34.3 and by 1987, the incidence had decreased to 6.1 per 100,000 population. During 1999–2002, the measles incidence increased from 10.2 to 17.5 cases per 100,000 population, and most cases occurred among persons aged 10–25 years. In 2001, Iran officially adopted the regional measles elimination objective. To respond to the measles elimination target, a nationwide campaign targeting persons aged 5 to 25 years was planned.

[30] Subsequent SIAs were conducted during 2007 and 2008 in Chile (1.3 million males aged 19–29 years in 2007), Brazil (70 million males and females aged 20–39 years and 12–39 years in five selected states in 2008), and Argentina (6.5 million males aged 16–39 years in 2008).

As of 2001, Iran had not introduced RCV into their national program. To introduce RCV, Iran conducted a MR campaign instead of measles only. Rubella seroprevalence data from 2001 showed 96% seropositivity among persons aged 14 to 70 years. The campaign had a significant impact on both epidemiology of rubella and measles.

Using rubella epidemiology data

For countries introducing RCV, most will target 9 months to 14 years 11 months; however, a few countries may want to expand their age group. In evaluating whether to expand the target age group, countries should review their epidemiology including the age distribution of rubella cases. If available, countries should review their seroprevalence data. If available, countries should review the age of mothers of infants with CRS, which will help to identify the susceptible age group. After a decision has been made to expand the age target, countries may want to review their age specific fertility data so they can cover a majority of the women in the childbearing age.

Some of the country examples that were used included: Nepal, Tajikistan, Oman and Cape Verde. Two countries are briefly summarized here to illustrate how a comprehensive review of the available information helped to determine the target age range for the MR SIA.

Nepal

In Nepal, the rubella epidemiology documented that >95% of rubella cases were among persons less 15 years of age – that is only 5% of IgM positive rubella cases were occurring in persons ≥15 years of age; seroprevalence data conducted documented that 91% of women 15-39 years had acquired rubella immunity – that is <10% of WCBA were susceptible to rubella. A study in the school for the deaf documented the presence of CRS among the students. The decision was to introduce MR through a wide age campaign targeting persons aged 9 months to 14 year 11 months.

Oman

In 1992 in Oman, a rubella outbreak started that peaked in 1993 with 85% of the cases among persons less than 15 years. This outbreak resulted in 60 infants with CRS. In 1994, Oman conducted a nationwide MR campaign targeting persons aged 15 months to 17 years. The Ministry of Health chose to extend the age range due to the ease of reaching persons from 15-17 years of age in school. In 1988-89, a rubella seroprevalence study was conducted among pregnant women and documented that 92% were seropositive. In 1994, MR vaccine was introduced at 15 months of age and switched to MMR in 1997. In 2001, postpartum vaccination was introduced. Since 2006, the number of reported rubella and CRS cases has been < 20 and <2 (mostly 0).

Discussion

There are two potential situations for expanding the age range beyond 15 years of age, these include to accelerate progress towards the targeted elimination goal and if the available data on measles or rubella support the expansion. Even though there is no magic formula for determining the age range, an approach countries have used in the past has been to consider two important criteria. First countries should review the epidemiology of rubella and measles including the age distribution of cases, if possible at least over the most recent years. If recently investigated outbreak data is available, it is important to

review the age distribution of cases. Seroprevalence data, if available should also be reviewed. Another source to review if available is the maternal age distribution of CRS cases to see if one specific age group is more susceptible than others. After reviewing the available data, countries should determine the appropriate age range needed to achieve the targeted goal.

Recommendations:

- Ensure high coverage (≥95%) during MR SIAs
- Verify coverage for all MR SIAs through statistically valid and generally accepted methodology
- Encourage recording of doses given during SIAs (by age group, number of zero-dose children vaccinated)
- MR catch-up SIAs should be extended beyond 15 years either to accelerate the progress toward established rubella/CRS elimination goals or to fill gaps in population immunity based on similar epidemiologic and programmatic considerations as above for M SIAs. Additional information to consider for MR SIAs include levels of immunity among women of child bearing age, epidemiology of rubella and CRS, and population characteristics – e.g., age-specific fertility rates and age of mothers of CRS affected infants.
- However, when countries decide to expand the age limit above 15 years, WHO/SAGE recommends both adult males and females should be targeted. Adolescent and adult female only SIAs are not recommended.
- Need for on-going review of country specific epidemiology to inform additional strategies that may be needed to address persistent immunity gaps

VII. Vaccination of Health Workers

- A PubMed literature review of nosocomial transmission of measles or rubella as well as a search of existing WHO global and regional policy documents was conducted to determine the risk and guide recommendations for vaccination of health workers
- In both developed and developing countries, nosocomial transmission, usually involving health workers, is an important mode of transmission for measles and rubella outbreaks
- Because of their role in care of patients and vulnerable persons, health workers have a duty of care to be vaccinated
- In addition to vaccination of health workers, enforcement of infection control practices is needed to prevent nosocomial transmission of measles and rubella
- Draft recommendations are proposed that health workers be immune to measles and rubella (either through vaccination or serological testing) and that standard infection control measures be enforced to prevent or reduce the spread of measles and rubella

Background

Health workers (HW) are critical to the promotion of health globally. Health workers are persons who engage in the promotion, protection or improvement of the health of the population[31]. Health workers include persons who may have contact with patients, visitors or persons with suspected infections or with the organism that causes the disease. Health workers include persons in health care such as health care providers, nurses, laboratory, janitors, secretaries, etc. and persons in public health such as field workers, epidemiologists, laboratorians and community workers. Even though they are associated with the promotion of health, infection risks occur in the setting where they work. In both developed and developing countries, transmission of vaccine-preventable diseases continues to occur in health care settings with health care workers (HCWs), that is persons directly involved in patient care, being the source of exposure for susceptible patients or other HCWs. The consequences of transmission within health care facilities can be serious even fatal and costly. For measles, several outbreak reports document this risk of transmission of measles among HCWs[32,33]. For rubella, several outbreak reports document the risk of transmission of rubella HCWs and patients[41]. In addition, health workers who investigate or respond to suspected cases of infectious diseases are at risk of contracting and/or transmitting the disease[34].

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[31] M.R. Dal Poz, Y. Kinfu, S. Dräger and T. Kunjumen. Counting health workers: definitions, data, methods and global results. WHO publication. 2007

[32] Choi WS, Sniadack DH, Jee Y, etal. Outbreak of measles in the Republic of Korea, 2007: importance of nosocomial transmission. J Infect Dis. 2011;204 Suppl 1:S483-90.

[33] Komitova R, Kunchev A, Mihneva Z, Marinova L. Nosocomial transmission of measles among healthcare workers, Bulgaria, 2010. Euro Surveill. 2011;16(15).

[34] WHO. Dr. Carlo Urbani of the World Health Organization dies of SARS. Accessed WHO website 9/19; http://www.who.int/mediacentre/news/notes/2003/np6/en/

All six WHO regions have goals for measles elimination and two have rubella elimination goals; however, measles and rubella outbreaks continue to occur including outbreaks associated nosocomial transmission. To interrupt the transmission of measles and rubella, uniform and high levels of immunity must be ensured in the population including health workers. To ensure immunity among HWs in order to reduce or prevent nosocomial transmission, we reviewed WHO global and regional recommendations. A literature review was conducted to identify current national recommendations on HWs policy, the reinforcement of and attitudes toward policy and cost of nosocomial transmission.

Methods:

1) To identify existing WHO recommendations, several data sources were searched including online portals of Immunization, Vaccines and Biologicals (IVB) policies catalogue, IVB documents centre and publications section within WHO webpage and Weekly Epidemiological Records (WER). Eight main keywords related to HWSHWs were used to search for literature: HWSHWs "health care providers", "health workers", "health-care workers", "health workers", "health providers", "health staff", "health care staff" and "health professional". In addition, publication section websites and files from Immunization Vaccines department webpages from the six different regions were screened for all existing WHO and regional recommendations for vaccination of HWs.
2) To identify reviews and policy papers for health workers and nosocomial transmission or public health workers and transmission in the literature, we searched PubMed and references from relevant articles for studies in English. Search terms used were "health care workers, health workers, public health workers", "measles", "rubella" and "nosocomial transmission or transmission".

Results

The results of the search in the WHO documents identified 2 global documents and 4 regional (AMR, AFR, EUR, WPR) documents that mentioned the importance of vaccination or recommendations for Health workers. The latest two WHO position papers for measles and rubella highlight the importance of vaccinating health workers but do not make a formal recommendation:

- The Measles Vaccine position paper, published in 2009, states that "The importance of vaccinating health workers is underlined by the numerous measles outbreaks occurring in health institutions, affecting both health workers and patients."
- The Rubella Vaccine position paper, published in 2011, states that "The importance of vaccinating health workers has been demonstrated by outbreaks that occurred in health institutions and affected both health workers and patients."

Of the WHO regions, two regions have recommendations to ensure health care workers were vaccinated or had documentation of immunity, two regions strongly encourage the same, while two regions have not formulated any recommendations or guidance on vaccinating or ensuring immunity among health care workers.

AMR and WPR have published recommendations to ensure immunity among health care workers:

- In 2005 in the AMR measles elimination field guide, it states "all health care workers must be immune to measles and rubella." This recommendation has also been re-emphasized by the International Experts Committee on the Documentation of Elimination of measles and rubella.

- In the WPR recommendations, the 2011 TAG "recommends that all countries implement measures to prevent or reduce nosocomial transmission of measles virus, including ensuring immunity against measles among HCWs [and] … investigation and effective isolation of suspected measles cases." In the 2009 accelerated rubella/CRS Strategic Plan, it states for all countries and areas ensure immunity in health care workers to prevent nosocomial transmission of rubella.

AFR, EUR strongly encourage ensuring that all are immune to measles:

- The report from the first AFRO Measles Technical Advisory Group (TAG) meeting in 2005 states that "Countries are strongly encouraged to implement WHO/AFR recommendations on vaccination for all health workers, regardless of previous vaccination status or history of measles.
- The 2005-2010 EUR Strategic Plan recommends that a second opportunity be provided to "those attending schools or universities, those in the military and those working in health care settings.

Literature review

Throughout the literature are many examples from many countries (e.g., US, Bulgaria, Korean, Italy) documenting the importance of measles and rubella nosocomial transmission and the lack of immunity among health care workers[35,36,37]. A recent review of nosocomial transmission of measles[38] highlighted the frequency of nosocomial transmission of measles, even in developed countries, and the importance of ensuring that health care workers are immune. A second review examining HCW policies for vaccination in EURO[39] found that only 12 of the 30 countries recommend measles vaccination for all HCWs. In two additional countries, it was recommended only for a select population of HCWs (e.g. direct patient care or pediatricians). In Finland HCW vaccination against measles is mandatory. In the remaining 15 countries no recommendations for HCW vaccination against measles are in place. The second review also canvassed recommendations for rubella vaccination and found that it is recommended for all HCWs in 11 countries of the 30 countries. In 3 countries vaccination is recommended for specific groups of HCWs (e.g., pediatricians only, pediatric and maternity departments, HCWs who have contact with pregnant women. As with measles, vaccination of HCWs against rubella is mandatory in Finland. The 15 remaining European countries have not published any recommendations for rubella vaccination of HCWs.

For rubella, similar situation with nosocomial outbreaks have been occurring. The two differences between rubella and measles is the risk of infecting the susceptible pregnant women[40] and infants with

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CRS shed rubella virus and have infected hospital staff[41,42]. In several of the nosocomial rubella outbreaks, either susceptible pregnant women were exposed or some were infected and may have chosen to terminate their pregnancy[43].

The practice of isolation measures for measles and rubella are part of the standard of care and are an important aspect for preventing nosocomial spread. There have been guides/guidelines published by WHO[44] and several countries[45,46],[47,48],[49]. In some of the recent nosocomial measles outbreaks, transmission occurred among the patients without spread to the HCWs. In these articles, it is highlighted that environmental infection control measures were not enforced or conducted, thus reinforcing the importance environmental infection control measures.

Conclusions

In both developed and developing countries, nosocomial transmission, usually involving health workers, is an important mode of transmission for measles outbreaks. In addition, public health workers are also at risk of acquiring/transmitting infectious diseases. Though no global recommendation for vaccination of HWs including HCWs exists, the WHO measles and rubella position papers highlight the importance of vaccination of health care workers to prevent nosocomial transmission. Policies of WHO regions Health Care workers are evenly split: two regions recommend that HCW be immune, two recommend it, while two regions have no recommendations.

Health workers have a duty of care to be vaccinated. As health workers, they promote, protect and improve health. As health workers, they may be in contact with or treat persons that are vulnerable such as persons with cancer or HIV. Measles infection in the immunocompromised host (eg, persons with malignancies or human immunodeficiency virus [HIV] infection) can be prolonged, severe, and

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frequently fatal[50]. For rubella, health workers may come in contact and infect susceptible pregnant women which may result in an infant with CRS born.

To achieve the elimination goals for both measles and rubella, countries must ensure high population immunity for both vaccines. Through this review of WHO policies, it has been documented that no global recommendations exist to ensure immunity among health workers. To reduce the threat of nosocomial transmission global recommendations should be put in place to ensure that all health workers are immune to both viruses. These recommendations should include follow-up to ensure that these policies have been implemented in Member States.

Nosocomial transmission will not be prevented only by immunization of health workers.
Another aspect to prevent nosocomial transmission is the enforcement of infection control. Only one region (WPR) had policies in place that we could identify for enforcing infection control policies. In addition to the recommendation of vaccination of health workers, global recommendations should include enforcing good infection control practices.

Draft Recommendations

The following draft recommendations are proposed to SAGE:

- WHO/SAGE recommends that health workers should be required to demonstrate they are immune to measles (either through vaccination or serological testing)
- WHO/SAGE recommends that health workers should be required to demonstrate they are immune to rubella, as soon as rubella vaccine is introduced into the national program
- WHO/SAGE recommends that standard infection control measures be enforced to prevent or reduce the spread of measles and rubella.
- WHO/SAGE recommends that regions and countries develop plans to operationalize these recommendations.

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VIII. Prioritizing the Research Agenda for Measles and Rubella

Twelve high priority research areas were identified to address gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets.

The prioritization process included adaptation of prior prioritization criteria, generation of a list of potential research areas, and identification of experts to participate in an electronic survey.

Background and Rationale

Research is critical to achieving global disease control, elimination and eradiation goals. The eradication of smallpox was made possible by technical and logistical advances conducted during the course of the program, and the failure of the malaria eradication program of the 1950's and 1960's was in part attributable to the neglect of research (Henderson 1999). The Polio Research Committee was only established two decades after the polio eradication goal was first proclaimed in 1988. Recently, research priorities have been developed for the reduction of child deaths from pneumonia (Rudan 2007, Rudan 2011) and diarrhoea (Rudan 2007, Fontaine 2009, Wazny 2013) and the eradication of malaria (malERA 2011), among others, and are on-going for immunization implementation research.

Several methodological approaches have been developed for systematic priority setting for child health, most notably those developed by the Child Health and Nutrition Research Initiative (CHNRI) (Rudan 2008, CHNRI) and the Essential National Health Research (ENHR). Common to most approaches is the identification of research questions or areas, development of prioritization criteria and application methods, implementation of a prioritization process with appropriate experts and stakeholders, and an analytical approach including scoring and weighting of responses.

The SAGE Working Group on Measles and Rubella was charged with identifying gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets. To identify gaps in evidence and programme barriers, the SAGE Working Group on Measles and Rubella adapted previously developed methodological approaches and built upon the work of an expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011 to begin the process of prioritizing research questions for measles eradication and rubella/congenital rubella syndrome (CRS) control and elimination (Goodson 2012). This report summarizes the methods and findings for the prioritization of the measles and rubella research agenda.

Methods

Prioritization Criteria

The Measles and Rubella Working Group adapted prioritization criteria developed by CHNRI ENHR with the goal of designing prioritization criteria that were simple and appropriate for the types of research areas relevant to measles and rubella/CRS elimination targets (Table). Five prioritization criteria were identified to address these needs, each weighted equally and scored from 1 to 4:

1. **Relevance**: The purpose of this criterion was to determine if the proposed research addresses a knowledge gap or if it duplicates prior knowledge or studies. The specific question was: How

large is the knowledge gap to be addressed by the proposed research? Answers and scores included: 1=Large; 2=Moderate; 3=Small; 4=No gap.

2. **Importance**: The purpose of this criterion was to ensure the proposed research addresses a problem of importance to achieving the measles and rubella global and regional goals. The specific question was: How significant is the problem addressed by the proposed research? Answers and scores included: 1=Highly significant; 2=Moderately significant; 3=Low significance; 4=None.

3. **Urgency**: The purpose of this criterion was to assess how urgently the research needs to be conducted, recognizing that some research areas may be of high importance and relevance but may not be needed urgently. The specific question was: How urgently should research on this problem be addressed? Answers and scores included: 1=As soon as possible; 2=Within two years; 3=Within five years; 4=Not essential within the next five years.

4. **Impact**: The purpose of this criterion was to assess the benefit of the proposed research results by assessing their potential merit and usefulness. The specific question was: How likely is it that the proposed research will result in knowledge that will significantly advance regional or global measles and rubella goals? Answers and scores included: 1=Highly likely; 2=Moderately likely; 3=Very unlikely; 4=Not possible.

5. **Chances of Success**: The purpose of this criterion was to assess the feasibility of completing the proposed research within five years. The specific question was: Is it possible to complete studies to answer the research question within five years? 1=Highly likely; 2=Moderately likely; 3=Very unlikely; 4=Not possible.

Respondents also could respond that they were unable to answer or did not know the answer to the prioritization question.

Table: Comparison of the Measles and Rubella Research Agenda Criteria to ENHR and CHNRI Prioritization Criteria

Measles and Rubella Research Priorities	**ENHR**	**CHNRI**
Relevance	Appropriateness	Maximum potential for disease burden reduction
Importance	Relevancy	Maximum potential for disease burden reduction
Urgency	*Not asked*	*Not asked*
Impact	Impact of the research outcome	Maximum potential for disease burden reduction Likelihood of efficacy and effectiveness Likelihood of deliverability, affordability
Chances of success	Chances of success	Likelihood of answerability in an ethical way Likelihood of efficacy and effectiveness Likelihood of deliverability, affordability
Not asked	Ethical appropriateness	Likelihood of answerability in an ethical way
Not asked	*Not asked*	Likely effect on equity in population

Research Areas

The SAGE Measles and Rubella Working Group drew upon several sources to identify potential research areas critical to achieving the measles and rubella/CRS elimination targets. The most important source was the expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011 (Goodson 2012). This panel, consisting largely of experts from the Centers for Disease Control and Prevention, the World Health Organizations and academia, identified more than 130 research questions that were later condensed to 26 key research questions in six domains. These research questions were further condensed and supplemented with additional research areas from four sources: 1) the Measles Landscape Analysis conducted for the Bill & Melinda Gates Foundation; 2) the Global Measles and Rubella Management Meeting in March 2012; 3) the Measles and Rubella Initiative and SAGE Working Group meetings in September 2012; and the Global Measles and Rubella Management Meeting in February 2013. This process resulted in 24 research areas within seven broad domains:

1. Population immunity (6 questions)
2. Monitoring and surveillance (3 questions)
3. Outbreak preparedness and response (4 questions)
4. Public confidence and demand for vaccines (2 questions)
5. Pathogenesis, vaccines and diagnosis (4 questions)
6. Rubella specific issues (4 questions)
7. Integration with polio eradication efforts (1 question)

Measles and Rubella Experts

Survey participants were identified in three phases: 1) SAGE Measles and Rubella Working Group members; 2) participants of the Global Measles and Rubella Management Meeting in March 2012; and 3) a list of measles and rubella experts (including academics) originally drafted following the expert advisory panel convened by the U.S. Centers for Disease Control and Prevention in May 2011. Survey participants who did not respond initially were included in subsequent survey rounds.

Survey

Each survey question was framed as a broad research area for which potential specific research questions were provided as examples and the order of the questions were randomly scrambled. For example, the question addressing Strategies to increase vaccine coverage among difficult to reach populations was presented as follows:

> Studies to evaluate novel strategies to increase measles and rubella vaccine coverage among difficult to reach populations, including nomadic populations, migrants, refugees and internally displaced persons.
>
> Examples include studies of GIS mapping of susceptible populations, mobile phone reminder recall systems, and house-to-house vaccination strategies.

The goal in selecting the research areas was to address the broad range of potential research gaps with some specificity, while minimizing the number of research areas so as not to overburden the participants. With 24 research areas and five prioritization criteria, participants were asked to answer 120 questions not including the demographic questions.

Surveys were conducted electronically using SurveyMonkey™ in February, April and August 2013. Links to the survey were sent by email with a cover letter explaining the purpose of the email.

The overall prioritization score was the sum of the scores for each of the five prioritization criterion. The maximum score was 20.

Results

Respondents

The measles and rubella research agenda prioritization survey was sent by email to 158 individuals of whom 55 (35%) completed the survey. Sixteen (10%) individuals started but did not complete the survey and were not included in the analyses.

Characteristics of respondents

The respondents represented a range of professional positions, expertise (including rubella) and geographical areas (Table). The majority of respondents (58%) worked for more than 10 years on measles or rubella. However, few respondents worked in the areas of vaccine procurement and economics and few represented the Eastern Mediterranean WHO region. The high proportion of respondents from the Americas reflects in part the number of participants associated with the Centers for Disease Control and Prevention and US based universities.

Table: Characteristics of Respondents

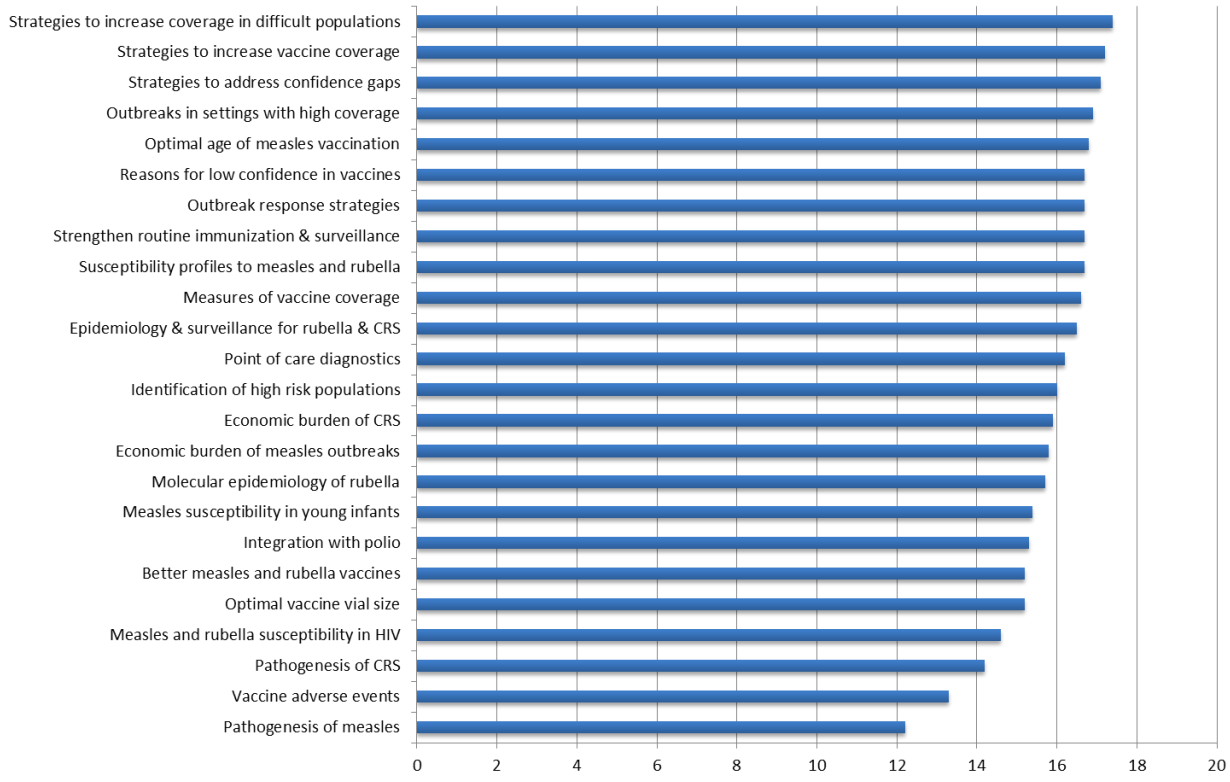
Characteristic	Proportion of Respondents
Professional Position	
Global partner	29%
Researcher	24%
Technical advisor	18%
Other	18%
Regional program officer	7%
Country program officer	4%
Measles and Rubella Expertise	
Both measles and rubella	52%
Measles only	41%
Rubella only	7%
Duration of Work in Measles and Rubella	
More than 20 years	29%
10 to 20 years	39%
5 to 9 years	21%
Less than 5 years	11%
Expertise	
Epidemiology	36%
Surveillance	34%
Outbreak response	19%
Health systems	19%
Vaccine delivery	16%
Pathogenesis	10%
Immunology	10%
Health behaviors	10%
Vaccine development	9%
Diagnostics	8%

Molecular epidemiology	8%
Modeling	7%
Vaccine procurement	3%
Economics	2%
WHO Region	
Americas	33%
Europe	14%
Global headquarters	14%
Africa	11%
Western Pacific	9%
South-East Asia	7%
Eastern Mediterranean	2%
Organizations	
University	33%
Other	27%
World Health Organization	23%
Centers for Disease Control and Prevention	13%
UNICEF	4%

Survey results

The overall prioritization scores ranged from a high of 17.4 (Strategies to increase coverage in difficult populations) to a low of 12.2 (Pathogenesis of measles), with a median score of 16.1 (IQR 15.3, 16.7) (Figure).

Figure : Overall prioritization scores for 24 research areas to achieve the measles and rubella elimination targets



The prioritization criteria did not clearly distinguish research areas of high and low priority, although four research areas were clearly of lower priority (Measles and rubella susceptibility in HIV-infected persons; Pathogenesis of CRS; Vaccine adverse events; and Pathogenesis of measles).

The research areas with scores above the median are shown in the box below.

1. Strategies to increase vaccine coverage in difficult to reach populations
2. Strategies to increase vaccine coverage
3. Strategies to address confidence gaps
4. Outbreaks in settings with high coverage
5. Optimal age of measles vaccination
6. Reasons for low confidence in vaccines
7. Outbreak response strategies
8. Strengthen routine immunization & surveillance
9. Susceptibility profiles to measles and rubella
10. Measures of vaccine coverage
11. Epidemiology & surveillance for rubella and CRS
12. Point of care diagnostics

Discriminatory power of prioritization criteria

The discriminatory power of each of the prioritization criteria differed, although no specific criterion clearly distinguished high from low priority research areas (Table). The range in scores for individual criterion (maximum of four) was greatest for Urgency (range 1.7 to 3.3) and least for Chances of Success (2.9 to 3.6). The range in scores for the remaining three criteria spanned 1.2 points.

Table: Median, IQR and range for overall scores and scores for each prioritization criteria

	Median	IQR	Range
Overall score	16.1	15.3, 16.7	12.2, 17.4
Relevance	3.2	3.1, 3.3	2.3, 3.5
Importance	3.3	3.1, 3.5	2.4, 3.6
Urgency	2.7	2.6, 3.1	1.7, 3.3
Impact	3.3	3.1, 3.4	2.5, 3.7
Chances of success	3.4	3.3, 3.4	2.9, 3.6

Comparisons across prioritization criteria

The rankings of the top six research areas by overall score were compared across the five prioritization criteria to assess consistency (Table). The overall score ranking most closely resembled the Urgency ranking.

Table: Ranking of top six overall research areas by individual prioritization criteria

Top Six Research Areas	Relevance Rank	Importance Rank	Urgency Rank	Impact Rank	Chances of Success Rank
Strategies to increase vaccine coverage in difficult to reach populations	1	2	1	2	10
Strategies to increase vaccine coverage	13	1	3	1	9
Strategies to address confidence gaps	2	7	6	9	12
Outbreaks in settings with high coverage	6	3	4	8	5
Optimal age of measles vaccination	15	4	2	4	3
Reasons for low confidence in vaccines	8	6	5	17	18

Additional research questions

Fourteen respondents offered additional potential research questions although none was mentioned more than once. Examples include the need for serological assays that distinguish wild-type from vaccine induced immunity, risk assessment of animal morbilliviruses and the potential for cross-species transmission, and management systems for immunization programs.

Discussion and Next Steps

The SAGE Measles and Rubella Working Group identified twelve high priority research areas to address gaps in essential evidence and programme barriers to achieving measles and rubella/CRS elimination targets based on a prioritization process that included adaptation of prior prioritization criteria, generation of a list of potential research areas, and identification of experts to participate in an electronic survey. The research areas of highest priority reflect the urgent need for research on strategies to increase vaccine coverage and thus population immunity, build public confidence in measles and rubella vaccines, and enhance surveillance for measles, rubella and CRS.

There are several limitations to the methods employed that could impact on the prioritization process. First, the prioritization criteria were adapted from previous efforts to establish prioritization criteria for childhood diseases but were not independently validated. Second, the research areas were drawn from prior efforts to establish a research agenda for measles and rubella but were not exhaustive and were framed broadly. Respondents were provided an opportunity to suggest additional research questions and several did; however, these could not be incorporated into this prioritization process. Third, the "universe" of measles and rubella experts was not systematically sampled potentially leading to biased results. Individuals with expertise in vaccine procurement and economics were particularly under-represented. The composition of the respondents almost certainly impacted the findings. Fourth, even with a condensed set of research areas, the survey was burdensome, with respondents asked to address five prioritization criteria for 24 research areas. Respondent fatigue was evident in that some started the survey but failed to complete it. Fifth, the lack of discriminatory power of the prioritization criteria was likely due to the fact that the research areas had all been previously vetted and proposed as potential

priority research areas. Thus, all of the research areas were relevant to to achieving measles and rubella/CRS elimination targets.

The Measles and Rubella Working Group considers this prioritization process a first step in setting, promoting and revising the measles and rubella research agenda. The next step is to disseminate these findings through a published report and at the Global Vaccine Research and Implementation Forum in March 2014. Next, we plan to draft specific research questions, study designs and outcomes for the top six to twelve research areas and will identify potential funding agencies and mechanisms. Finally, the Measles and Rubella Working Group views this list of highest priority research areas as a working document that will be updated and revised as research questions are addressed and the understanding of the epidemiology and control of measles and rubella evolve.

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IX. Questions to SAGE

The questions to SAGE will be posed following each presentation:

1. Global and Regional progress and challenges:

- Is the programme on track to achieve global and regional targets?
- If yes, what needs to be done to maintain elimination; if no, what additional strategies, tactics, and/or innovations are needed to get back on track?

2. Use of MR vaccine in the routine schedule and determination of the appropriate target age range for M and MR SIAs

- Does the evidence presented support the draft recommendation to use RCV with first dose of MCV?
- Does the evidence presented support the use of the same formulation of MR or MMR vaccine for both routine doses?
- Does the evidence presented support the draft recommendations on the criteria to be used to determine the target age range for M and MR SIAs?
- Is it appropriate to merge the measles and rubella position papers?

3. Vaccination of health workers

- Does the evidence presented support the draft recommendations to vaccinate health workers against measles and rubella?

4. Prioritizing the Research Agenda

- Does SAGE endorse the approach taken by the working group to identify a prioritized list of research topics?
- Is additional work needed before disseminating these findings?