Proceedings of the SAGE Working Group on Rubella

March 17, 2011
Preamble

Rubella is usually a mild viral rash illness in children and adults; however, infection early in a woman’s pregnancy, particularly during the first 16 weeks, can result in miscarriage, fetal death, or an infant born with birth defects (i.e., congenital rubella syndrome [CRS]). In 2000, the World Health Organization (WHO) published the first rubella vaccine position paper (PP) to guide introduction of rubella-containing vaccine (RCV) in national childhood immunization schedules.

Since the publication of the PP in 2000, several areas have changed including additional countries have introduced RCV, 2 regions (AMR, EUR) have established rubella elimination goals, and additional information on rubella vaccine safety when administered to unknowingly pregnant women.

As part of updating the PP, a working group (WG) was established and was asked to review and propose necessary updates to the WHO rubella vaccine PP of 2000. In addition, identify the information gaps, guide the work required to address information gaps, and prepare for a SAGE review of the updated vaccination strategies. Specifically the working group was asked to address the following questions:

1. What are the possible goals for rubella/CRS prevention and rubella/CRS elimination (country, regional or global)?

2. With the goals mentioned in question 1, what are the most appropriate vaccination strategies to achieve these goals?

3. What is the minimum required routine childhood immunization coverage that should be achieved and maintained to ensure that the introduction of rubella-containing vaccine does not increase the risk of CRS?

To address these requests, the WG has had 10 teleconferences in addition to a face-to-face meeting. To address the first two questions on the possible goals and appropriate strategies, WG members heard either through the conference calls or the face to face meeting, several presentations on various topics including update on the global vaccine use; regional goals and strategies and experiences; regional and country experiences with different vaccine strategies; strawman document on proposed goals and strategies; optimal age for administration of 1st dose of RCV; cost-effectiveness of rubella vaccination; update on the global and regional burden of rubella and CRS; and information on the safety, precautions/contraindications, duration of immunity and vaccine effectiveness of rubella vaccines.
To address the 3rd question on the minimum required routine childhood coverage, the WG heard presentations on modeling to assess the impact of different vaccination strategies on CRS and country experiences with different vaccine strategies. Additional presentations addressed surveillance needs and challenges.

**The 2000 Rubella Vaccine Position Paper**

The 2000 rubella vaccine PP was reviewed and its key contents are summarized in the subsequent five paragraphs. The primary objective of rubella vaccination is to prevent the occurrence of congenital rubella infection including congenital rubella syndrome (CRS) which is an important cause of deafness, blindness and mental retardation. It noted that while an estimated 100,000 cases of CRS occur annually in developing countries, the global burden of CRS in all regions had not been well described. Cost-benefit studies conducted in middle to high income countries have demonstrated that the benefits of rubella vaccination outweigh the costs.

In the 2000 rubella vaccine PP, WHO recommended the use of RCV in all countries with well-functioning childhood immunization programs where reduction or elimination of CRS is considered a public health priority and where resources are available. For all countries, they should assess their rubella situation and if appropriate, make plans for introduction of RCV.

When introducing rubella, two approaches are recommended: 1) prevention of CRS only and 2) elimination of rubella as well as CRS. For CRS prevention only, adolescent girls and/or women of childbearing age (WCBA) are targeted for vaccination. Vaccination strategies include delivery through mass campaigns or routine services. For elimination of rubella and CRS, RCV is introduced through the universal childhood immunization program while assuring immunity among WCBA. All countries undertaking rubella elimination should achieve and maintain an immunization coverage of >80%. In deciding which approach to use, several areas need to be considered including: burden of CRS, level of susceptibility in WCBA; strength of the immunization program; resources both financial and personnel; and other disease/public health priorities.

In considering the two approaches, vaccination of adults is essentially free of risks for altering the rubella transmission dynamics. However, if a childhood vaccination program doesn’t achieve and/or maintain high coverage (>80%), the low vaccination coverage may decrease virus circulation sufficiently to shift both the average age of exposure to rubella and rubella susceptibility from children to older age groups including women of childbearing age, and therefore potentially increase the risk for CRS. Routine childhood immunization in the private sector should be monitored closely because it may also alter the rubella transmission dynamics.
Countries with measles elimination goals should consider taking the opportunity to eliminate rubella/CRS as well by using combined measles-rubella (MR) vaccine or measles-mumps-rubella (MMR) vaccine.

**Burden of CRS**

In 1996, it was estimated that approximately 110,000 infants with CRS were born in developing countries annually. Even with the introduction of RCV into additional countries, the burden of CRS remains significant especially in the African and South East Asian Regions. In 2009, the global estimates for CRS were revised yielding an estimated 120,000 infants born with CRS in 1996 and 112,000 CRS cases in 2008. The changes in the estimates were due to the availability of more seroprevalence data and success in the immunization programs in the Region of the Americas and Europe.

**Rubella Vaccines**

There are 5 different rubella virus vaccine strains that are currently being administered. The RA 27/3 virus strain is the most commonly used vaccine strain globally. Other vaccine strains include: Takahashi, Matsuura, and TO-336 strains used primarily in Japan whereas the BRD-2 strain is used in China.

The adverse events following vaccination with the RA27/3 rubella vaccine are mild, particularly in children. Most of the available data on adverse events are for the MMR combination. Common adverse events include pain, redness and induration at the site of injection. Low grade fever and rash, lymphadenopathy, are commonly reported. Acute joint symptoms tend to be rare in children (0%-3%) and in men, but are common among vaccinated susceptible adolescent and adult females; they include arthralgias (25%) and arthritis (10%) that usually last from a few days to 2 weeks. These transient reactions seem to occur in non-immunes only, for whom the vaccine is important. For MR containing vaccine, thrombocytopenia is reported in 1/30,000 doses as compared to 1/3000 cases in wild rubella disease.

Rubella vaccine is contraindicated in pregnant women, people who are severely immunocompromised due to congenital disease; severe HIV infection; advanced leukaemia or lymphoma; serious malignant disease; treatment with high-dose steroids, alkylating agents or antimetabolites; or who receive immunosuppressive therapeutic radiation. However, asymptomatic HIV-positive persons can be immunized. Combining all available data, follow-up of more than 2,700 susceptible women, who were unknowingly pregnant and received a rubella vaccine in early pregnancy, found no infants with CRS.

The seroconversion rates are similar between the different formulations using RA 27/3 vaccine (i.e., monovalent rubella vaccine, MR, MMR, MMRV). Rubella-
containing vaccine is highly protective. Studies on the RA 27/3 virus vaccine documented a vaccine effectiveness ≥ 95%. In a review of several studies for duration of protection of one dose of RCV spanning 10-21 years documented seropositivity of ≥ 95%.

In the 2000 WHO PP, “rubella vaccine is usually administered at 12-15 months but can also be administered to children as young as 9 months of age”. The age of administration of RCV is based on the appropriate age for measles vaccination. In the published literature on safety and immunogenicity of RCV, the reactogenicity between various MMR formulations between infants and children was similar. The immunogenicity in infants and children ≥12 months of age was similar with seroconversion rates of ≥94% in infants (<12months). Unpublished data from Dr. Grangeot-Keros, documented that the cell-mediated immune response at 9 months of age was adequate. In conclusion, published studies and unpublished data support that infants given RCV at nine months have just as good an immunological response as older children. Even though RCV can be administered to infants at 9 months of age, some countries with longstanding programs administer RCV in children ≥12 months and consider RCV doses received before ≥12 months as not a valid dose.

**Economic Analyses on the use of Rubella-containing vaccine**

In a literature review of economic analyses of use of rubella vaccines published between 1980 and 2010, 26 studies on the economics of rubella and rubella vaccination were identified; 20 studies were conducted in high-income countries, 5 in upper middle-income countries and 1 in a lower middle-income country. No studies were conducted in low-income countries. Other gaps in the literature include studies on the efficiency of including rubella vaccination with measles immunization and studies that establish the most cost-efficient rubella vaccination schedule. Some methodological limitations were also noted in the studies.

The findings in high and middle-income countries indicate that CRS is costly. The costs of treating CRS are estimated to be between $1,994 and $13,482 per case annually in middle-income countries and $18,664 and $43,920 in two high-income countries. The findings indicated that rubella vaccination programs are economically justifiable and demonstrated favorable cost-effectiveness or cost-benefit ratios in high-income and middle-income countries.

**Vaccine Introduction, Goals and Experiences**

Since 1996, there has been a steady increase in the number of member countries introducing RCV. In 2009, 130 countries (66%) of WHO member countries use
rubella vaccine in their routine program. There are regional differences in the use of RCV. All countries in AMR and EURO have introduced RCV into their routine childhood program. Since 1996, there is a steady increase of countries in EMRO and WPR that have introduced RCV. However, only 2 of 46 member countries in AFRO and in SEAR, 4 of 11 member countries use RCV.

Among the 130 countries with RCV in their national immunization schedules as of December 2009, the first dose is recommended to be administered at ages 12–24 months in 122 (94%) member countries. Although only one RCV dose is recommended routinely, 119 (92%) countries use a 2-dose schedule because rubella vaccine is combined with measles vaccine, which requires a 2-dose schedule. Measles-mumps-rubella (MMR) vaccine is used in 115 (88%) countries, measles-rubella (MR) vaccine is used in 12 (9%) countries, measles-mumps-rubella-varicella vaccine is used in two (2%) countries, and single-antigen rubella vaccine is used in one country. Regions with highest estimated CRS burden are also the regions with the lowest uptake of vaccine.

In 2009, median MCV1 coverage was 96% (inter-quartile range: 92%–99%) for the 130 countries using RCV, including nine countries (Azerbaijan, the Cook Islands, the Dominican Republic, Ecuador, Haiti, Iraq, Lebanon, Palau, and Samoa) with MCV1 coverage <80%. For countries not using RCV, the median MCV1 coverage was 76% (inter-quartile range: 74%–91%), including 22 countries with sustained MCV1 coverage >80% in 2009 that have met the vaccination coverage criteria for introduction of RCV (See WER 2010;85:413-418).

Two regions (PAHO, EURO) have established rubella elimination goals by 2010. One region (WPRO) has established an accelerated rubella and CRS prevention goal by 2015. One region (EMRO) has established a goal of CRS prevention without a target date for countries that have introduced rubella vaccine in their national immunization schedule. Two regions (SEARO, AFRO) have not established any elimination, control or prevention goal. Vaccination strategies are defined according to the goals and the target dates set.

Regional Experiences

Status of Rubella Elimination in the Region of the Americas

Prior to establishing initial regional initiatives, some of the challenges that PAHO faced included: rubella was considered a mild disease; lack of information on burden of CRS and need for surveillance infrastructure. Prior to setting the elimination goal, the burden of CRS was documented in several countries in the region of the Americas.
In 1997, the Technical Advisory Group (TAG) of the Americas recommended that all countries in the Region introduce RCV into their childhood vaccination programs and reduce the number of susceptible WCBA through targeted efforts (e.g., post-partum vaccination). In 1999, TAG recommended an accelerated rubella control and CRS prevention initiative. Countries wishing to eliminate rubella and CRS rapidly were advised to conduct a one-time mass campaign that targeted adolescent and adult females and males with measles-rubella (MR) vaccine. Countries wishing to prevent and control CRS were advised to conduct a one time mass campaign in females only 5-39 years with MR vaccine. In 2003, the Directing Council for the Member States for the Americas established a goal for the elimination of rubella and CRS by 2010. Rubella and CRS elimination is defined as the interruption of endemic rubella virus transmission in all the countries of the Americas for a period greater than or equal to 12 months without the occurrence of CRS cases associated with endemic transmission, in the presence of high-quality surveillance.

In 2003, the TAG recommended that mass campaigns be conducted in both males and females. The target age group was selected on the basis of year of vaccine introduction, campaigns conducted, epidemiology and fertility rates in the countries. In 2007-2009, the three countries (Chile, Argentina, Brazil) that initially conducted female only mass campaigns documented outbreaks in adult males. All three countries subsequently conducted additional mass campaigns, two in males only (Argentina, Chile) and one in both males and females (Brazil).

Lessons learned from conducting adolescent and adult mass campaigns include: targeting of non-traditional groups (e.g., adult males); understanding the importance of broad and timely social mobilization; developing and implementing detailed plans of action with adequate monitoring and conducting mass campaigns involving large proportion of the population in a very short time period(< 6 weeks). These campaigns also strengthened vaccine safety practices such as monitoring and responding to events allegedly attributable to vaccination or immunization, ensuring and monitoring safe injections, identifying, evaluating and following up unknowingly pregnant women that have been vaccinated and coordination with blood banks. In 1999, TAG recommended that rubella vaccination is contraindicated for pregnant women; however if a pregnant woman is vaccinated, the available data does not support that abortion should be recommended. After the 1999 TAG recommendation, all countries in the Americas that planned to conduct adult mass campaigns chose to systematically follow-up pregnant women who had received rubella vaccine using a standardized protocol. Based on serological evaluation, 2,894 (10%) women were classified as susceptible at the time of vaccination from 6 countries; of their pregnancies 1,980 resulted in a live birth and were followed up. None of the infants had features of CRS as a result of rubella vaccination. With the
success of the PAHO elimination strategy, as of October 2010, the last endemic rubella virus was isolated in Argentina in early 2009 indicating that rubella and CRS have been successfully eliminated from the Americas.

The rubella/CRS elimination goal has benefitted from the measles elimination goal and the measles elimination goal has benefitted from the rubella/CRS elimination goal. Several aspects of rubella and measles elimination goals are integrated including use of combined vaccines (MR, MMR) and integrated rubella-measles surveillance. The vaccination strategies recommended for rubella/CRS elimination have helped to sustain measles elimination.

With PAHO’s successes, there are challenges to maintaining elimination of measles, rubella and CRS. These include risk of importations, secondary spread due to importations, and the financial and human resources needed to prevent and respond to outbreaks.

Discussion focused on the successes of the PAHO strategies including the strategies used to successfully vaccinate adult males. Costa Rica was cited as an example of low immunization coverage (<70% for first 10 years of vaccination program) resulting in a shift in rubella susceptibility to adolescents and young adults and potential increase risk of CRS. As a result of the increased susceptibility among adolescents and adults, a vaccination campaign covering susceptible cohorts was conducted and high childhood immunization coverage was achieved and maintained through enhanced immunization efforts.

**Status of Rubella Elimination in European Region**

The current goal is the elimination of rubella and prevention of congenital rubella (CRS) by 2015. This goal is an extension of the goal endorsed in 2005; however, the goal was not met by the original deadline of 2010.

The strategies recommended to achieve both measles and rubella elimination goals include: 1) ensure high coverage (>95%) with 2 doses of measles vaccine and 1 dose of RCV; 2) strengthen measles-rubella and CRS surveillance; 3) provide rubella vaccination opportunities to all susceptible children, adolescents and WCBA and 4) enhanced communication and education about the benefits and risks of immunization. For example, European Immunization Week (EIW) provides an opportunity for countries to target communication to boost awareness and increase the uptake of immunization services. Country participation in EIW has increased from 6 countries in 2005 to 47 countries in 2010.

By end of 2009 in the EUR, all 53 member states had introduced 2 doses of measles- and rubella-containing vaccine (MMR in 52 and MR in 1). Of the 53 member states, 32 have reported a coverage of >95% with first dose and 22
reported a coverage of >95% with second dose. Since 2000, 22 measles and rubella SIAs have been conducted with over 57 million persons vaccinated. The age groups targeted included: 11 countries conducted speed-up campaigns targeting adolescent and adult males and females; 4 countries conducted catch-up campaigns targeting children aged less than 15 years and 9 countries conducted campaigns targeting WCBA and adolescent females.

With the completion of these mass campaigns, the number of cases of rubella has decreased by 97% from 800,000 reported in 1999 to approximately 24,000 reported cases in 2008. Even with decline in cases, rubella outbreaks continue to occur. From 2007-2010, outbreaks were reported from Austria, Bosnia and Herzegovina, Italy, Kyrgyzstan, Malta, Russian Federation and Ukraine.

In 2008, a survey of rubella and CRS surveillance activities was conducted by EUVAC.NET and WHO. The results of this survey document that 80% of countries conduct national rubella surveillance activities. However, only 60% of countries conduct the recommended case based surveillance. In addition, 4 large, economically developed countries do not have a national rubella surveillance system. The majority of countries reported having a nationwide CRS surveillance system. However, 6 (13%) countries reported having no CRS surveillance system. To strengthen MR and CRS surveillance updated surveillance guidelines were published in 2009.

Lessons learned from implementing rubella elimination strategies include:
1) Integrating measles and rubella surveillance is the most efficient way to manage resources and build upon the laboratory network on the pre-existing polio network.
2) Conducting successful SIAs targeting wide age ranges rapidly decreases rubella incidence enabling achievement of the elimination goal.
3) Immunization Registries provide useful information on vaccination status of cases.
4) European Immunization Week strengthens the political commitment and mobilizes communities towards the goal.

The main challenges for EUR include: underreporting, lack of immunization of Health Care Workers, sustaining high level commitment, and adequate required resources in the face of health system reforms that have led to weakened public health systems. Strategies are needed to reach unimmunized population such as migrants, Roma, persons with religious or philosophical objections.

During the discussion, three main topics were highlighted. First, how elimination will be achieved with the occurrence of measles and rubella outbreaks among high
risk unimmunized populations (e.g., Roma, philosophical/religious objectors). Second, the weak state of the rubella and CRS surveillance in many countries and third the role of seroprevalence surveys in determining age-specific susceptibility and the need for standardized methods such as those used in the European Sero-Epidemiology Network. It was noted that seroprevalence studies are methodologically challenging (need a statistically valid sample and accurate reproducible laboratory methods) and should not replace necessary improvements in coverage and surveillance data.

**Status of Rubella Control in the Western Pacific Region**

In the Western Pacific Region (WPR), from 1993 to 2003, less than 8,000 rubella cases (range: 965 to 7,854 cases per annum) were reported annually in the WPR. Beginning in 2004, China initiated reporting of rubella cases, and from 2004 to 2009, the number of reported rubella cases in the WPR has increased from 27,124 to 73,655, with a peak of 127,305 in 2008. RCV is used in 30 (83%) of the 36 member states. Of these 30, 23 (77%) use MMR and the other 7 use MR. Rubella incidence in the WPR is highest in the countries that have not introduced RCV or just recently introduced RCV. In 2009, most of the countries (21) in the WPR have an incidence <1 rubella case per 1,000,000 population; however, 4 countries (China, Cambodia, Singapore, Macau (China)) had an incidence ≥ 20 per 1,000,000 population. From 2007-2009, of the 286,196 reported cases, 4,351 (1.5%) included age and sex data. Among the latter, 83% occurred among persons aged <20 years.

In 2003, the WHO Regional Committee of the Western Pacific Region passed a resolution on measles elimination and hepatitis B control that urged member states to “use measles elimination and hepatitis B control strategies to strengthen EPI and other public health programmes, such as prevention of congenital rubella syndrome.” In 2009, a regional goal to achieve and maintain control of rubella and prevention of CRS was established. Rubella control is defined operationally as rubella incidence < 10 per million population, excluding imported cases and CRS prevention is defined operationally as a CRS incidence < 10 per million live births, excluding imported cases.

The epidemiology of rubella varies according to the duration of rubella vaccine use, strategies employed, and coverage achieved in national immunization programmes. Depending on the history of their vaccination programs, countries in the WPR were divided into 3 groups: 21 countries with long standing programs resulting in protection of all age cohorts including females ≥ 20 years; 4 countries using RCV > 10 years, protecting female and males up to 15 years but < 20 years, and 11 countries who recently introduced, or have yet to introduce, RCV.
Strategies for rubella surveillance included: enhancing or integrating with measles surveillance and encouraging the use of measles surveillance indicators. For CRS surveillance, countries were encouraged to establish sentinel surveillance.

The measles elimination goal has provided opportunities for accelerating rubella control and CRS prevention through integrated approaches using combined vaccines/strategies and measles case-based surveillance systems. However, the challenges for rubella/CRS goal include lack of CRS burden information in the many of the developing countries in the region; lack of motivation to embrace another goal; insufficient domestic production capacity (China, Vietnam) and missed opportunities to incorporate RCV in SIAs.

Discussion focused on production of vaccines in both China and Vietnam. Currently both countries manufacture their own vaccine. In China, the BRD-II strain is used; whereas, globally the RA 27/3 strain is used. As of 2011, China will have enough rubella for the entire birth cohort. Vietnam produces only measles single antigen vaccine, but plans to produce rubella-containing vaccine in the future. After review of some country data, discussion focused on the need to correlate surveillance data with the history of the vaccination program and the coverage achieved.

**Status of Rubella control in the Eastern Mediterranean Region**

For EMR countries that have introduced, or are planning to introduce RCV, the goal is to reduce the incidence of CRS to <1 CRS case per 100,000 live births. The recommended strategies include: MCV1 coverage > 80% for 3 years before introduction of RCV; administration of RCV together with MCV1; and ensuring rubella immunity in WCBA.

In 1995, the Gulf countries agreed to implement a rubella vaccination strategy that included adopting standardized case definitions for measles, rubella and CRS; achieving and maintaining high routine coverage; vaccination of susceptible (unvaccinated) postpartum women and establishing a laboratory network.

As of 2010, 16 of the 23 EMR countries have introduced RCV into their routine childhood program with 14 countries providing 2 doses of MR/MMR. One country (Tunisia) provides a single dose to school girls. Between 1994 and 2009, 154 SIAs were conducted of which 57 (37%) in 16 countries used RCV. In 2009, 18 countries had MCV1 coverage >80%.

During 2008-2010, reported rubella cases decreased from 1,783 to 614, with a majority of cases coming from 2 countries with relatively strong surveillance systems (Tunisia, Qatar). All countries have an integrated measles rubella surveillance. For suspected measles or rubella cases, some countries test
simultaneously for both measles and rubella. CRS surveillance is established in 9 countries; however, these countries do not report CRS cases to the Regional Office of WHO.

Several challenges in implementing regional rubella control goals include inaccessible populations in conflict-affected countries; polio in Afghanistan and Pakistan, and rubella occurring in non-residents in several countries. However, there are several opportunities including integration of measles and rubella surveillance, integration of the goals, use of combined vaccine during follow-up campaigns and strengthening the regional laboratory network.

Discussion focused on the region’s plan to move forward with rubella control goals including integrating the rubella goal with measles elimination. In EMR, there are 6 GAVI eligible countries. Should countries with a 2 dose schedule and MCV1 coverage less than 80% introduce RCV into their program? Also, discussed was the role of the private sector in providing RCV.

**Status of Rubella Control in the Southeast Asian Region**

Of the 11 countries in the Southeast Asia (SEAR) region, 4 (Bhutan, Maldives, Sri Lanka, Thailand) have introduced RCV into their routine EPI. At the 2008 SEAR Immunization TAG meeting, recommendations for countries that have not introduced RCV included: 1) strengthen/establish rubella and CRS surveillance, and 2) review burden of rubella and CRS, build political and financial commitment to introduce RCV using the WHO guidelines.

Of the 4 countries that have introduced RCV, the impetus for introducing RCV was an outbreak. Of the 4 countries that have introduced RCV, 2 (Bhutan, Maldives) conducted wide-age range mass campaigns targeting in both males and females with additional age groups for adult females. The other two countries (Sri Lanka, Thailand) initially targeted females followed by introduction in the routine childhood program and a catch-up campaign (in Sri Lanka). Three of the 4 countries that have introduced RCV do not have CRS surveillance established. Of the remaining 7 countries, Nepal has plans to introduce RCV and the Democratic Peoples Republic of Korea, Bangladesh, Myanmar, and Indonesia have MCV1 coverage over 80% but have not yet introduced RCV.

All countries have identified rubella through the measles case-based surveillance system. For the countries that have not introduced RCV, most of the cases occur among children less than 15 years of age. Since 2007, in Bangladesh with excellent measles control, almost all of the outbreaks are caused by rubella.

Discussion focused around the factors (e.g., susceptibility in WCBA, private sector use) that would influence a country to introduce RCV into the national routine
childhood program. Dr. Bose noted that in India that there is private sector use in many urban areas and this could shift rubella susceptibility to the older age groups as described in the paradoxical effect. As for susceptibility in WCBA, there is no absolute cut-off for susceptibility that would lead to the introduction of RCV; there are other factors including risk of exposure that need to be considered.

**Status of Rubella control in the African Region**

Currently, two countries (Seychelles, Mauritius) in the African Region use RCV in their routine program and Cape Verde is planning to introduce RCV by end 2010. There is no regional goal for rubella control or CRS elimination. The 2008 AFR TAG recommended that countries considering introduction of RCV should be committed to a goal of rubella control and CRS prevention; ensure high levels of coverage with RCV (MCV1>80%) through routine services and have sufficient resources to use combined MR vaccine in subsequent measles SIAs.

Since the 1980s, the number of measles cases has decreased and the regional MCV1 coverage has increased to 73% in 2009. In 2008, using WHO-UNICEF coverage estimates, 20 of the 46 MS had MCV1 coverage ≥80%. However, in 2008, it was estimated that 7.6 million infants missed their first dose of measles vaccine. In 2009, of the countries with MCV1 coverage ≥80% for three years, several had large measles outbreaks occurring in 2009-2010 raising questions about the MCV1 coverage.

Rubella cases are being effectively identified through the measles case-based surveillance system. Between 2005-2009, there has been an increase in the number of measles IgM negative cases that have been tested for rubella IgM antibodies. Approximately 95% of the rubella IgM+ cases occur among children aged <15 years of age.

There are both challenges and opportunities that rubella control and CRS prevention provide for the AFR. The challenges include: lack of information on the use of RCV in the private sector; incomplete information on the burden of disease; weak infrastructure to maintain MCV1 coverage >80% and simultaneous introduction of new vaccines (rotavirus, pneumococcal) in several countries. The opportunities include: identification of rubella cases through the existing measles case-based surveillance system, increasing routine immunization coverage in a number of countries and the experience of conducting wide age range measles SIAs.

To assist in the documentation of the burden of CRS and rubella seroprevalence, the Bill and Melinda Gates Foundation has provided support for several selected countries to establish CRS surveillance and conduct rubella seroprevalence studies.
Discussion focused on the other competing priorities such as AIDS, TB and malaria in addition to the introduction of new vaccines against pneumonia and diarrhea that have a higher burden of disease than rubella and CRS. Discussion also focused on what is the minimum amount of data required to influence policy. It was noted by participants that the data requirements may vary from country to country and by region.

**Strategies used by Countries and the impact on rubella and CRS**

Background information for strategies used and examples of country experiences that have used different vaccination strategies was discussed. The goal of any rubella vaccination program is the prevention of congenital rubella infection which includes CRS.

With the introduction of RCVs in 1969 in the United States and 1970s and 1980s in other developed countries, two basic approaches were implemented: CRS prevention only by vaccination of adolescent and adult susceptible females only and 2) rubella and CRS elimination by providing universal vaccination to both males and females through the routine childhood program. After several years of experience, it was decided that a combination of these two strategies works the best.

One of the major concerns about introduction of RCV into their routine childhood program is that if high vaccine coverage in the routine childhood program is not achieved and maintained, the risk of CRS may increase due to a shift in rubella susceptibility to the older age groups including WCBA. In the 2000 WHO rubella vaccine position paper, it is recommended that countries achieve an immunization coverage of >80% before introducing RCV into the routine childhood program. One cited country example for the paradoxical effect is Greece. In 1975, RCV was introduced in the private sector only which was responsible for vaccinating approximately 50% of the children. Not until 1989 was RCV introduced into the national routine childhood program. Between 1975 and 1989, the vaccination coverage was not monitored; however, the estimated coverage was <50%. Between 1971 and 1991, several seroprevalence studies among women of childbearing age were conducted. Prior to introduction of RCV in 1975, the seropositivity was 88%; however, in 1984-1989, the seropositivity dropped to 76% and then by 1990-1991, the seropositivity was 64%. In 1993, a rubella outbreak occurred with 64% of the cases reported among persons >15 years of age. Following the outbreak, 25 laboratory confirmed CRS cases were confirmed. Review of previous outbreaks in Greece noted that there was no increase in CRS cases.
Seven different countries/subregions examples were presented representing different vaccination strategies used for rubella control and CRS prevention goals. In England/Wales and Singapore that initially introduced RCV through vaccination of adolescent and susceptible adult females only, impact on CRS was not immediate and to eliminate rubella/CRS, introduction of RCV through the routine childhood program with and without SIAs was essential. Approximately 70% of the countries/territories in the Caribbean initially introduced RCV through a selective program offering vaccine to females only. The United States introduced RCV through the routine program; whereas, Albania and Brazil conducted catch-up SIAs in addition introduction into the routine childhood program. The table below summarizes the result of the vaccination strategies used and the time to impact on CRS and time to elimination of rubella and CRS.

<table>
<thead>
<tr>
<th>Country</th>
<th>Strategy</th>
<th>Time to Impact on CRS*</th>
<th>Time to Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Universal (2dose) +adol/adult</td>
<td>10-11 yrs</td>
<td>31 years</td>
</tr>
<tr>
<td>England/Wales</td>
<td>Selective +Univ (2dose)+SIA</td>
<td>15-16 yrs</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Selective, Univ (2 dose)</td>
<td>5 yrs (selective vax)</td>
<td>15 yrs after univ</td>
</tr>
<tr>
<td>Caribbean</td>
<td>Selective, Univ, SIAs</td>
<td>CRS surveillance established later</td>
<td>10 yrs after catch-up conducted</td>
</tr>
<tr>
<td>Albania</td>
<td>Univ, SIAs (catch-up, F/U), WCBA</td>
<td>Immediate</td>
<td>immediate</td>
</tr>
<tr>
<td>Brazil</td>
<td>Univ. catch-up, WCBA, m/adult SIA</td>
<td>CRS surveillance established later</td>
<td>15-20 yrs</td>
</tr>
<tr>
<td>Singapore</td>
<td>Selective, Univ (2dose)+SIA</td>
<td>16 yrs (probably sooner)</td>
<td></td>
</tr>
</tbody>
</table>

* ≥50% reduction from pre-vaccine era

1 Sweden had a similar experience requiring universal vaccination to achieve elimination.
Proposed Goals and Strategies

A “Strawman” Proposal for Updated Vaccination Strategies

Proposed vaccination goals and strategies were discussed. Experiences from regions and countries have capitalized on the use of combined measles-rubella-containing vaccine and incorporating RCV into the measles vaccination strategies. MCV delivery strategies vary depending on the strength of the infrastructure of the routine childhood program. Countries with stronger health care infrastructure have higher MCV1 coverage and usually both doses of MCV are given through the routine program. In countries using two doses routine only; all 40 countries have introduced RCV; among countries with a 2 dose routine program that have conducted one SIA, 33 of 35 (92%) have introduced RCV; among countries with a 2 dose routine program that conduct regular SIAs, 47 of 58 (82%) have introduced RCV; and among countries that have a 1 dose routine program and conduct regular SIAs, only 9 of 59 (15%) have introduced RCV.

Of the 4 regions with measles elimination goals, 2 (AMR, EUR) have rubella elimination goals and the other two (WPR and 16 countries in EMR) have accelerated rubella control and CRS prevention goals. For the two WHO regions with rubella elimination goals, each region started with rubella control or CRS prevention goal prior to establishing the rubella elimination goal. For AMR, in 1997, the TAG recommended to implement a rubella control and CRS prevention initiative, in 1999, an accelerated rubella control and CRS prevention goal was established, followed by in 2003, rubella and CRS elimination. In EUR, the initial goal established in 1998 was reduction of incidence of CRS by 2010 and in 2005, the goal was changed to rubella elimination and prevention of CRI by 2010.

The options for regional or country rubella and CRS control goals are

- CRS prevention without rubella control
- Rubella control and CRS prevention
- Accelerated rubella control and CRS prevention
- Rubella and CRS elimination

These proposed goals represent a continuum of different levels/phases of rubella control and CRS prevention. The figure below highlights the proposed goals with the vaccination strategies. With the rubella control goals, each vaccination strategy when implemented well will ultimately result in elimination of rubella and CRS, but over different time frames. Rubella and CRS will be eliminated in 20-30 years using
the rubella control and CRS prevention goal strategies; within 10-20 years using accelerated rubella control and CRS strategies and within 1-10 years using the rubella and CRS elimination strategies.

In determining the most appropriate goal/strategy for countries and regions, several issues should be assessed including: disease burden of rubella and CRS; cost-effectiveness of proposed strategies; establishing rubella/CRS prevention as a health priority and identifying sustainable financing. Each goal established should have a time frame in which this goal should be achieved. For countries planning to establish a rubella control or elimination goal, the preference is to administer RCV with the MCV1 dose in the routine childhood program instead of with the MCV2 dose due to the higher coverage that is usually achieved with the MCV1 dose. Based on country experience and the available information on the seroconversion, duration of immunity and vaccine effectiveness of 1 dose of RCV, only one dose of RCV is necessary. However, when combined with the measles vaccination strategy, it may be programmatically easier to provide a 2nd dose of RCV using the same combined measles-rubella vaccine for both doses. This strategy also provides an opportunity for those few vaccinees who were not protected following the first RCV dose to seroconvert.

As part of goal and vaccination strategy, countries and regions should establish or strengthen rubella and CRS surveillance system. In all stages of rubella control including countries that have not introduced RCV, rubella surveillance should be integrated with the measles case-based surveillance system and all febrile rashes in
pregnant women should be investigated. CRS surveillance should be established. As rubella control progresses towards elimination, the sensitivity and specificity of the surveillance systems should increase.

Discussion focused on the need to integrate the rubella and CRS prevention strategies with the measles goals and vaccination strategies. However, there may be additional strategies needed to ensure that the rubella/CRS goals are achieved. Questions were posed regarding the type of data necessary for monitoring impact and the costs of each of the goals/strategies. For the CRS prevention only goal, communication and establishing partnerships was an effective way to successfully target adolescent and adult females.

It was felt that countries should also be given the option not to introduce RCV, so it was recommended that the diagram be modified to include this phase of rubella control. In addition, a summary table should be prepared that includes immunization and surveillance strategies according to the programme goal (see below).

<table>
<thead>
<tr>
<th>Goal</th>
<th>Vaccination Strategy</th>
<th>Surveillance Strategy</th>
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| No introduction           | Not applicable       | • Detection of rubella cases through measles case-based surveillance  
                          |                      | • During outbreaks  
                          |                      |   o Investigation of all rash illness (suspected rubella) in pregnant women including laboratory testing  
                          |                      |   o Conduct laboratory testing of at least first 5-10 rash illnesses per month to confirm rubella as cause of outbreaks  
                          |                      |   o Investigate outbreaks  
                          |                      |   o Conduct active CRS surveillance  
                          |                      | • Collection of specimens for molecular epidemiology (may want to include earlier)  
                          |                      | • Sentinel case-based CRS surveillance in infants 0-11 months  
| CRS prevention only       | • Target adolescent girls and/or women of childbearing age for immunization either through routine services or mass campaigns | • Including strategies above and Rubella vaccination coverage monitoring* |
| Rubella control and CRS Prevention | • Including strategy above and  
  • **Introduction of RCV into the routine childhood program** – preferable to be introduced combined with both MCV1 and MCV2.  
  • **“Follow-up” MR or MMR campaigns targeting preschool-aged children (aged 1 to 4 years)†** | • Including strategies above and  
  • Detection of rubella cases through measles case-based surveillance – transition to integrated measles-rubella case-based surveillance  
  • Enhance investigation of outbreaks with laboratory testing of suspected cases |
| --- | --- | --- |
| Accelerated Rubella Control and CRS Prevention | • Including strategies above and  
  • **“Catch-up” MR or MMR campaigns targeting children aged less than 15 years.** | • Including strategies above and  
  • Enhancing integrated measles-rubella case-based surveillance – start to investigate every suspected case |
| Rubella/CRS Elimination | • Including strategies above and  
  • **“Speed-up” campaigns targeting adolescents and adults, men and women.** | • Including strategies above and  
  ◦ Strengthening integrated measles-rubella or febrile rash illness surveillance – testing and investigating all suspected cases  
  ◦ Seroprevalence studies in WCBA?, as appropriate |

*The red italicized text indicates new activities/strategies in comparison to the previous strategy

†Follow measles guidelines for continuing or discontinuing follow-up campaigns

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**Levels of Coverage needed for rubella vaccination**

**Minimum levels of rubella vaccination coverage needed to ensure a reduction in CRS**

Preliminary results from a mathematical model to assess the minimum immunization coverage required to ensure that the introduction of rubella-containing vaccine does not increase the risk of CRS was presented. The current strategies used for measles mortality reduction and elimination provide a unique opportunity to introduce RCV into the routine childhood schedule and SIAs. Previously, different modelling approaches have theoretically shown that if high routine childhood vaccination coverage is not achieved and maintained, this could result in an increase in the average age of infection and potentially increase the
burden of CRS. In the 2000 WHO rubella vaccine PP, countries are recommended to achieve and maintain childhood vaccination coverage of >80% as a requirement for introduction of RCV.

Various combinations of rubella vaccination through routine services and SIAs proposed in the “Strawman” modelled using different routine coverage levels (50, 80, 90%) and different parameters such as birth and transmission rates to compare the short- and long-term effects of the different vaccination combinations were presented. Birth rates vary; however, most countries in the world have birth rates <40 births per 1,000 persons with exception of several countries mainly in AFR (14 of the 46 countries). Magnitude of transmission was captured via the basic reproduction number, R₀, i.e. the number of secondary infectious cases that would be caused by a single infectious individual in a completely susceptible population. R₀ for rubella varies by region and countries; however, previous published values for R₀ include: 2.4-7.8 (Europe), Mexico (3.1-10.8) and Addis Ababa, Ethiopia (6.9-11.8). Based on these ranges, R₀ values of 6, 8 and 12 were used.

Discussion focused on considering the birth rates as an important factor in determining when to introduce rubella vaccine and the minimum coverage required. With higher birth rates, rubella infection occurs in younger individuals resulting in relatively higher immunity among women of childbearing age; the reverse is true for low birth rates (for example in Europe and China) where introduction of rubella vaccination is imperative to reduce the risk of rubella infections during pregnancy. Declining birth rates may be a factor of relevance in considering introduction of rubella vaccine.

Even though R₀ may be important in modeling risk of CRS, it is dependent on the population interaction (i.e., contact rates) and may vary within or between countries. Unlike birth rates, R₀ is an estimated parameter that requires specific data that may be hard to obtain for specific countries and hence is less useful for determining immunization policy. New graphs (Annex 1) were generated that reflected routine coverage and birth rate on the axes. In each square is the number is the critical R₀, above which a population with the given birth rate and coverage characteristics will experience an increase in the burden of CRS over 30 years. There are 4 graph: one graph with routine childhood vaccination only and 3 of the 4 graphs include the impact of follow-up campaigns (targeting preschool-aged children (aged 1 to 4 years)) at different coverage levels (60%, 80%, 90%). Colors range from green, indicating a high confidence of a reduction in CRS burdens (less than a 5% chance R₀ is above the stated value), to red, indicating a high confidence of an increase in CRS cases (at least a 95% chance R₀ is above the stated value). The graphs highlight the impact of SIAs even at 60%. Even at the
highest birth rate (50 per 1000 population), countries would be able to introduce RCV with a sustained routine immunization coverage of 80% (MCV1) or greater. Countries with routine coverage <80% may also safely introduce RV if they conduct regular SIAs achieving immunization coverage of 80% or greater. In making any recommendation for rubella control/elimination, RCV will be combined with the measles vaccine which requires a higher coverage than any of the estimates projected for rubella vaccine. Thus, aiming for the measles vaccine coverage requirement would provide a “safety” net for rubella vaccine.

Other variables that may affect the burden of CRS are social and spatial factors. Critical community size is the population size above which rubella will persist (in the absence of vaccination) because the number of new births is sufficient to sustain transmission in the community. The smaller the community the greater the likelihood that transmission will "fade out" periodically and persons will make it to adulthood still susceptible. If one country/community is vaccinating and the neighbouring country/community is not, depending on the vaccination coverage achieved and migration pattern, the country that is vaccinating may be at risk for increase burden of CRS. This situation is relevant to public versus private vaccination in countries, and highlights the importance of considering regional or social variability in vaccination coverage in assessing whether immunization systems are strong enough to support the introduction of the rubella vaccine: national levels of coverage attained should not be the only feature considered.

With the experiences of AMR and EUR, it was felt that the rubella strategy needs to be integrated with the measles strategy. With the measles goals, a higher coverage is necessary which exceeds the coverage required for rubella vaccination even at the highest R₀ and birth rate. Again, given the potential for build-up of pockets of older susceptible individuals, regional or social variation in vaccine coverage should be especially considered for rubella.

**Rubella vaccination coverage needed to interrupt transmission**

Various rubella transmission models have been developed to assess the level of coverage needed to eliminate/eradicate rubella. For two of the models (Anderson/Grenfell for the UK- 1986, Gay-1998), a vaccine coverage of 80-84% and >85%, respectively are needed to eliminate rubella/CRS. Models based on the epidemiological profile of disease in the United States in the pre-vaccine era suggest that population immunity must be >87.5% to interrupt rubella virus transmission. In a national serosurvey conducted between 1999-2004, the overall seropositivity was 91.3%. In 2004, an independent panel of internationally recognized experts in public health, infectious diseases, and immunizations reviewed the available data and unanimously agreed that rubella is no longer endemic in the United States. Country experience and mathematical modeling
indicate that >75-88% population immunity is required to stop transmission of rubella virus thereby eliminating cases of CRS due to endemic virus transmission. Assuming rubella vaccine effectiveness of 95%, this translates to an immunization coverage of 80-93%.

**Rubella control and Elimination: Surveillance Needs and Challenges**

The primary purpose of a rubella surveillance system is to detect in a timely manner, all areas where the rubella virus is circulating, to implement outbreak control and CRS prevention measures. In the 2000 PP, several recommendations were made for rubella and CRS surveillance. Rubella surveillance should be integrated with measles and dengue surveillance. CRS surveillance should include hospital record review, deaf/blind surveys, clinician reporting, and active searches for CRS cases after outbreaks of acquired rubella. Surveillance of therapeutic abortion registries should be examined. If possible, longitudinal sero-surveys in antenatal clinics should be conducted.

For all surveillance systems, there are general requirements such as standardized case definitions; guidelines; trained personnel; collaboration between epidemiologists, laboratory workers and health care workers; availability of an accredited laboratory; standardized case investigation forms and standardized reporting system. In addition to these requirements, rubella and CRS surveillance have additional requirements. Rubella surveillance should be integrated with measles case-based surveillance system. For rubella surveillance, all febrile rashes in pregnant women need to be investigated. As a part of the rubella and CRS surveillance, specimens for virus detection, isolation and genotyping should be collected and analyzed. CRS surveillance system requires the collaboration of multiple sites and medical specialties (e.g., cardiology, ENT, ophthalmology). Programmatic and performance indicators should be developed and monitored for both surveillance systems.

Some of the challenges for the surveillance systems include: obtaining adequate and timely clinical specimens for testing, availability of an accredited laboratory, reporting from the private sector, and follow-up of infected pregnant women.

Because of the different goals, the surveillance systems should match the country goal and strategies. There are surveillance requirements for all levels of rubella control. These include: case-based CRS surveillance, outbreak investigations, investigation of all febrile rash illnesses in pregnant women and coordination between field surveillance and the laboratory. As rubella control progresses, additional requirements include integration of rubella surveillance into the measles case-based surveillance system.