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**WORLD HEALTH ORGANIZATION  
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**WESTERN PACIFIC REGIONAL GUIDELINES:  
INTRODUCING RUBELLA VACCINE**

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## Summary

As the Region moves towards measles elimination there is an opportunity for countries to add rubella and eliminate both diseases at the same time. However, there is an important risk to rubella immunization if high coverage is not achieved and maintained. There is also the added cost of the vaccine that must be sustained.

For countries that are able to assure sustained high immunization coverage as well as the additional funding for rubella vaccine, the different options for the introduction of rubella vaccine are outlined. For all countries, it will be important to include rubella in the measles surveillance so that the importance of rubella can be assessed.

## Purpose

This document provides guidelines for National Immunization Programmes (NIPs) to consider adding rubella vaccine to their immunization schedule. Such a consideration can be precipitated by an outbreak, but ideally should happen before it. The document includes guidelines for epidemiological assessment of the outbreak to provide additional information on the need for rubella immunization.

It supplements the WHO position paper on rubella vaccines,<sup>1</sup> the WHO discussion document,<sup>2</sup> and is set in the context of the 2003 Regional Committee Resolution on measles elimination [WPR/RC54.R3]. Measles elimination creates an opportunity to also eliminate rubella.

## Background

### Disease burden

Rubella occurs worldwide and is normally a mild childhood disease. However, infection during early pregnancy may cause fetal death or congenital rubella syndrome (CRS) – with multiple defects, particularly to the brain, heart, eyes and ears. Up to 90% of babies are affected if infection is early in pregnancy. Infection in the second trimester may result in deafness alone.

Rubella infection sometimes leads to serious complications, including bleeding disorders, Guillain-Barré Syndrome (GBS), and encephalitis. Encephalitis had been previously reported to occur in 1 per 6000 cases – based on limited data from the USA and Japan. In the outbreaks in Tonga (2002) and Samoa (2003), encephalitis was seen more commonly and estimated to occur in between 1 in 300 and 1 in 1,500 cases. Although most cases of rubella encephalitis have a complete recovery, there can be serious complications and even deaths. Even with complete recovery such cases cause additional burdens to families and health services that are preventable.

The higher risk of encephalitis in these two Polynesian populations may reflect host/viral factors or may represent better recognition in an area where measles is well controlled and cases are not misclassified as measles. Whatever the cause, the encephalitis risk adds to the case for rubella immunization, especially for the Pacific. (See Annex 1 for more details about rubella infection).

### Risks of rubella immunization

The primary aim of rubella immunization is prevention of CRS. Immunization programmes must achieve a higher level of population immunity than natural infection or there is a risk that more pregnant women will be infected (leading to more CRS cases) than happened in the pre-vaccine era.<sup>3</sup> This means that rubella immunization is only recommended for countries that can achieve and maintain high immunization coverage (>80%).

An additional factor is private sector use of rubella vaccine potentially increasing CRS.<sup>4</sup> Private sector can reduce transmission among children leading an increase in adult susceptibility after about 20 years of use. A 2003 review of measles surveillance in selected areas of four province of China found rubella to be the leading identified cause of rash and fever. Of concern was the apparent increase in the average age of rubella infection as a result of private sale of rubella vaccine and hence a likely an increase in CRS cases in the future.

## Link with Regional measles elimination

In September 2003, the Regional Committee resolved to eliminate measles from the Region. As countries move towards measles elimination, there is the opportunity to eliminate rubella at the same time. Failure to take advantage of this opportunity means ongoing rubella and fetal damage.<sup>5</sup> Rubella vaccine addition can also be used as an opportunity to strengthen measles elimination efforts.

The importance of rubella in some countries may only be recognised after measles is controlled, as both cause acute fever and rash (AFR) illness. The importance of rubella infections in China is becoming evident in those areas where AFR cases are being tested for measles and rubella, with up to half of those negative for measles having rubella infection.

## Adding rubella vaccine

Adding rubella vaccine to the immunization schedule is simple: change from measles vaccine to measles-rubella vaccine (MR) or measles-mumps-rubella vaccine (MMR).

The 2003 UNICEF price for a 10-dose vial of measles, MR, and MMR is US\$1.21, \$4.80, and \$12.40, respectively. The UNICEF supplied MMR has Urabe strain mumps, which is known to have an increased risk of aseptic meningitis in about 1 in 10,000 recipients. (Several countries in the Region MMR with the Jeryl-Lynn strain mumps vaccine, which does not cause aseptic meningitis.) The rubella component does not cause any vaccine reactions apart from joint pains in adults.

The added cost and complication with mumps vaccine means that MR vaccine will be the preferred choice in the poorest countries. Measles and rubella are higher priorities than mumps control, because of its lower disease burden.<sup>6</sup> However, WHO recommends the use of MMR for countries that have the capacity and resources to control all three diseases, as the mumps disease burden is not trivial (encephalitis, deafness, and other complications including the risk of testicular cancer).

In the current market, the price of rubella vaccine on its own is greater than for MR. Rubella vaccine on its own would also require additional injections and/or visits, and is therefore not recommended.

MR vaccine is likely to be the preferred way to introduce rubella in most countries that have not yet done so. MMR is also acceptable, but adds substantial costs.

## Timing and number of doses

MR may be given from age 9 months or later. The timing of the first dose will be determined by measles epidemiology. WHO recommends measles vaccine at age 9 months, even though efficacy is lower than if given at 12 months, because when measles is common there are many children under one who get measles, and this age group has the highest mortality.

As countries move towards elimination and measles is no longer common, there are advantages to giving the first dose at age 12 months, because of the greater vaccine efficacy – even though it means that infants remain unprotected for longer.

Unless measles is endemic, the first dose of MR vaccine should be at age 12 months.

A single dose of measles vaccine has around 85% efficacy if given at 9 months of age, rising to 95% efficacy if given at 15 months. Because measles is so infectious it is recommended that a second dose of vaccine be given at least one month after the first dose. A second dose (given at the age of 12 months or older) results in 99% of recipients being protected.

Rubella vaccine failure is lower (only 2 to 5%) – even when given at nine months.<sup>7</sup> Rubella is also less infectious than measles. A single dose of rubella would be adequate, but it is operationally simpler for the immunization programme to use the same vaccine for both doses of measles. The second dose of rubella vaccine will also protect those who failed to be protected by the first.

A second dose is needed for measles, but not necessarily rubella; two doses of MR are operationally simpler and preferred (if affordable).

The second dose can be given at any time, but at least one month after the first dose.

## Action for all countries

The Western Pacific Region has resolved to eliminate measles, and to “use measles elimination and hepatitis B control strategies to strengthen EPI and other public health programmes, such as prevention of congenital rubella syndrome” [WPR/RC54.R3]. Therefore, all countries should:

- incorporate rubella surveillance (including laboratory confirmation) as part of their measles (acute febrile rash {AFR}) surveillance system.
- assess the burden of rubella disease so as to help make informed decisions
- consider adding rubella vaccine as part of the measles elimination programme

### Incorporating rubella with measles surveillance

The Western Pacific Regional resolution included a resolve “to develop or strengthen measles surveillance systems and laboratory confirmation of cases” [WPR/RC54.R3].

Patients with acute febrile rash (AFR) who are suspected of having measles need laboratory tests to confirm the diagnosis. Those who are negative for measles should be tested for rubella. Thus, rubella surveillance can easily build on the requirements of measles surveillance.

#### All countries should include:

- Rubella IgM testing for suspected measles (or febrile rash) cases if measles–negative.
- Routine analysis of rubella cases as part of the measles (AFR) surveillance system

### Laboratory network

Establishing a formalized laboratory network and ensuring that all samples are tested or confirmed in an appropriate network laboratory will enable reliable laboratory testing. A laboratory network allows standardised testing and reporting structures to be developed and establishment of a strong environment of quality assurance and referral procedures.

The WHO Measles Laboratory Network currently consists of 671 laboratories globally that test for rubella as well as measles to confirm the diagnosis in cases of rash and fever. The network consists of three tiers of laboratories (Global Specialized, Regional reference and National). Some countries are also establishing sub-national laboratories.

### Estimating rubella disease burden

In countries without immunization programmes rubella epidemics occur every 5 to 9 years, with additional rubella cases during the inter-epidemic periods. There will be between 10 and 40 cases of CRS per 10,000 births from an epidemic, but many less between epidemics. An overall estimate of CRS burden (without immunization) is thus between 1 and 10 cases per 10,000 births.

Because of the substantial costs and difficulties in assessing disease burden, some countries (that do not have existing CRS surveillance) may choose to make the decision about rubella vaccine, based on the likely estimated incidence of between 1 and 10 cases per 10,000 births.

Countries with no CRS surveillance have these options for assessing CRS burden:

1. Use existing data in the literature (or the estimated incidence as above)
2. Conduct a serosurvey (including in pregnant women)
3. Conduct retrospective study for CRS – using hospitalisation data, or data on blindness and/or deafness

A decision based on likely incidence of disease can be strengthened with data from neighbouring countries. In the case of the Pacific island countries, large rubella epidemics have been documented to occur six-yearly in Tonga and Samoa. However, CRS surveillance has not yet identified the CRS burden in these countries, highlighting the challenge of undertaking CRS surveillance. However, in both Tonga and Samoa there was also an important additional burden from rubella encephalitis.

A serosurvey can establish the age-profile of immunity, and hence the likelihood of CRS cases. A serosurvey will require a study protocol, ethical clearance, informed consent for the participants, as well as actions to be taken in relation to advising the individuals who were negative. Alternatively, a convenience sample may be undertaken using the residual sera of bloods taken for other purposes; however this would still require a proper protocol, and the testing undertaken by a laboratory with the appropriate quality control (or part of the Measles Laboratory Network).

Retrospective identification of cases from hospital data has been used to identify cases.<sup>8</sup> In addition, data on the incidence (by year of birth) of new cases of deafness and blindness can identify possible rubella outbreak years and also give an indication of CRS burden. The retrospective surveillance is also complex, but can be achieved much faster than prospective CRS surveillance.

### **Establishing CRS surveillance**

The primary disease burden from rubella is from CRS. Establishing surveillance for CRS is not straightforward and requires considerable resources. Even then, many cases of CRS may be missed – because of failure to present to health services or lack of clinical and/or laboratory expertise needed to detect them. For example, in Costa Rica there were no notifications of CRS from 1992, but active search at the National Children’s Hospital for the period 1996-2000 identified 49 CRS cases.<sup>9</sup>

CRS surveillance is important for monitoring the impact of immunization, as well as for estimating disease burden. However, the challenges of establishing CRS surveillance should not delay implementing rubella immunization. But, it is essential to have access to laboratory tests for rubella, and to have at least one major hospital site that can monitor for CRS cases by testing the blood of infants with defined congenital defects. Annex 3 provides guidance on establishing CRS surveillance, and gives an indication of the resources that will be needed.

### **Considering rubella vaccine for the NIP**

Guidelines on adding a new vaccine have been prepared by WPRO.<sup>10</sup> A draft set of indicators of a country’s capacity to add a new vaccine is being developed by WPRO (see Annex 5).

As countries move towards measles elimination, the decision-making for rubella immunization needs to be reframed. Measles elimination provides the opportunity, at little extra cost, to also eliminate rubella. Furthermore, as it is recommended to have a wide-age range immunization campaign to introduce rubella vaccine, this campaign can have substantial benefits for measles control.

A key question in deciding about adding a new vaccine is comparing the costs and benefits from investing in the new vaccine compared with other available health investments. Because the full burden of rubella can be hard to estimate in some countries, Annex 5 provides a rough economic justification that is likely to apply to most settings.

For both measles and rubella elimination, over 95% immunity must be maintained for all cohorts in all districts. Lower levels of coverage can still provide reasonable control, but there will eventually be outbreaks. As measles is more infectious than rubella, the immunization efforts to eliminate measles should be more than adequate to eliminate rubella. Thus, adding rubella elimination to a country’s measles elimination initiative does not pose additional logistic challenges.

Rubella elimination can be easily added to a country’s measles elimination programme, and all countries moving towards measles elimination should consider adding rubella, as long as they meet the criteria of high coverage and sustainable funding.

## **Adding rubella vaccine**

### **Issues for adding rubella vaccine**

Although replacing measles with MR vaccine is simple, there are important considerations:

1. The risk of increasing the number of CRS cases if high coverage cannot be achieved: coverage must be greater than the pre-vaccine era percentage of adults who are immune for the programme to be worthwhile.

2. The extra cost of vaccine, and its relative priority in limited health budgets.
3. The potential to create cohorts of susceptibles among those born before the introduction of rubella immunization.

### Ensuring high coverage

Rubella is less infectious than measles. For countries that are moving towards measles elimination, rubella can be eliminated at lower levels of coverage (as it is less infectious). Therefore, this should not be an issue for countries that have adopted measles elimination. It becomes a political and financial decision to add rubella to the measles elimination programme.

Countries will require at least 95% coverage for measles elimination; therefore rubella can be safely introduced in countries that are committed to measles elimination.

### Cost

Economic analyses have shown that rubella immunization is very cost-effective in both industrialised and developing countries.<sup>11</sup> The costs and impacts of a single case of CRS can be very high compared to the cost of the vaccine. In addition for Pacific people who frequently move to Australia, New Zealand, and the USA, the costs to the health and disability sectors of those countries create incentives for sub-regional control of rubella.

Although rubella immunization is cost-effective, and even potentially cost saving, additional funds are still needed (either internal or external) to enable its addition. The ongoing costs will be about US\$1 for every newborn child. [Assumptions: two doses of MR given; additional cost is US\$0.36 per dose (based on 2003 UNICEF costs for the 10-dose vial, above); and 40% wastage.]

As the cost to fully immunize a child in developing countries is estimated to be between US\$15 to 30, the addition of rubella will only increase the overall immunization costs by 3 to 7%. In many countries, reducing the level of vaccine wastage of all EPI vaccines could generate sufficient savings to cover most or all of the cost of MR vaccine. [refer to Vaccine Security plan on reducing wastage]

There should be no operational implications or costs for the change from measles to MR, as it is simply a substitution of one 10-dose vial with another one that is identical – except for addition of rubella vaccine. There may be an increase in uptake as a result of the addition, which would increase costs, but would have correspondingly greater benefits.

Adding rubella vaccine is likely to be very cost effective, and will cost US\$1.00 per newborn child for the routine programme (for two doses of MR).

### Impact on older cohorts

Children born before the introduction of rubella immunization are more likely to enter adulthood susceptible to rubella, thus potentially increasing the risk of CRS (They are less likely to get infected as children because of the impact of immunization in preventing spread of the virus, but will not have protection from immunization). Therefore, at the same time (or before) routine rubella immunization is added, it is necessary to either:

1. deliver a mass immunization campaign to all children aged 1 to 14 years (or even older); or
2. protect all childbearing age women (CBAW) through immunization of girls at school, a mass immunization campaign, and/or post-partum.

A campaign has the advantage of having immediate effects in preventing the circulation of rubella virus; possibly eliminating the virus and creating sufficient population immunity to prevent re-establishment from any imported case. It will also be beneficial for measles control.

In most countries many adults remain susceptible to rubella. Therefore, the campaign would ideally be extended to include young adults. However, adults will require considerably more resources to reach. Therefore, a careful decision will be needed on the upper age range of the campaign based both on affordability and any data on the age-profile of susceptibility to rubella.

The danger of selective immunization of women, whether as school children or as CBAW, is that large numbers of people, including all males, may be still susceptible. Experience has shown that these susceptible groups have then suffered outbreaks with spread to pregnant women. Thus, if a campaign is feasible for adults, it is best to immunize both men and women.

If it is not feasible to deliver a campaign to protect these women a strategy of immunizing women after their first child can be a useful addition if it is known that CBAW remain unprotected.

A mass immunization campaign for all aged 1 to 14 years (or older) is recommended when introducing rubella vaccine so as to prevent ongoing infection, including epidemics, among older children and young adults.

The campaign's upper age range depends on affordability; data on susceptibility; and the need to achieve very high coverage (>95%) in all of the targeted cohorts.

Protection of pregnant women is an adjunct control strategy that may be needed if the campaign does not protect most susceptible women.

### **Options for adding rubella vaccine**

Once a decision is made to add rubella vaccine the following issues need consideration:

1. The type of introductory campaign
2. The timing of the first dose
3. The timing of the second dose
4. Any need for additional measures to protect pregnant women

#### **Introductory campaign**

The introductory campaign may be delivered as a one-off event, or can be delivered as part of routine immunization services over a longer period of time. The best approach to implementation will depend on the local circumstances, as well as previous experience with mass campaigns.

The age range for the campaign requires determination of age profile of susceptibility. If that is not available, then the target age should be those aged 1 to 9 years, at a minimum.

Unlike with measles pre-immunization, many adults remain susceptible to rubella – the percentage varies in different settings but is generally between 10 and 25%.<sup>12</sup> As the aim is to ensure that the entire population has over 95% immunity, and this may require extending the campaign to older age groups. However, as it will be harder to reach those who have left school, and because of the additional costs, careful consideration of the benefits and costs of extending the age range will be needed. If high coverage can be achieved, the upper age should be to as high an age group (with inadequate immunity) as is affordable.

Another option may be to target young adults who are in institutions such as the military, training colleges, and large workplaces where there is a lot of mixing of adults. These groups are more likely to spread infection, and are relatively easy to reach through that institution.

#### **Timing of first dose**

The change from measles to MR provides a good opportunity to change the timing of the first dose from age nine to 12 months – provided that measles is already under good control. If measles is still common, that means that it may be premature to introduce rubella. However, a successful introductory campaign with MR should improve measles control.

MR can be scheduled at age nine months, if there are other reasons for this scheduling.

#### **Second dose**

A second dose of measles vaccine is necessary for measles elimination. It is not necessary for rubella elimination. Therefore, the decision about the second dose will need to balance the extra cost versus the operational simplicity of using only MR rather than two vaccines. For countries that have not yet

introduced a scheduled second dose of measles, but deliver the second dose through regular campaigns there would be a preference for using MR as the campaign vaccine and measles for the scheduled dose. [Assumption: second dose is given as campaign because higher coverage is achieved, therefore best to give rubella through the higher coverage option].

### Pregnant women

The introductory campaign would ideally include all people at school. This will protect the next generation of pregnant women directly, as well as indirectly protect all pregnant women by reducing the spread of rubella virus.

However, depending on the proportion of adults who remain susceptible, there will still be a risk of rubella outbreaks affecting adults. Should additional measures be undertaken to protect these women?

In industrialized countries, women are screened antenatally, and those without rubella immunity are immunized post-partum. As the blood test is more expensive than MR vaccine, resource-poor countries could simply immunize (unvaccinated) women post-partum without any screening. However, this would be an adjunct to rubella control, and only becomes necessary if sufficient population immunity has not been achieved.

Rubella vaccine is contraindicated in pregnancy because of the theoretical risk of CRS from the vaccine virus. But, there is no evidence of CRS from vaccine, so if a pregnant woman is accidentally given MR, there is no need to consider termination of the pregnancy, but the outcome should be monitored.

## Outbreak response

A rubella outbreak leads to urgent consideration of rubella vaccine. Early recognition (and hence timely response) requires laboratory testing to be in place. As countries implement intensified measles surveillance and incorporate rubella surveillance as part of that system, so countries will need to plan how they will respond when a rubella outbreak is identified.

To control an outbreak through immunization requires a very rapid response as well as epidemiological assessment of the outbreak. Preparing a plan for investigation and emergency response with a wide-age range campaign can then be useful for other public health emergencies. Unless such plans are already in place, it is unlikely that there will be adequate assessment of the need for a campaign, nor that it could be implemented rapidly enough to stop the outbreak.

Even if a plan is in place, there will be considerable challenges to achieving a response that is timely enough to prevent the outbreak. At present, there is no evidence of an outbreak being curtailed by immunization, and hence the need to implement an immunization campaign before an outbreak occurs.

Rubella immunization must not be introduced unless very high levels of coverage can be achieved and maintained indefinitely (to prevent a potential increase in CRS cases as discussed above). The requirement for very high coverage also applies to the initial campaign.

All countries should develop plans on implementing a wide-age range immunization campaign for preparedness to a wide range of potential emerging diseases, including rubella.

### Assessing disease burden during a rubella outbreak

A detailed epidemiological assessment of an outbreak provides useful information about the age-susceptibility profile of the population, and hence the risk of CRS. As with any outbreak, the first step is to confirm the diagnosis with laboratory tests on at least 5 to 10 of the cases, using standard case definitions.

Experience in Tonga and Samoa has shown that it is also important to assess the incidence of any complications, especially rubella encephalitis to get the total picture of disease burden.

As rubella tends to be an epidemic disease with long gaps between outbreaks (particularly in island or isolated populations), it may be useful to search for evidence of previous outbreaks to assess how frequent any future outbreaks are likely to be.

### Age distribution

The age-distribution of cases will show the overall pattern of immunity by age, and hence give an indication of adult susceptibility. The age distribution can also provide some evidence of previous outbreaks as well as provide guidance on the upper age to be targeted by immunization. Data from health clinics and hospitals need to be collated and analysed, using standard case definitions (Annex 4).

Counting cases presenting to health clinics can lead to a significant ascertainment bias, as parents are more likely to seek advice for young children while older children and adults may not present if the disease is mild.

The attack rate can also be used to give an indication at the stage of the epidemic cycle at the time of the survey and inform the urgency and requirement for any intervention. The highest attack rates are usually in 5 to 9 year-olds. As about half the cases can be asymptomatic, as the attack rate in this group approaches about 30% epidemic is likely to have peaked.

A community survey in one or more representative villages or communities should be undertaken, using a simple clinical case definition such as recent acute rash and fever illness, to estimate the attack rate in all age groups

### Risk to pregnant women

The risk to pregnant women can also be measured more directly by undertaking serosurvey. To be most useful, the survey needs to be early in the outbreak so as to get a better assessment of immunity before the outbreak peaks. Ideally, a random sample of all pregnant women would be tested, but a convenience sample of women attending for an antenatal clinic is likely to provide adequate results in most cases. However, these women may not be representative of all pregnant women in some countries, and if so a more widely based random survey should be undertaken.

In general a serosurvey of about 100 women will provide sufficient reliable information on susceptibility.

A serosurvey of pregnant women provides an estimate of the potential CRS burden – this is best undertaken before rather than during an outbreak

The exposure history of pregnant women to cases of fever and rash, as well as their own experience of illness should be routinely collected at antenatal visits during a rubella outbreak to enable identification of potential CRS cases for screening and follow-up of their babies. Procedures need to be established and disseminated for follow-up of pregnant women who are suspected or known to have been exposed to rubella infection.

Women attending for antenatal care during the outbreak who have been exposed to, or suffered, an illness with fever and rash need to have their babies followed-up for CRS

### Incidence of complications

Although it is usually a mild disease in children and adults, there may be an increased rate of complications in certain populations. The recent finding of high rates of encephalitis in the Tonga and Samoa outbreaks emphasise the need to monitor and evaluate any complications. These can be monitored primarily in hospital-based cases.

All rubella complications, especially rubella encephalitis, should be monitored and evaluated.

## Delivering an immunization campaign to stop the rubella outbreak

In the face of a rubella epidemic, there will be strong demand to respond with an immunization campaign. For many countries, the **priority will be to first strengthen the routine programme** and deliver a planned campaign after the outbreak to prevent future cases.

For countries that are already reaching high routine coverage, the addition of rubella vaccine should be considered before any outbreak. Even for countries that have high routine coverage, an immunization campaign to stop the outbreak should only be considered if:

1. Political commitment and additional funding for routine rubella immunization
2. Ability to deliver the immunization campaign rapidly and at very high coverage

An immunization campaign can potentially interrupt rubella transmission – if rapidly and effectively implemented (high coverage). It needs to be borne in mind that in addition to the time required to plan and implement a campaign, because of the incubation period of the disease it will take a further 2-3 weeks before any reduction in numbers will be seen. However, as previously pointed out an immunization campaign will be far more effective if delivered before an outbreak than during it.

Because of the potential long term risks of poorly or irregularly implemented rubella immunization it is vital to obtain political commitment and funding for routine rubella immunization before considering a campaign.

### Effective implementation

There are several key requirements to enable rapid and effective implementation, including:

- Political support for the rubella immunization programme
- Availability of funding
- Sourcing the vaccine
- Sufficient cold chain capacity for the additional load
- Sufficient health staff to immunize
- Social mobilisation to ensure high uptake (including intersectoral coordination)

All these elements need to be in place and coordinated by a national taskforce and secretariat for effective implementation. Effective implementation usually requires careful monitoring and evaluation to identify those who are being missed so that special efforts can be made to reach them.

### Options for campaign target groups

**Primary school children and pre-school children should always be included in the target group**, as they are likely to have the highest attack rates and to be most important groups in spreading the virus in the community. Age-susceptibility profile and age-specific attack rates can help to define which other age groups should also be targeted.

At present WHO does not recommend immunizing pregnant women because of the small theoretical risk of CRS from the vaccine virus. No actual risk has ever been found. During an outbreak, the risk (of CRS) to pregnant women is likely to be greater than the theoretical risk from the vaccine. However, if a vaccinated woman gets infected before she is protected by the immunization, the laboratory test will no longer be able to determine that she has been infected (and thus offered termination) and any subsequent problems in the unborn child will lead to false blame for the vaccine. Therefore, the primary way to protect CBAW is through preventing virus circulating in the community.

If young adults (aged 15-24) have high attack rates, they should be considered for inclusion. However, young adults can be very difficult to target, and it may be possible to focus on adults who are attending institutions or who are in large work places. Although young adults do transmit infection to each other, it is more often infection from school-aged children that drives the outbreak.

It is also possible to protect all childbearing age women (CBAW), not so much because of the impact on the outbreak, but for their future protection. However, an immunization campaign for this wide age-range group should generally happen after all the children have been immunized, and does not have much impact in stopping the outbreak compared to its huge logistic demands.

The logistic challenges of delivering an effective campaign multiply as the target groups increase. Therefore, it is important to plan for initial coverage among the groups where high coverage can be most easily assured (e.g., school-children). It is possible to protect other groups later on, so as to ensure the highest possible coverage in the priority groups who are likely to be the main transmitters of infection in the community. This will usually be school children.

Again, it must be emphasised that a campaign will be much more effective if planned ahead of any outbreak.

## References

- <sup>1</sup> WHO position paper. Rubella vaccines. *Wkly Epidemiol Rec* 2000 (20); 75: 161-9
- <sup>2</sup> World Health Organization. Control of rubella and congenital rubella syndrome (CRS) in developing countries. Geneva: WHO, 2000. [WHO/V&B/00.03].
- <sup>3</sup> Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. *BMJ* 1999;319: 1462-7.
- <sup>4</sup> Vynnycky E, Gay NJ, Cutts FT. The predicted impact of private sector MMR vaccination on the burden of Congenital Rubella Syndrome. *Vaccine* 2003; 21: 2708–19.
- <sup>5</sup> Plotkin SA. Rubella eradication. *Vaccine* 2001; 19: 3311–9.
- <sup>6</sup> WHO position paper. Mumps virus vaccines. *Wkly Epidemiol Rec* 2001 (45); 76: 346-55
- <sup>7</sup> Robertson SE, Cutts FT, Samuel R, Diaz-Ortega JL. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 2: Vaccination against rubella. *Bull World Health Organ* 1997; 75(1): 69-80.
- <sup>8</sup> Lawn JE, Reef S, Baffoe-Bonnie B, Caul EO, Griffin GE. Unseen blindness, unheard deafness, and unrecorded death and disability: Congenital Rubella in Kumasi, Ghana. *Am J Public Health*. 2000; 90: 1555–61.
- <sup>9</sup> Anonymous. Accelerated rubella and congenital rubella syndrome programme, Costa Rica. *Wkly Epidemiol Rec* 2001; 76 (35): 265-70.
- <sup>10</sup> World Health Organization. Assessing New Vaccines for National Immunization Programmes. A framework to assist decision makers. Manila: WHO, 2000.
- <sup>11</sup> Hinman AR, Irons B, Lewis M, et al. Economic analyses of rubella and rubella vaccines: a global review. *Bull World Health Organ*, 2002; 80 (4): 264-70.
- <sup>12</sup> Cutts FT, Robertson SE, Diaz-Ortega JL, Samuel R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 1: Burden of disease from CRS. *Bull World Health Organ* 1997; 75(1): 55-68.

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## Annex 1: Rubella infection

### The virus

Rubella is single-stranded RNA virus (family: togaviridae; genus: rubivirus) spread by the respiratory route. It only infects humans, leading to the potential for eradication.

The incubation period is 12 to 23 days (usually 16-18) preceding rash. The infectious period is from seven days before to seven days after the onset of the rash; but the virus can be found in the nasopharynx for up to two weeks after rash onset and babies infected in the womb can shed virus for a year or more.

### The illness

Rubella is a common viral infection of childhood that can affect adults. It is usually a mild illness, and often infection does not cause any symptoms. Clinical features include a transient erythematous rash, lymphadenopathy (particularly in the posterior auricular and suboccipital nodes), and, in adults, arthritis or arthralgia.

Rubella may present as a more severe illness, clinically indistinguishable from measles. Rubella encephalitis may occur more frequently than the previously estimated 1 in 6,000 cases. It can result in residual neurological damage or occasionally death, but more often has a benign outcome. Thrombocytopenia has been reported at a rate of one per 3,000.

### Congenital Rubella Syndrome

Rubella infection in early pregnancy can lead to fetal death or Congenital Rubella Syndrome (CRS). The risk of fetal damage depends on timing of the infection: up to 90% at 8 to 10 weeks, declining to about 10% to 20% by about 16 weeks and after this stage of pregnancy, fetal abnormalities are rare.

CRS can cause a wide range of congenital defects (singly or in combination), with hearing impairments the most common. It also causes eye (e.g. cataracts, microphthalmia, glaucoma, pigmentary retinopathy), heart (e.g. patent ductus arteriosus, peripheral pulmonary artery stenosis, or ventricular septal defects), face (e.g. microcephaly) and other defects (encephalitis, mental retardation, autistic behaviour, intrauterine growth retardation, hepatosplenomegaly, interstitial pneumonitis, thrombocytopenic purpura, diabetes, hypothyroidism).

In CRS cases the presence of rubella-specific IgM declines with age: ~100% at 0-5 months, ~60% at 6-11 months and rarely after the age of 18 months (although occasionally it may be absent in the first month after birth)

### Epidemiology

Before the use of vaccines, countries usually experienced epidemics every five to nine years, with the highest attack rates in five to nine year old children. Rubella also circulates in between epidemics. Rubella is not as infectious as measles and many adults remain susceptible to rubella.

Immunization can eliminate rubella. In countries with selective immunization of girls/women, outbreaks have occurred that predominantly affect adult males.

### Laboratory diagnosis

Diagnosis cannot be reliably be made on clinical grounds and laboratory testing is needed to confirm the diagnosis. The standard test is rubella-specific IgM test (positive from 6 days to 6 weeks after rash onset) [**\*\*note WHO99 states 4 days to 4-12 weeks\*\***].

Diagnosis can also be made from an increase in rubella-specific IgG in paired serum, viral isolation, or PCR. Virus can be isolated from nasal, blood, throat, urine, stool or cerebrospinal fluid samples. Samples are best taken within four days of rash onset when the viral load is highest. The best results come from throat swabs. Isolates or PCR results can be used for genotyping the virus that may help determines the source.

## Annex 2: Rubella vaccine

Rubella vaccine is available on its own or in combination as measles-rubella vaccine (MR) and measles-mumps-rubella vaccine (MMR). The rubella vaccine strain that is most often used is the Wistar RA27/3 strain. The vaccine virus is cultured in human diploid cells

All these vaccines (as well as measles vaccines):

- are freeze-dried live viruses, modified from the original virus so that ‘infection’ leads to immunity without causing illness or spread to contacts
- come as a dry powder that can be frozen, but are generally stored at 2° to 8°C.
- should be reconstituted only with the diluent supplied by the manufacturer and used within six hours of reconstitution
- are sensitive to light as well as heat, especially when reconstituted
- are usually given in the deltoid region of the upper arm as a dose of 0.5ml, by the subcutaneous or intramuscular route.

### Vaccine effectiveness

A single dose of rubella vaccine induces an antibody response in 95-98% of recipients, and effectiveness in outbreaks has been between 90 and 97%. Even though antibody levels decline with time, there is no evidence that protection has declined – even after decades of follow-up.

A second dose will protect the small proportion who fail to be protected by the first dose.

Although the vaccine virus is excreted (mostly from the pharynx), there does not appear to be transmission to susceptible contacts.

### Vaccine reactions

Vaccinees can develop mild rubella, including fever, sore throat, lymphadenopathy, rash, arthralgia and arthritis. Less than 1% of infants get mild rubella, but up to a quarter of adult women get joint symptoms (arthralgia or arthritis). Symptoms begin one to three weeks after immunisation and are usually only of short duration.

No major or long-lasting reactions are caused by rubella vaccine.

Although rubella vaccine virus is excreted following immunization, there are no reliable reports of vaccine viral transmission leading to infection of contacts.

### Immunization in pregnancy

There is a small theoretical risk of rubella vaccine to a pregnant woman leading to CRS. Therefore, rubella vaccine is contraindicated in pregnant women, and vaccinees are advised to avoid pregnancy for at least one month after immunization.

However, follow-up of women who were accidentally given rubella vaccine in pregnancy has not found a single case of the vaccine causing CRS. Therefore, rubella vaccine given in pregnancy is not a reason to consider termination of the pregnancy.

### Immunization strategies

Experience in the Australia, United Kingdom, New Zealand, and other countries have shown that aiming for the individual protection of pregnant women is less effective as a control strategy than the prevention of rubella circulation by immunising both male and female children. This is because of the failure of many women to be vaccinated, as well as occasional vaccine failure.

### **Annex 3: CRS Surveillance**

CRS surveillance is complex and requires human, laboratory, and financial resources. Therefore, it should be initially established in a limited area (a pilot) and evaluated before extending to national surveillance.

Establishing pilot CRS surveillance requires:

- defined populations (selecting pilot site(s))
- screening process (questions, signs & symptoms)
- referral for clinical diagnosis
- laboratory testing to confirm diagnosis
- data collection (reporting) and analysis
- evaluation of pilot.

#### **Coordinator**

Many people will need to be involved for surveillance to be effective. The coordinator will help all parts of the surveillance system to work well with each other. The coordinator can also ensure that all procedures and guidelines are in place where needed and provide oversight on the system and the day-to-day management of the data. The coordinator also ensures that adequate priority is given to establish the system.

#### **Populations**

1. The surveillance will focus on one or more hospitals where most births occur and with the clinical and laboratory resources to undertake the surveillance. Usually, thousands of babies will need to be screened to provide an accurate estimate given the expected rate of CRS after a rubella epidemic is 1-4 per 1000 live births.
2. Attendances at immunization visits under the age of one year provide another opportunity to identify cases of CRS. This is important as hearing loss will not usually be apparent at birth.

#### **Screening**

The first step is screening newborns and infants, using a standard procedure, to identify those who need further review so that a diagnosis (CRS or not) can be made.

The screening can consist of:

- Asking mother for:
  - any history of fever and rash during the pregnancy
  - any suspicion of hearing loss or blindness/eye problems
- Looking for:
  - hearing (heard turning to noise)
  - eye problem (white eyes / small eyes / large eyes / wobbly eyes)
  - heart disease (blue baby / hear murmur)
  - abnormal body (small head)

To enable screening to take place effectively requires:

- training of the health workers to undertake the screening
- system to ensure that every child in the target population (i.e., every birth or every child who attends for DTP3 or measles vaccine) is screened

- system for referral and follow-up of every child who screens positive.

### Clinical diagnosis

Every newborn or infant who tests positive needs to be referred to an experienced doctor who is able to diagnose CRS, using the established case definition (see Annex 4), modified as needed for local use.

The doctors who are able to do the clinical review need to be identified. It may be appropriate for doctors of different specialties to review the case depending on the kind of defect (e.g., ophthalmologist for any eye defect). A list of suitable doctors, identified by specialty and location, will assist the referral process. The doctors also need to agree to review the cases, which screen positive, and to follow a standard procedure and report on the cases referred to them.

### Laboratory testing

The doctor will require laboratory testing (Rubella IgM antibody) to confirm a clinical diagnosis of rubella as well as for those cases where the diagnosis is uncertain. The capacity to take the blood from newborns and infants and for the laboratory to do the testing needs to be able to meet the extra demand.

### Data management

A system for collecting the data on the number:

- of children screened;
- who screened positive;
- clinically confirmed CRS; and
- laboratory confirmed CRS.

Initially, this should be kept separate from the other disease reporting, but integration with AFP and other disease reporting can be planned for the future.

### Evaluation

In addition to regular review of the programme, a formal evaluation after about six months of operation, is needed to follow-up on the pilot. Decisions made about rubella immunization and/or surveillance, including extending it, will influence the type of evaluation.

### Additional strategies for estimating CRS disease burden

Additional strategies for identifying CRS disease burden:

- identifying evidence of previous outbreaks and ongoing circulation.
- analysis by year of birth of data from institutions from the blind and/or deaf to identify previous epidemics
- population screening for rubella IgG to define the pattern of infection from which CRS burden can be estimated

## Annex 4: Case Definitions

### Rubella

#### *Suspected rubella case*

A suspected rubella case is any patient of any age in whom a health worker suspects rubella. A health worker should suspect rubella when the patient presents with:

- (1) fever
- (2) maculopapular rash, and one of the following:
- (3) cervical, sub-occipital, or post-auricular adenopathy; or arthralgia/arthritis.

It will usually be difficult to distinguish rubella from measles, dengue, or a number of other febrile rash illnesses without laboratory testing.

#### *Laboratory-confirmed rubella case*

A laboratory-confirmed rubella case is a suspected case with a positive blood test for rubella-specific IgM (or other laboratory test) from a laboratory that is part of (or linked to) the Measles Laboratory Network.

#### *Epidemiologically-confirmed rubella case*

An epidemiologically-confirmed rubella case is a suspected case with contact/exposure to a laboratory-confirmed case of rubella during the 23 days before rash onset (maximum incubation period) while the source was infectious (one week before and after rash onset).

### Rubella encephalitis

#### *Suspected rubella encephalitis case*

History of current or recent (14 days) rash-with-fever illness consistent with rubella AND seizures in person and/or acute confusional state (ACS) - in a person with no other identified cause of seizures or ACS (including no clinical or laboratory evidence of bacterial meningitis)

#### *Laboratory-confirmed rubella encephalitis case*

A suspected rubella encephalitis case with rubella IgM positive from CSF or viral detection from CSF

### Congenital Rubella Syndrome (CRS)

#### *Suspected CRS case*

A suspected case is any infant less than one year of age in whom a health worker suspects CRS. A health worker should suspect CRS when either

- (1) there is a maternal history of suspected or confirmed rubella during pregnancy.
- (2) the infant presents with heart disease, and/or suspicion of deafness, and/or one or more of the following eye signs: white pupil (cataract); diminished vision; pendular movement of the eyes (nystagmus); squint; smaller eye ball (microphthalmos); larger eye ball (congenital glaucoma).

Health workers should refer all suspected CRS cases to a qualified physician.

#### *Clinically-confirmed CRS case*

A clinically-confirmed case is one in which a qualified physician detects two of the complications in section (a) OR one from group (a) and one from group (b):

- (a) Cataract(s) and/or congenital glaucoma; congenital heart disease; loss of hearing; pigmentary retinopathy.
- (b) Purpura; splenomegaly; microcephaly; mental retardation; meningoencephalitis; radiolucent bone disease; jaundice with onset within 24 hours after birth.

#### *Laboratory-confirmed CRS case*

A laboratory-confirmed CRS case is an infant with a positive blood test for rubella IgM who has clinically-confirmed CRS.

#### *Congenital rubella infection (CRI)*

An infant with a positive blood test for rubella IgM who does not have clinically-confirmed CRS is classified as having congenital rubella infection (CRI).

## **Annex 5: New vaccine introduction (NVI) capacity indicators (DRAFT)**

There are many vaccines that countries could add to their National Immunization Programme (NIP). To assist countries in deciding whether to introduce a new vaccine, WPRO prepared a booklet [Assessing New Vaccines for National Immunization Programmes. Manila: WHO, 2000].

An important issue is whether the investment for the new vaccine would be better spent on other improvements to the existing programme. These draft indicators can be used to assess capacity to introduce new vaccines. In this way, specific programme improvements can be made ahead of the introduction, to ensure that the new vaccine delivers its full potential benefit. It also provides a framework to help decide if investments are better made on first improving the routine programme.

It must be emphasised that the indicators are intended to help thinking and identify areas that may be of higher priority for a country than new vaccine introduction, and not categorical hurdles that countries need to 'pass' in all areas before they should consider new vaccine introduction.

### **1) obtaining full benefits from existing vaccines**

- a) national strategic plan and annual workplans for the NIP, with regular updating of all policies (safe injection, cold chain, immunization schedule)
- b) 95% coverage for all vaccines; no district/lowest admin level with <90% [in general, this is the level to obtain the full benefits from a vaccine. It should not be construed that this level of coverage is an absolute before adding any other new vaccines.]
- c) no gaps in immunity for existing vaccines (eg, for measles in older age groups)
- d) Two dose measles schedule adopted (can have second dose implemented as regular campaign)
- c) 95% coverage for timely (ie, within 24 hours) birth dose of HepB (timeliness may be defined differently for births outside hospital)

### **2) fully functional cold chain**

- a) National cold chain policy and management systems that includes a functional cold chain inventory that is used for vaccine stock management and planned placement, maintenance and replacement of equipment (including costing)
- b) adequate for existing vaccine - at all levels; i.e., able to provide vaccines to the end-user at correct temperature; cold chain failure or freezing infrequent and causes addressed
- c) able to meet any additional demands of the proposed new formulation
- d) spare capacity to be able to meet campaign or unforeseen need

### **3) vaccine supply secure**

- a) 5-year forecasts for all existing vaccines (including any planned/likely campaigns)
- b) appropriate levels of wastage (as defined by national programme)
- c) no history of stock-outs at national or sub-national level
- d) funding for existing vaccine secure over next 5 years
- e) forecasts for new vaccine (including impact on existing vaccines) for new vaccine introduction and for next five years
- f) funding adequate for new vaccine, and able to mobilise additional resources without impact on existing funding

### **4) immunization safety**

- a) all vaccines given with sterile needle and injection and placed in safety box without recapping
- b) adequate disposal and destruction methods
- c) capacity to procure, distribute, and dispose of additional injection materials for new vaccine, if needed
- d) capacity to investigate and respond to adverse events following immunisation (AEFI)

### **5) surveillance**

- a) Timely, reliable, and comprehensive surveillance for existing EPI diseases
- b) Surveillance with baseline data pre-introduction to monitor impact of new vaccine

### **6) establishing relative priority of new vaccine for health sector**

- a) assessment comparing disease burden (may be from local or other data) with costs of new vaccine introduction

## **Applying the NVI indicators for rubella vaccine**

### **1) obtaining full benefits from existing vaccines**

The priority for rubella is at least 80% coverage to prevent potential harm of increased adult susceptibility. Measles elimination has more stringent coverage requirement – at least 95% coverage, and countries should only consider rubella when they are moving towards measles elimination. The introduction of rubella as a wide-age range MR campaign can fill in any holes in measles immunity. As MR does not place any additional logistic challenges to the programme, the requirement to first get the full benefit is more relaxed, as adding MR can be an opportunity to strengthen the rest of the programme.

### **2) fully functional cold chain**

As MR places no additional demands on the cold-chain, there is no need for any special preparations for rubella. However, the introduction of rubella requires a wide age-range campaign and to implement it requires establishing a ‘surge’ capacity for the campaign. Thus, the whole cold chain, its functional status and capacity to meet the additional demands of the campaign will need to be reviewed. This review and any needed upgrades should increase the overall functionality of the cold chain for any future demands.

### **3) vaccine supply secure**

Replacing measles with MR again requires no special calculations, but for many countries simply reducing wastage for all EPI vaccines can cover the additional cost of MR. Ongoing funding for the additional cost of MR needs to be identified.

### **4) immunization safety**

There will be no additional injection safety requirements except during the initial campaign. As this will ideally be a wide age-range campaign it will place considerable demands for the disposal of used injection material, as well as in relation to response to adverse events following immunisation (AEFI) (see Annex on AEFI in campaigns in Measles guidelines)

As with the cold chain, preparing for the immunization safety for the campaign should have beneficial impacts for the ongoing routine programme. There is no additional challenge for immunization safety from using MR as compared with measles, except for vaccine reactions from the rubella component (joint pains).

### **5) surveillance**

Adding rubella to the measles surveillance system should be straightforward and will provide new impetus for both. The issue of CRS surveillance is more complex, but needs to be initiated in at least one national hospital.

### **6) establishing relative priority of new vaccine for health sector**

The additional cost of rubella vaccine is very small compared to the huge impact of a single CRS case. A formal cost benefit can still help decision-making, but will be based on assumptions unless there are good CRS data. As the average lifetime cost (to families as well as the government) of a case of CRS is likely to be over US\$10,000, even if the incidence is at the lower bound of 1 per 10,000 births, rubella immunization is likely to be cost-saving for society.

From the perspective of countries like Australia and New Zealand where most cases of CRS are now born to mothers from other countries, and the lifetime health and disability costs to the Government alone are likely to be of the order of US\$100,000 or more, there are also considerable interests in eliminating rubella in neighbouring countries, especially the Pacific island countries.