



Technical Consultation on Measles, Rubella and Congenital Rubella Syndrome Surveillance

Copenhagen, Denmark, 12-13 April 2005

**Vaccine-preventable Diseases and
Immunization**

ABSTRACT

The *Strategic plan for measles and congenital rubella infection in the WHO European Region*, was developed and implemented in 2002 and includes two objectives for 2010: interruption of indigenous measles transmission and the prevention of congenital rubella infection (CRI; less than one case of congenital rubella syndrome [CRS] per 100 000 live births). It has been recommended that the plan be revised to include the objective of measles and rubella elimination by 2010 along with CRI prevention. The *Surveillance guidelines for measles and congenital rubella infection in the WHO European Region*, published in 2003, were developed to meet the previous measles and rubella control targets but need to be revised to strengthen the CRS surveillance component and accommodate the rubella elimination objective. Thirty-five participants representing 20 Member States and WHO participated in a technical consultation to address outstanding surveillance issues related to these diseases. Eight recommendations were made regarding definitions and surveillance performance indicators for use in the WHO European Region.

Keywords

MEASLES
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Background

The *Strategic plan for measles and congenital rubella infection in the WHO European Region*, was developed and implemented in 2002 and includes two objectives for 2010: interruption of indigenous measles transmission and the prevention of congenital rubella infection (CRI; less than one case of congenital rubella syndrome [CRS] per 100 000 live births). The plan was reviewed at the Regional meeting of Immunization Programme Managers (October 2004) and the European Technical Advisory Group of Experts on Immunization (ETAGE; November 2004); both groups recommended that the plan be revised to include the objective of measles and rubella elimination by 2010 along with CRI prevention. It is currently planned to present a resolution to the WHO European Regional Committee in September 2005, supporting the adoption of these objectives by all Member States and seeking their commitment to meet the 2010 targets. The *Surveillance guidelines for measles and congenital rubella infection in the WHO European Region*, published in 2003, were developed to meet the previous measles and rubella control targets but need to be revised to strengthen the CRS surveillance component and accommodate the rubella elimination objective.

Opening of the meeting

Dr Nedret Emiroglu, Regional Advisor, Vaccine-preventable Diseases and Immunization (VPI) opened the meeting. A list of participants is provided in Annex 1, and the meeting programme in Annex 2.

Scope and purpose

Using the existing Surveillance guidelines for measles and congenital rubella infection in the WHO European Region as a starting point, the scope and purpose of the meeting was to:

- Review, and if necessary revise, existing case definitions and surveillance methodologies;
- Recommend methods for CRI/CRS surveillance in low, medium and high incidence countries;
- Develop clearly defined measles, rubella and CRI/CRS surveillance performance indicators; and
- Recommend methods for the further integration of surveillance for measles and rubella.

Measles and rubella elimination in the WHO European region

Presented by Dr John Spika

Important progress has been made since the implementation of the Strategic plan for measles and congenital rubella infection in the WHO European Region. All 52 Member States now have routine two-dose measles immunization programmes, and at present, 48 (92%) have childhood immunization programmes against rubella; 46 are using measles-mumps-rubella (MMR) vaccine. Supplementary immunization activities (SIAs) in support of the elimination goals have been conducted or are planned in a number of countries; in 2004/2005 these are: Turkey (2003-5) and Tajikistan (2004)

using measles vaccine, Belarus (2005) using rubella vaccine, Kazakhstan (2005) and Azerbaijan (2005) using measles-rubella vaccine, and Italy (2004-5) using measles-mumps-rubella (MMR) vaccine.

The number of Member States reporting an incidence of measles of less than 1 case per million population has increased from 13 (25%) in 2001 to 26 (50%) in 2004; however, only 24% of the total population of the Region resides in these 26 Member States and 29% of the Region's population resides in nine Member States with a measles incidence of ≥ 1 case per 100 000 population. In 2003, nine Member States also reported a rubella incidence of < 1 case per million population, but the majority reported an incidence of ≥ 1 case per 100 000 population; six, representing 25% of the Region's population, do not have national surveillance for rubella. Surveillance for CRS is very weak in almost all Member States. From 2000 to 2003, 35 (35%) of 100 CRS cases were reported by Romania, a country with 2.6% of the Regional population.

In 2004, 47 Member States reported measles cases through the WHO CISID/EUVAC.net system, but WHO has case-based surveillance results for only five (10%). Completeness of reporting was 77%; however, only 30% of reports were received in a timely manner, within 25 days following the previous month. Although no Member States report rubella cases through CISID/EUVAC.net, 44 reported cases through the annual WHO/UNICEF Joint Reporting Form. While 36 countries reported data on CRS in 2003, only four reported one or more cases. In 2004, monthly reports were also received from 37 (79%) of 47 Member States with national measles/rubella laboratories. These laboratories evaluated 13 828 samples for measles IgM and 22 773 for rubella IgM, with 21% and 14% positive respectively; 40% and 44% of samples respectively were received in the laboratory within 4-7 days of collection.

WHO Regional surveillance strengthening plans for 2005 to 2007 include gaining consensus on appropriate laboratory and epidemiological definitions and methods and indicators for measles and rubella surveillance; developing CRI/CRS surveillance methods and indicators; revising the Regional surveillance guidelines; supporting further development of the Regional Laboratory Network; and facilitating laboratory and epidemiology assessments and training.

Thematic session I: Measuring the elimination targets for measles and rubella

Measles elimination indicators

Presented by Dr John Spika

Current definitions and performance indicators for measles surveillance used within the WHO European Region are detailed in the *Surveillance guidelines for measles and congenital rubella infection in the WHO European Region*, published in 2003. At the WHO meeting, *Monitoring the interruption of indigenous measles transmission; a consensus meeting*, held in Cape Town, South Africa in October 2003, it was agreed that indicators for measles elimination were an incidence of < 1 case per 1 million population, not including imported cases, and measles coverage of $\geq 95\%$ with a first dose (MCV1) and $\geq 80\%$ with the second dose (MCV2). Indicators for assessing strength of surveillance identified at the meeting were:

- ≥ 1 suspected measles case detected per 100 000 population per year in at least 80% of districts;

- Serum samples adequate for detecting measles IgM collected from $\geq 80\%$ of suspected cases, excluding cases epidemiologically linked to a laboratory-confirmed case;
 - ≥ 1 specimen for virus genotype analysis collected from every detected chain of transmission.
- Further discussions during 2004 occurred in the WHO Americas Region, leading to the following recommended definitions:
- Measles case: a fever & rash illness or when a health care worker suspects measles;
 - Re-establishment of endemic transmission: chain of virus transmission continues uninterrupted for ≥ 12 months;
 - Imported measles case: cases exposed to infection outside of the country/Region 7 to 21 days prior to rash onset as supported by epidemiological and/or virological evidence;
 - Import-related cases: locally acquired infection occurring as part of a chain of transmission originated by an imported case as supported by epidemiological and/or virological evidence.

The Pan American Health Organization (PAHO) Technical Advisory Group on Vaccine-Preventable Diseases also identified in 2004 the following critical measles surveillance indicators that should be used in the Region:

- The proportion of suspected measles cases with an adequate investigation completed;
- The proportion of suspected cases with an adequate blood sample collected;
- The proportion of transmission chains with a representative sample collected for viral isolation.
-

Recognising these recommendations, WHO/ Geneva requested Dr. Lisa Cairns, Centers for Disease Control and Prevention (CDC), Atlanta, to carry out a reassessment of measles surveillance indicators. Subsequent discussions with WHO and CDC personnel have led to the following draft definitions and surveillance performance indicators:

- Suspected measles case: any person in whom a clinician suspects measles or any person with fever and maculopapular rash, coryza or conjunctivitis;
- Re-establishment of endemic transmission: chain of virus transmission continues uninterrupted for ≥ 6 months;
- Chain of transmission: ≥ 2 laboratory-confirmed cases that are temporally related and linked epidemiologically but separated by time sufficient for an incubation period;
- Reporting rate indicator: ≥ 1 suspected case reported per 100 000 population per year in $\geq 80\%$ of districts, but at the national level, a rate of > 2 per 100 000 should be considered a minimum;
- Sample collection indicator: samples adequate for measles IgM from $\geq 80\%$ of suspected cases;
- Virus isolation indicator: sufficient samples for virus detection from $\geq 90\%$ of identified transmission chains;
- Adequacy of investigation indicator: $\geq 80\%$ of all suspect cases with an adequate investigation within 48 hours of notification.

Meeting participants were asked to consider these definitions and reach consensus on:

- The definitions for measles surveillance indicators;

- Surveillance performance indicators that are useful and feasible for implementation throughout the Region, yet sufficiently robust to permit the monitoring of measles elimination in the Region, and also be applicable to rubella elimination.

Rubella elimination indicators – integration with measles

Presented by Dr Mary Ramsay

Countries using MMR vaccine for measles elimination have substantial reasons for integrating measles and rubella surveillance. The vaccine programme is targeted at the same individuals, and because of the lower effective reproductive value for rubella, it is likely that rubella will be eliminated before measles in these countries. Both infections present with similar rash and fever symptoms, they require similar clinical and epidemiological investigation, and they require similar confirmatory methods. Integration would probably be made even easier if a non-invasive sampling method, such as collection of oral fluids rather than serum, could be implemented.

It may not be advantageous to integrate measles and rubella surveillance in countries where rubella elimination is not a target or where combined measles/rubella vaccine is not in use. Some countries in the region have only recently introduced rubella vaccine, while in others, measles vaccine has been used for decades, thus making it likely that the epidemiology of measles and rubella are very different. Experience suggests that without an established history of rubella surveillance, rubella cases are less likely to present for medical attention, and less likely to be admitted to hospital or have appropriate diagnostic samples collected. In addition, in countries where a clinician's main concern with regard to rubella is infection in pregnant women, and this may have a negative impact on willingness to comply with reporting and investigation of infection in infants and young children.

The real incidence of non-measles rash-and-fever illness is not known, and may vary both between and within countries, based on the underlying epidemiology of non-measles infections. The incidence may also vary by age group, with the age distribution of non-measles infections not corresponding to the group at highest risk of measles infection. Studies conducted in Europe have shown that parvovirus B19, group A streptococci, enterovirus, adenovirus and group C streptococci are the most common pathogens associated with rash-and-fever illness, accounting for between one-third and one-half of all cases. In children less than two years of age, however, human herpesvirus type 6, which appears uncommon in older children, can be identified in 10%-15% of cases. Current experience in the UK is that most suspected measles and rubella cases occur in children 1 to 4 years of age, but < 5% are confirmed as measles and < 1 % as rubella. More data are required on the expected level of rubella infection in different epidemiological conditions before appropriate surveillance indicators can be developed.

Measles and rubella infection have similar, but not identical presentations. Rubella may present with lymphadenopathy or arthralgia, symptoms not commonly associated with measles. Potential differential diagnoses for the two diseases may be different, based on their different epidemiology. Rather than integrate their surveillance, reliance on clinicians to differentiate between the two infections may reduce the requirement for simultaneous investigation and testing for both diseases. More experience is needed before it can be predicted whether use of a clinical case definition is helpful in distinguishing between infections, or if use of a rash-and-fever definition presents the most efficient use of resources.

Discussion

A common theme of the discussion was the failure to confirm a very large proportion of suspected measles or rubella cases in all countries with surveillance systems in place. If measles/rubella incidence is very low, it may be more effective to investigate rash-and-fever for other pathogens, e.g. group A streptococci or parvovirus B19, before testing for measles or rubella. It remains unclear if, in conditions of very low incidence of measles and rubella, it is necessary to maintain surveillance sensitive enough to detect individual cases, or whether it is acceptable only to detect clusters of cases. It is clear that implementation of rash-and-fever surveillance is not standardised even within some countries. An analysis of currently available data on how rash-and-fever surveillance is being applied may help determine some of the key surveillance indicators.

It was highlighted that there were considerable difficulties in predicting target detection rates for measles/rubella surveillance. Questions were raised over the ability to monitor the true incidence of rubella infection, when many cases are asymptomatic. Monitoring rubella susceptibility in women of childbearing age (WCBA) may be the most appropriate way of providing supplementary information on the status of rubella control in the Region.

Introduction of case-based reporting for measles and rubella – guidelines

Presented by Dr Pawel Stefanoff

In Poland, mandatory reporting of aggregate data on measles cases began in 1919; mandatory vaccination of children aged 13 to 15 months started in 1975 and a second measles dose was introduced in 1991. In 1999, individual reporting on suspected and confirmed measles cases, using WHO case definitions, was initiated; however, within the country, the main source for data on measles cases remains the bi-weekly, aggregated data reporting system. The decrease in measles incidence since 1999 has been accompanied by a decrease in the number of suspected cases reported and investigated; this rate in 2004 was 0.12 per 100 000 population. National case-based reporting using EU and WHO surveillance case definitions is being introduced in 2005 through the introduction of new surveillance forms, but issues to be resolved include how to monitor and ensure surveillance quality and how to incorporate the concept of suspected measles cases given the differences between the WHO and EU measles case definitions.

Mandatory aggregate data reporting of rubella cases began in Poland in 1966. Vaccination of 13-year old girls with monovalent rubella vaccine started in 1989, and vaccination of 13- to 15-month old children with MMR began in 2003. A register of CRS cases was started in 1997, with un-validated data collected through a passive surveillance system. The incidence of rubella cases has dropped markedly in the past 4 years, and consideration is now being given to introducing case-based surveillance, using a computerized data system and starting January 2007. It is likely that even with the ability to more easily collect data and report on cases, resources will not be available to perform laboratory testing on all rash-and-fever cases even when better rubella control is achieved, so more specific case definitions for suspected measles and rubella cases will be required for the system to be affordable.

EUVAC.net – approaches to meet reporting requirements for elimination targets

Presented by Dr Steffen Glismann

EUVAC.net was established in 1999 as a surveillance network for vaccine preventable diseases within the European Community. The network initially included the 15 EU members plus the 3 EFTA countries and Malta. Since its initiation, the network has documented a progressive

improvement in measles surveillance among member countries, with a shift towards case-based reporting and an increased proportion of laboratory-confirmed cases. There remain a number of quality control issues in many countries, and there is wide divergence in surveillance performance, particularly with regard to timeliness of reporting. Available data suggest that approximately 70% of confirmed measles cases in the network countries are unvaccinated, and that almost 50% of imported measles cases originate in other European countries. The nature and quality of rubella surveillance systems throughout the reporting countries also vary considerably.

In general, surveillance systems in most reporting countries need to be improved, with better linking of laboratory and clinical data and improved timeliness of reporting. In several countries, laboratory diagnostic procedures need to be standardised and improved. Many countries also need to develop more effective national plans for measles and rubella control.

In 2005, EUVAC.net was expanded to include all 25 EU member states, the 3 EFTA countries and Romania, Bulgaria and Turkey. The terms of reference have been extended to include advocacy for and support of measles elimination and congenital rubella prevention goals.

Laboratory methods for confirming measles and rubella infections

Presented by Dr Liliane Grangeot-Keros

Primary measles and rubella virus infections are most commonly demonstrated through the detection of virus-specific IgM, demonstration of seroconversion or a significant rise in IgG titre. The sensitivity for IgM detection is highly dependent on the time of sample collection in relation to the progression of the infection. Measles-specific IgM usually appears 2 to 3 days after the appearance of rash. In studies on IgM detection in confirmed measles cases, approximately 77% of samples collected within 72 hours of rash onset were found to be positive; 100% were when collected between 4 and 11 days; 94% at 4 weeks; and 63% at 5 weeks. Rubella-specific IgM appears around the time of rash onset, and in studies on rubella-confirmed cases, approximately 78% of samples collected in the first 48 hours of rash were IgM positive; 100% of samples collected from 3 days to 8 weeks were positive; and 35% of samples collected between 8 and 18 weeks were positive.

Commercial assays for measles and rubella IgM detection are generally $\geq 95\%$ specific. The most common causes for false positive reactions include the presence of rheumatoid factor (tends not to be a problem in IgM capture assays) and non-specific, cross-reacting IgM. After measles infection or vaccination, specific IgM levels usually fall to below the level of detection within 2 to 3 months, but rubella-specific IgM can often be detected for many months and sometimes years, especially after vaccination. This makes interpretation of the detection of rubella-specific IgM in the absence of clear clinical symptoms very difficult, particularly in low incidence countries, and it is in these situations where use of a confirmatory assay, such as RT-PCR or IgG avidity, becomes more important.

Detection of seroconversion or a significant rise in specific IgG titre can be used to demonstrate recent primary infection but may also represent reinfection or non-specific stimulation of the immune system. In general, IgG antibodies formed in a secondary response are often of higher avidity (antigen binding strength) than those of the primary response. Using a suitable antibody avidity assay, IgG antibodies produced in response to a primary infection can be distinguished from those produced in response to reinfection. IgG avidity assays are, however, not easy to run, and at present there are few if any commercial assays available.

In the case of rubella infection, distinguishing acute primary infections from past infection or vaccination on the basis of IgM serology can be difficult because of the longevity of the IgM response. IgM titre rises sharply with the appearance of rash but tends to decline rapidly over the first 2 to 3 months, the titre halving approximately every 3 weeks. The demonstration of no significant change in IgM titre in two sequential serum samples will exclude primary infection.

Oral fluid samples represent a good alternative to serum in many circumstances. Sensitivity and specificity of specific antibody detection from oral fluid samples tends to be slightly lower than from serum samples, but this may only present a problem in very low incidence areas. Oral fluid samples can be used to test for IgM and IgG, and can also be used in IgG avidity assays. Studies have shown that oral fluid can be used successfully for measles RT-PCR, but they produce many false negatives by rubella RT-PCR. This may reflect the low viral load of rubella in oral fluids. For successful RT-PCR, samples must be stored and transported at -70°C , which can be a problem in some countries.

Collection of blood spots on filter paper also provides a useful alternative sample collection method in some circumstances. There is generally very good concordance between filter paper samples and serum samples for both IgM and IgG detection. The advantages of filter paper blood collection are that finger- or heel-stick blood samples are easier to collect and more acceptable for young children, and samples can be stored and transported dried at room temperature for 15 days and at $+4^{\circ}\text{C}$ for many months prior to processing.

Prenatal laboratory confirmation of CRS can be achieved through rubella IgM analysis of foetal blood if a sample is collected ≥ 6 weeks after rash onset and ≥ 22 weeks gestation. Amniotic fluid collected ≥ 6 weeks after rash onset or at 18 to 22 weeks gestation can also be used to detect virus genome by RT-PCR. Postnatal confirmation can be provided by detection of specific IgM in serum and oral fluids collected within 3 months of birth. From 3 months after birth, there is a steady decline in IgM titre, which usually completely disappears by 18 months. Serum samples can be used to measure low avidity IgG.

Providing an accurate cost assessment of laboratory confirmation methods is very difficult because of the many different circumstances under which samples are collected and assays performed. In France, the cost of reagents to perform an IgM assay have been estimated at €3-5 per test; €1.5-3 per test for IgG; and €30-50 per test for RT-PCR. These estimates do not include labour or the use of immunoassay systems. There are also costs for sample collection and transport (for both serum and oral fluids), probably amounting to €4-5 per sample.

Measuring rubella vaccination coverage in older adolescents and WCBA

Presented by Dr Alenka Kraigher

Although many countries have now adopted rubella vaccine into their routine childhood immunization systems, very little data are available on vaccine coverage in older adolescents and WCBA. In general, vaccine coverage can be monitored directly through immunization registries or indirectly through surveys and vaccine distribution and administration records. Several countries conduct routine screening of antenatal clinic attendees and some have conducted serosurveys to determine the proportion of WBCA susceptible to rubella infection. Immunization registries exist in several countries, usually in the form of central population registers or pre-school or school-age registers, which include data on vaccination history. Other countries carry out annual surveys of households to determine immunization levels for key age groups. Information is often collected remotely, i.e. by telephone, and usually relies on parents or guardians recalling immunizations

received over the previous 12 months. Another common indirect method includes use of the WHO EPI 30 Cluster Survey, the principal advantage of which is the potential for aggregation of data from smaller geographical areas, although this method is insensitive to pockets of unvaccinated individuals.

Vaccine distribution and return records can be used to rapidly generate estimates of vaccines administered. This is particularly useful when all or the majority of vaccines are delivered through government immunization services and accurate data are available on the size of at-risk populations. If the number of doses of vaccine administered and the number of persons in the target age group (e.g. number of surviving infants, number of school-age children, number of WCBA) are known, an administrative estimate of vaccine coverage in the group can be calculated. If the same enumeration methods and same target groups are used, aggregation of data is possible.

Improvements in monitoring rubella vaccination coverage in adolescents and WCBA are clearly required in many countries. A possible approach may be to adopt the model used to monitor tetanus vaccine coverage and develop the concept of a lifetime immunization record for all women.

Discussion

Discussion focussed mainly on aspects of laboratory confirmation of measles and rubella infection. It was stressed that collection of serum samples remained the recommended method in the Region. Collection of oral fluid samples posed problems in some countries as they currently lack the infrastructure to collect and transport these samples. WHO supports purchase of measles and rubella IgM detection kits for national laboratories in some countries. These kits currently cost approximately €160 per kit for measles and €320 per kit for rubella. A process is in place to evaluate locally produced kits, which will be cheaper than currently available commercial kits. In general, many national laboratories are moving towards parallel testing for measles and rubella. Although this it is expensive, it is may be the most appropriate strategy when the incidence of measles and rubella is low.

The problem of the longevity of rubella-specific IgM causing misdiagnosis was discussed. With up to a 10% false positive rate, it was questioned if the assay should be used in low prevalence areas. In pregnant women, a confirmatory assay must always be used, and confirmation of infection must be strictly linked with the clinical presentation. In symptomatic pregnant women, the false positivity rate will be lower than 10%. IgG avidity or IgM kinetics can be used as confirmatory assays, but both are difficult to set up in a laboratory. It was noted that the PAHO Ad-Hoc Panel of Experts on Measles and Rubella also stated that “In some areas of some countries, pregnant women are likely to be tested for both IgG and IgM rubella antibodies. Unless there is a suspicion of rubella in the pregnant women or that she has been recently exposed to rubella, rubella IgM testing should not be done because of the low but real possibility of false positivity or true detection of persistently positive IgM circulating antibodies.”

Thematic session II: Measuring targets for congenital rubella infections

CRS surveillance – a global experience

Presented by Dr Susan Robertson

Globally, routine surveillance for CRS remains very weak. Carefully conducted population-based surveillance for CRS carried out in countries prior to rubella vaccine introduction suggests that under conditions of endemic rubella transmission the expected rate of CRS is 0.1 cases per 1 000 live births, and under epidemic rubella transmission it is between 0.5 to 3.5 cases per 1 000 live births. Given these rates, the expected global annual total of CRS cases is >100 000; but the annual reported totals from 1999 to 2003 ranged from 39 to 181 cases. CRS surveillance is rapidly improving in the WHO Americas Region. Reasons for this improvement include the adoption of a rubella elimination goal; weekly reporting of suspected and confirmed CRS cases, with publication of the results; and a series of training workshops on CRS surveillance. Strong social mobilization packages have been developed as an integral part of the elimination strategy.

CRS surveillance indicators are being field tested at pilot sites in Peru, and the programme is gaining an important understanding on where and how to identify CRS cases, and the importance of involving local obstetricians, paediatricians, midwives and nurses. Although CRS presents with a constellation of symptoms, some appear to be more important clinical indicators than others. Eye signs, for example, may occur in more than 50% of confirmed cases, so it is important to engage ophthalmologists in the surveillance system.

There are a number of alternative methods for identifying CRS cases, including retrospective record reviews, which can include an analysis of private doctors' records; birth defects surveillance, although many reports may lack laboratory confirmation; laboratory registers of results on autopsy specimens from infant deaths and stillbirths; CRS registries monitoring long-term follow-up for late emerging manifestations of CRS; and economic studies on treatment costs and disabilities.

Specialty physician-based reporting systems for CRS

Presented by Dr Pat Tookey

CRS is now a very rare condition in England, Scotland and Wales. During the 1990s, an average of 4 CRS cases and 8 rubella-associated terminations were reported each year; however, from 2000-2004, only 9 infants with CRS were reported; 3 had maternal infection acquired in the UK. Surveillance systems for rubella in the UK include surveillance for acute infections, rubella susceptibility monitoring; and the number of rubella-associated terminations and diagnosed rubella infection in pregnancy are also monitored. Infants with congenital rubella are reported to the National Congenital Rubella Surveillance Programme, which has been running since 1971, initially as a passive reporting system but as an active reporting system since 1990.

Active surveillance is carried out through the British Paediatric Surveillance Unit (BPSU), which has a reporting network of >2 000 consultant paediatricians. They submit standardized monthly reports on whether or not they have seen any one of approximately 10 rare conditions under surveillance. Positive reports of congenital rubella are followed up with the reporting paediatrician for further details, including maternal demographic information; immunization history, details of the location, timing and type of maternal infection; symptoms and test results. The BPSU is a member of the

International Network of Paediatric Surveillance Units, which currently includes units in more than a dozen countries.

Factors which have contributed to the success of this active reporting system include the perception that the condition being reported is rare, that they are likely to come to the attention of reporting physicians, and that reporting a case is not associated with excessive paperwork. Changes in presenting characteristics over time (e.g., reduction in proportion of children presenting with hearing loss as their only defect) suggests that reporting may not be complete. It is possible to assess completeness of reporting by comparison with other data sources (e.g., laboratory reports of pregnant women), use of capture-recapture techniques, and by exploring changes in presenting characteristics or other relevant factors over time.

Use of routine surveillance reporting systems for CRS in Romania

Presented by Dr Adriana Pistol

A case-based CRS surveillance system was introduced in Romania in January 2000. Initially a passive reporting system, it was made active after the 2002-2003 rubella epidemic. Very clear case definitions for suspected and confirmed CRS are used. Reports are collected on a weekly basis from key reporting sites, including maternity and neonatology wards and paediatric hospitals. Data collected include patient ID, gender, ethnicity, date of birth, date of notification, date of sample collection, list of clinical signs (ocular, hearing, and cardiac), date of death, and mother's age. Between 2000 and 2004, 612 suspect CRS cases were reported; 45 (7.5%) were confirmed by IgM detection.

Establishing the system has required political approval and support; commitment from medical professionals; training; supervision; laboratory services and significant human and financial resources. The advantages of the system include the provision of CRS incidence estimates, which can be used to develop appropriate control strategies; the data can be presented to decision makers to influence resource allocation; and the potential to evaluate possible changes to the vaccination strategy via mathematical modelling. Disadvantages are that it is a costly system to run; there are recurrent communications problems with the wide range of professionals involved in reporting and investigation; and physicians require a lot of encouragement to report.

Implementation of CRS surveillance in Kyrgyzstan

Presented by Dr Ludmila Shteinke

The CRS surveillance system in Kyrgyzstan was initiated in 2002. CRS is reported through the same mechanism as suspected measles and rubella cases; and there is also an active search for suspected CRS cases in designated specialized health centres. These centres include major paediatric hospitals and surgeries, the National Cardiologic Centre, the Centre for Human Reproduction, perinatal clinics and oblast hospitals. From 2002 to 2004, 186 suspected CRS cases were reported and investigated; one was laboratory confirmed. The current system has problems with sample collection and transport, with delays and lost samples reducing the proportion of adequately investigated cases.

Detecting rubella infection in pregnant women

Presented by Dr Isabelle Parent du Chatelet

Rubella is not notifiable in France, but there has been a laboratory-based surveillance system for rubella infection in pregnancy in place since 1976. In addition, since 1992 there has been a system for prenatal and antenatal rubella IgG screening in the first 12 weeks of pregnancy to detect susceptible WCBA and identify pregnant women for whom post-delivery rubella vaccination is advised. The surveillance system is based on a network of 291 laboratories; all perform IgM serological tests and some perform PCR detection for rubella, providing case-based notification of rubella IgM positive pregnant women, rubella positive foetal blood or amniotic fluid, and detection of rubella markers following pregnancy termination or birth. Questionnaires are sent to the clinicians of cases with a positive laboratory test, requesting demographic and clinical data on the pregnant women, complementary laboratory results, pregnancy outcomes and clinical data and laboratory results on newborn babies or fetuses.

From 2001 to 2003, 75 rubella infections during pregnancy were detected in France. Thirty-three (44%) were diagnosed on serological evidence alone; one was a suspected infectious contact; 35 (47%) had clinical signs of rubella; 4 (5%) were suspected infectious contacts with clinical signs; and 2 cases were not detected during pregnancy but CRS was confirmed at birth. Despite the successes of the system, the proportion of rubella infections that are not detected during pregnancy or at birth, and the proportion of detected rubella infections not reported are both unknown. In addition, investigation of reported cases is time consuming and the majority of rubella-positives reported by the laboratories end up not being true cases.

As the incidence of rubella declines, more thorough detection and reporting will be required. Additional surveillance performance indicators, including the proportion of cases with complete information and the proportion of IgM positive pregnant women excluded after investigation, could be added to strengthen the system. Other sources of data could also be sought, such as laboratories accredited for prenatal diagnosis and maternal and child health centres for rubella-associated induced pregnancy terminations. To gather more information on rubella susceptibility, a seroprevalence survey is being planned for 2006.

Policy considerations for the monitoring and testing of pregnant women for rubella

Presented by Dr Tove Rønne

There are two reasons for testing pregnant women for rubella infection: case detection and immunization programme monitoring. Case detection is conducted in order to provide prevention or treatment, and is carried out either on a sporadic basis or as part of a systematic screening programme. The outcome of such testing is relatively straightforward; the test is either positive or negative, and appropriate actions can be taken. The outcome of testing for immunization programme monitoring purposes is more complex, as the object is to make an evaluation of the programme; acceptable programme targets and performance indicators must be set, against which the test results can be compared.

Within the Region, there are essentially three scenarios with regard to rubella testing:

- In countries without rubella vaccination programme: case detection with or without systematic screening is carried out;

- In countries with a selective rubella vaccination programme: case detection/screening and programme monitoring are carried out; and
- In countries with a comprehensive rubella vaccination programme: programme monitoring is the norm, and case detection is rare.

The three scenarios can be compared according to the information obtained, ethical considerations, logistics and feasibility, and associated economic costs. Each of these factors assumes a different weighting in each of the three scenarios, with routine programme monitoring emerging the least problematic. Programme monitoring is only effective, however, in countries with comprehensive rubella vaccination programmes. When the costs of introducing a comprehensive rubella vaccination programme are considered, the potential savings in not testing for cases and in not having to respond to the consequences of positive test results should be considered.

Discussion

Some countries use routine screening of pregnant women to identify susceptibles but do not specifically test for infection; the effectiveness of this approach is rarely monitored. Attempts have been made to use these data to identify high-risk groups, but they are difficult to collect, and are often incomplete. Insufficient information often prevents a thorough analysis and the ability to make realistic predictions. The development of a system for collection of anonymized data, with essential epidemiological data linked, is needed before greater use can be made of the information being generated.

Conclusions and recommendations

I. Measuring the elimination targets for measles and rubella

The various surveillance case definitions were reviewed as well as performance indicators. The measles elimination indicator discussed at the WHO meeting Monitoring the interruption of indigenous measles transmission, Cape Town, of an incidence of <1 case per million population per year, excluding cases confirmed as imported, was generally accepted. The vaccine coverage indicators of at least 95% for the first measles vaccine dose and at least 80% for the second dose were not felt to be directly applicable to the WHO European Region given that our strategy is to strengthen routine immunization programmes, seeking at least 95% coverage for both measles vaccine doses, as well as other vaccines administered through childhood immunization programmes. It was also generally agreed that syndromic surveillance for rash-and-fever illness could not be implemented in many countries in the Region; therefore, surveillance should be for clinically suspected measles and clinically suspected rubella. Reporting of suspected measles cases was felt to be feasible in most countries present in the working group. The existing discrepancy between the measles case definition used by WHO and that used by the EU was not discussed as the European Centres for Disease Control has already indicated its intent to review communicable disease surveillance activities and issues in the coming months.

The discussion of a performance indicator for laboratory confirmation of measles and rubella brought out some of the diversity that exists within the WHO European Region regarding methods and procedures used for confirmation. While rubella-specific IgM can be detected very shortly after the appearance of rash, measles-specific IgM can be reliably detected after 2-3 days; this IgM response can then be detected in samples collected several weeks after rash onset. Although it was difficult to set an upper limit on when useful samples can be collected, for programmatic reasons, 28 days after

rash onset was agreed as reasonable. Samples for measles and rubella IgM detection would therefore be considered timely if collected between 3 and 28 days after rash onset. Measles and rubella virus RNA can often be detected using RT-PCR in samples collected at around the time of rash onset, but levels of detectable RNA decline within a few days. While time limits on collection of samples for RT-PCR analysis could be set at 0 to 7 days or 0 to 10 days, introducing different time limits for the collection of samples for different testing methods could cause confusion; therefore, more information is required before recommendations can be made on the collection of samples specifically for RT-PCR.

Recommendations:

1. The following definitions should be used in the WHO European Region:

- **Imported case:** a measles-confirmed case that was outside the country/region during the period 7–18 days before rash onset, or a rubella-confirmed case that was outside the country/region 14–21 days before rash onset; and the virus genotype, if available, is consistent with the likely exposure.
- **Measles import-related case:** locally acquired infections forming a chain of transmission originating from an imported case. Import-related cases will be included in national incidence calculations.
- **Chain of transmission:** two measles cases linked epidemiologically and/or with the same virus genotype with date of onset separated by up to 18 days.

2. Countries should implement case-based reporting to WHO for measles and/or rubella when:

- The disease incidence is $\leq 1/100\ 000$, and
- A computerized information system is in place at the national level for case-based reporting.

In the event a large outbreak occurs after implementation of case-based reporting, case-based data can be reported for the first 5–10 cases and the remaining cases (epi-linked) reported through the outbreak reporting form.

3. Countries are expected to report suspected cases when they have implemented national case-based reporting.

4. Cases of sub acute sclerosing panencephalitis should only be reported to WHO on a yearly basis. They should be excluded from measles incidence calculations.

5. Recommended measles vaccine coverage performance indicators and targets

Measles vaccine dose coverage	Definition	Targets
MCV*1†	In a given geographical area for a given calendar year, number of children who receive MCV1 between ages 12 to 23 months divided by the total number of children between ages 12 to 23 months - before end of second year.	> 95% nationally & 90% at first administrative level (equivalent to oblast)
MCV2	In a given geographical area for a given calendar year, number of children who receive MCV2 as per the national vaccine schedule divided by the total number of children in that birth year.	> 95% nationally & 90% at first administrative level (equivalent to oblast)

* MCV = measles containing vaccine

† Emphasis is placed on the importance of the first dose.

6. Recommended performance indicators and targets for national surveillance in countries approaching or achieving elimination status:

Performance Indicator	Definition	Target
Measles incidence	Number of confirmed measles (clinically, epidemiologically, laboratory) per total population, excluding imported cases and vaccine-related cases*.	<1 confirmed case per 1 000 000 population
Rubella incidence	Number of confirmed rubella (clinically, epidemiologically, laboratory) per total population, excluding imported cases and vaccine-related cases*.	<1 confirmed case per 1 000 000 population
Suspected case incidence	Clinically suspected measles and/or clinically suspected rubella†	Number of suspected clinical cases >2 per 100 000 population nationally AND >1 per 100 000 in 80% of the first administrative levels; or Number of specimens tested in laboratory for measles and/or rubella >1.6 per 100 000 population nationally AND >0.8 per 100 000 in 80% of the first administrative levels
Laboratory confirmation	Number of suspected measles or rubella cases with at least one specimen taken within 28 days of onset divided by number of suspected measles or rubella cases not epidemiologically linked to a laboratory-confirmed case.	>80% suspected cases have specimens assessed by the laboratory
Number of cases pending classification	Number of suspected measles or rubella cases without final classification 60 days after rash onset.	0
Source of infection identified	Number of measles/rubella cases with source identified (imported, import-related or indigenous) divided by number of epidemiologically or laboratory confirmed measles/rubella cases	>80% confirmed cases with source of infection identified
Reporting timeliness	Number of monthly reports received by EURO before the 25th of the following month divided by number of report expected	>80% of monthly reports received
Reporting completeness	Number of monthly reports received by EURO divided by number of report expected	>80% monthly reports received
% districts reporting	Number of districts reporting divided by total number of districts cumulative from 1st January	>80% districts reporting
Adequacy of investigation‡	Number of suspect cases having had an adequate epidemiological investigation within 48 hours of notification divided by the total number of suspect cases.	>80%
Outbreak investigation of chains of transmission	Number of <u>suspected</u> measles or rubella <u>outbreaks</u> with all or at least 5 cases with specimens taken divided by number of outbreaks	>90% chains investigated
Outbreak investigation of virus genotype	Number of <u>confirmed</u> measles or rubella <u>outbreaks</u> with genotype information divided by the number of outbreaks	> 90 % outbreaks with information

* Using this case definition, possible and probable EU cases correspond to clinical cases for WHO; a confirmed EU case corresponds to a laboratory or an epidemiologically-linked case for WHO. If a country is reporting aggregate data, all cases are considered clinically, epidemiologically or laboratory confirmed, and the incidence is cumulative from the 1st of January (based on 12 months).

† Suspected cases include clinical, epidemiologically-linked and laboratory-confirmed cases, plus cases initially suspected as measles and then discarded, plus cases that have not yet received a final classification.

‡ Optional indicator

II. Measuring targets for congenital rubella infections

Improving surveillance for congenital rubella infections was a clear priority; however, the diversity of countries in the WHO European Region requires that health systems and infrastructure need to be considered in making recommendations. The table identifies different sources of data that can be used to assess the CRS/CRI burden prior to implementation of routine surveillance and/or to evaluate existing surveillance systems. While the experience in the WHO Americas Region supports the concept that regular reporting will encourage further strengthening of surveillance, it was felt that at this time reporting to WHO should not occur on more than a quarterly basis.

Table. Sources of information on CRS/CRI useful to assess burden of disease

Information source	Level of rubella control	Laboratory requirements	Logistical support (forms, training, supervision)	Cost	Ethical or Legal issues	Notes
Retrospective record reviews	Pre-vaccine introduction, and evaluation of the system in subsequent phases	None		+	Access to data could be limited by confidentiality issues	Important to assess the burden prior to routine surveillance implementation. When the surveillance system is in place, it can be used as an alternative source to evaluate the system.
Birth defects registers	Pre-vaccine introduction, and evaluation of the system in subsequent phases	None		+	Access to data could be limited by confidentiality issues	Where in place, useful tool to assess the burden and evaluate the system
Rare disease registers	Pre-vaccine introduction, and evaluation of the system in subsequent phases	None		+	Access to data could be limited by confidentiality issues	Where in place, useful tool to assess the burden and evaluate the system
Cause of death by ICD codes	Pre-vaccine introduction, and evaluation of the system in subsequent phase	None		+	Access to data could be limited by confidentiality issues	Important to assess the burden prior to routine surveillance implementation. When the surveillance system is in place, it can be used as an alternative source to evaluate the system.
Lab tests on autopsy specimens	All stages	IgM on cardiac puncture	Limited by national practices on autopsy performing	+	No	Important to confirm cases; in countries where autopsies in children are routinely performed, can be used as a source of surveillance data.
Serosurveys of women of childbearing age	All stages	IgG	Logistical constraints to collect and analyse blood samples In order to compare results from different countries, standardization of lab methods is advised.	++	No	Population based serosurveys (<1000 individuals), or convenience samples from antenatal serum leftovers (< 500 individuals) to be conducted tot more every > 5 yrs. To be remarked that serosurveys are not intended as routine screening of WCBA.

Recommendations

- The following surveillance methods for CRS/CRI are ordered by the priority recommended for their implementation.

Surveillance Method	Level of rubella control	Laboratory requirements	Logistical support (forms, training, supervision)	Cost	Ethical or Legal issues	Notes
a. CRS surveillance	Control (if rubella outbreak ongoing, move to active CRS surveillance)	IgM	Training of different health professional categories needed. Crucial to involve gynaecologists/obstetricians/midwives	+	No	Affordable by all countries in the Region
b. Surveillance of infections in pregnancy	High level of control	IgM and confirmation tests (IgG and/or IgM kinetics) in women with suspected symptoms or exposure	Training and supervision for lab tests for infection confirmation	++	Yes	
c. Pregnancy termination registers	High level of control	None		+	Yes	Privacy issues can limit the access to these data. Can be used to evaluate surveillance of infection in pregnancy
d. CRI surveillance	Approaching elimination	IgM	Training of different health professional categories needed. Crucial to involve gynaecologists/obstetricians/midwives	++	No	This means including in the surveillance system asymptomatic cases with lab confirmation; it's therefore important to retrieve info on maternal history.

- Recommended performance indicators for national surveillance

Indicator	Targets	Comments
Annual incidence of suspected CRS per 100 000 live births	-	Surveillance limited to children 0-11 months
Proportion suspected CRS cases notified within 48 hours after detection	≥80%	
Proportion suspected CRS cases investigated within 7 days after detection	≥80%	
Proportion of suspected CRS cases with blood specimen (1 ml) collected at the age 0-5 months	≥80%	
Proportion of suspected CRS cases with blood specimen sent within 7 days after collection	≥80%	Number of days - to be discussed
Proportion of suspected CRS cases with test result notified within 14 days after receipt	≥80%	
Annual incidence of laboratory/ clinically confirmed CRS per 100 000 live births	-	Figure should differentiate imported cases (when approaching elimination)
Completeness of regional reports	≥80%	

Annex 1

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Annex 2

Meeting Programme

DAY 1, Tuesday, 12 April

- 08:30-09:00 Registration
- 09:00 Welcome remarks & meeting objectives
Dr Nedret Emiroglu
- 09:10 Measles and rubella elimination in the WHO European region
Dr John Spika
- 09:25 Thematic session #1: Measuring the elimination targets for measles and rubella
Chair: Dr Marta Ciofi degli Atti
- 09:30 Measles elimination indicators
Dr John Spika
- 09:45 Rubella elimination indicators – integration with measles
Dr Mary Ramsay
- 10:00 Discussion
- 10:30 Coffee- Break
- 11:00 Introduction of case-based reporting for measles and rubella – guidelines
Dr Pawel Stefanoff
- 11:15 EUVAC.net – approaches to meet reporting requirements for elimination targets
Dr Steffen Glismann
- 11:30 Laboratory methods for confirming measles and rubella infections
Dr Liliane Grangeot-Keros
- 12:00 Measuring rubella vaccination coverage in older adolescents and WCBA
Dr Alenka Kraigher
- 12:15 Discussion
- 13:00 Lunch
- 14:00 Thematic session #2: Measuring targets for congenital rubella infections
Chair: Dr. Mary Ramsey
- 14:05 CRS surveillance – a global experience
Dr Susan Robertson

- 14:20 Specialty physician-based reporting systems for CRS
Dr Pat Tookey
- 14:35 Use of routine surveillance reporting systems for CRS in Romania
Dr Adriana Pistol
- 14:50 Implementation of CRS surveillance in Kyrgyzstan
Dr Ludmila Shteinke
- 15:05 Round table discussion of approaches
- 15:30 Break
- 16:00 Detecting rubella infection in pregnant women
Dr Isabelle Parent du Chatelet
- 16:15 Policy considerations for the monitoring and testing of pregnant women for rubella
Dr Tove Rønne
- 16:30 Discussion
- 17:00 Breakout group assignments and process
- 17:10 Breakout group discussions:
Breakout groups:
Measuring the elimination targets for measles and rubella
Chair, Dr John Spika, Rapporteur, Dr Alya Dabbagh
- Measuring targets for congenital rubella infections
Chair, Dr Susan Robertson; Rapporteur, Dr Marta Ciofi degli Atti & Dr Pawel Stefanoff

DAY 2, Wednesday, 13 April

- 08:30 Breakout group deliberations
- 11:30 Review of recommendations from breakout groups
Chair: Dr. Nedret Emiroglu
- 12:30 Lunch
- 13:30 Breakout group deliberations
- 15:00 Final recommendations from breakout groups
- 16:00 Conclusions and closing remarks
- 16:30 Meeting closure