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## Proceedings of a Meeting of the Expert Advisory Group on Rubella in Canada



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**Proceedings of a Meeting  
of the Expert Advisory Group on  
Rubella in Canada**

**Winnipeg, Canada**

*November 22, 2001*



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# Summary

## Background

The Viral Exanthemata Section of the National Microbiology Laboratory, Winnipeg, and the Division of Immunization and Respiratory Diseases, Centre for Infectious Disease Prevention and Control, hosted a meeting of an Expert Advisory Group on Rubella in Canada on November 22, 2001. The objectives were to review the diagnosis and surveillance of rubella in Canada and to formulate recommendations that would rectify deficiencies in current diagnostic and surveillance methods.

## Clinical

Rubella is a viral disease that results in a transient exanthematous rash, lymphadenopathy and low-grade fever. It is generally a mild illness, and serious complications are rare. However, if acquired during the first trimester of pregnancy, there is a 90% risk of congenital malformations in the fetus – congenital rubella syndrome (CRS). Prevention of this syndrome is the main goal of rubella immunization and can be achieved by immunization of children through universal programs as well as immunization of susceptible women of childbearing age.

## Epidemiology

Rubella incidence rates in Canada have been approximately 2 cases per 100,000 in the last 12 years. Fewer than 30 cases of rubella were reported in Canada during the last 2 years, and there were only one to two cases of CRS per year from 1996 to 2000.

The elimination of indigenous rubella in Canada should be an achievable goal in the near future. However, Canada has not yet set a national goal for rubella elimination. The U.S. has set a goal to eliminate indigenous rubella and CRS by the year 2010. Importation of rubella cases and immigration of susceptible individuals from regions without rubella vaccination programs are important issues in countries with rubella vaccination programs, such as Canada, the U.S. and the U.K.

## Laboratory

Laboratory tests are required to confirm the diagnosis of rubella since the clinical symptoms are similar to other fever/rash illnesses, such as measles. Thus, rubella and measles laboratory surveillance are integrally linked. The detection of immunoglobulin M (IgM) antibodies is commonly used for diagnosing rubella. Virus isolation, polymerase chain reaction, or IgG serology on paired acute and convalescent sera may also be used for rubella laboratory diagnosis. When the prevalence of rubella is low, as it is in Canada, the positive predictive value of IgM testing decreases such that there can be a significant risk of a false positive result. An alternative laboratory method, such as antibody avidity serologic testing, is therefore needed as a confirmatory test, especially for the investigation of rubella in pregnant women, when decisions on termination of pregnancy must be made.

## **Susceptibility**

Studies carried out in Newfoundland indicate that over 20% of women over 14 years of age may be entering the child-bearing years without protective antibodies against rubella. It is clear that a significant proportion of those born in the postvaccine era and given a single dose of MMR vaccine are likely to exhibit waning immunity to rubella over time, as the absence of circulating wild virus means that there is no longer a natural booster effect. Whether waning immunity, as defined by the absence of detectable protective rubella antibody, necessarily means susceptibility to rubella infection in previously vaccinated populations has not been established. When a pregnant woman

is found to be susceptible to rubella on routine prenatal screening, it is suggested that she seek rubella immunization immediately postpartum. The use of printed, postpartum orders has been shown to increase rubella postpartum immunization rates.

## **Recommendations**

The Expert Advisory Group on Rubella in Canada has made 11 recommendations related to surveillance, immunization, susceptibility screening, and laboratory diagnostics, and has also identified five areas in which more data are required.

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# Recommendations

## **Epidemiologic and Laboratory Surveillance**

1. The surveillance of rubella and CRS should be integrated with the activities of the Working Group on Measles Elimination in Canada.
2. A national goal for rubella elimination in Canada should be proposed and submitted for endorsement by all federal/provincial/territorial deputy ministers, with the identification of associated resources. Note that currently measles is the only vaccine preventable disease that has a national goal for elimination, endorsed by all the Deputy Ministers.
3. The measles laboratory surveillance guidelines should be expanded to include rubella laboratory testing: "Measles-rubella surveillance: guidelines for laboratory support".
4. Selected commercial rubella serology (IgM and IgG) kits should be evaluated to ensure high quality assurance of rubella testing in Canada.

## **Rubella in Pregnancy**

5. A working group should be established to review and improve the laboratory diagnosis of rubella and other exanthematous illnesses in pregnant women.
6. Rubella specific IgM positive test results in pregnant women should be confirmed using an alternative method such as antibody avidity testing.
7. Rubella susceptibility in pregnant women should be considered for inclusion in provincial/territorial lists of reportable conditions to facilitate provision of postpartum rubella vaccination.
8. Rubella susceptibility testing of women of childbearing age (preconception counselling) should be done at every opportunity. Vaccine should be offered as per the National Advisory Committee on Immunization guidelines, and recipients should be advised to avoid pregnancy for 1 month after immunization.

9. Every effort should be made to immunize foreign-born adolescents and women of childbearing age from countries without rubella vaccination programs, as soon as they arrive in Canada.
10. Rates of postpartum vaccination of susceptible women in hospital before discharge should be improved. This practice should also apply to home births. The Society of Obstetricians and Gynaecologists of Canada or those health care providers who are involved in obstetric care are the key groups to address this issue.
11. Therapeutic abortions for congenital rubella infections should be monitored.

## **Other Issues**

12. Research and data are needed on
  - (i) rubella vaccine coverage rates;
  - (ii) markers of immune status in previously immunized individuals to assess waning immunity;
  - (iii) rubella cases in previously immunized individuals to assess vaccine failures;
  - (iv) susceptibility to rubella in immigrants and aboriginals;
  - (v) late onset manifestations of CRS.

# Rubella and Congenital Rubella Syndrome in Canada

Drs. Eleni Galanis and Paul Varughese

## Rubella

Infection with rubella virus, a member of the *Togaviridae* family of viruses, was endemic worldwide until the advent of rubella immunization. In Canada, epidemics of rubella occur every 3 to 10 years, and the incidence peaks towards the end of the year and again in the spring months.

Rubella is transmitted through direct contact with nasopharyngeal secretions or through droplet spread, and the disease is infectious from 7 days before to 7 days after the onset of rash. It presents as a generalized maculopapular rash that starts on the face, progresses to the whole body and may be accompanied by low-grade fever and lymphadenopathy. Adult infection often involves arthralgia or arthritis.

However, rubella can be asymptomatic in up to 50% of those infected.

Clinical diagnosis may be unreliable, since several childhood viral illnesses give rise to a similar exanthematous rash. In Canada, rubella has been a nationally notifiable disease since 1924 (with a brief gap in the 1960s). The national case definition<sup>(1)</sup> is shown in Table 1.

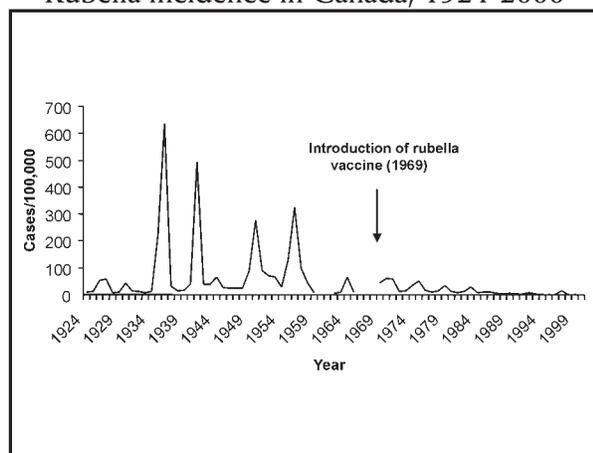
Incidence, epidemiologic and laboratory data are gathered locally by public health officials, sent to the provincial/territorial level and from there to the national case reporting system at Health Canada. From these data, it is clear that during the rubella epidemics occurring before immunization was introduced into Canada (in 1969) there was a much higher incidence rate

Table 1:  
Confirmation of rubella infection in the absence of recent immunization with rubella vaccine

<b>EITHER</b>
(a) Laboratory confirmation by one of the following: <ul style="list-style-type: none"><li>– isolation of rubella virus in a clinically appropriate specimen, OR</li><li>– significant rise in rubella IgG antibody between paired acute and convalescent sera, OR</li><li>– positive serologic test for rubella-specific IgM.</li></ul>
<b>OR</b>
(b) Clinical illness in a person who is epidemiologically linked to a laboratory-confirmed case and who has: <ul style="list-style-type: none"><li>– fever AND rash, AND</li><li>– at least one of the following:<ul style="list-style-type: none"><li>arthralgia or arthritis</li><li>lymphadenopathy</li><li>conjunctivitis</li></ul></li></ul>

(300-600 cases per 100,000 population, see Figure 1) than during the three epidemics in the last 12 years (from about 5 to 14 cases per 100,000).

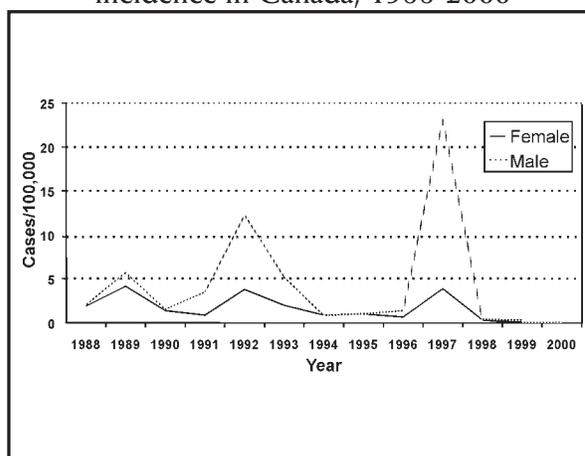
**Figure 1:**  
**Rubella incidence in Canada, 1924-2000**



Different immunization strategies have been used in Canada since the vaccine was introduced, and their effects are evident in the incidence data. Some provinces/territories (Ontario and Quebec) moved directly to routine infant immunization of both sexes, and others (Manitoba and Saskatchewan) immunized only adolescent girls until the early 1980s. By 1983, all provinces/territories were routinely immunizing all infants. During the 1989, 1992 and 1997 rubella epidemics, Ontario and Quebec saw much smaller incidence peaks than were evident in the national rate and, overall, have been reporting rates of about 2 cases per 100,000 over the past 12 years. The 1997 outbreak occurred primarily in Manitoba (the last province to begin routine infant immunization, in 1983), which reported incidence rates of approximately 350 cases per 100,000.

Figure 2 shows the rubella incidence rates broken down by sex, and it is clear that in epidemic years the high rates were occurring mainly among males, likely reflecting the susceptibility of boys in those provinces/territories practising selective immunization. Further analysis of the epidemic data by age group suggests that there is a cohort of males in certain provinces, starting at ages 10 to 14 and 15 to 19, that has remained susceptible to rubella, and these are the males who have the highest rates of the disease during each epidemic. It is possible that if there were another epidemic in the next 1 to 3 years, the group to be hardest hit would be males aged 24 to 29 years.

**Figure 2: Sex-specific rubella incidence in Canada, 1988-2000**



In the last 2 years, fewer than 30 cases of rubella have been reported in Canada. If a goal of elimination of indigenous rubella were to be adopted, one strategy worth pursuing might be to combine active surveillance of rubella with that of measles. As well, more data would need to be collected on risk factors, country of origin, and immunization history.

## **Congenital Rubella Syndrome**

The primary objective of immunization against rubella is to prevent the infection during pregnancy, when it can result in congenital rubella syndrome (CRS) in the developing fetus. In 1994 the goal was set, informally, to eliminate indigenous rubella during pregnancy in Canada by the year 2000. Currently, the policy throughout the country is to immunize all preschool children older than 12 months, female adolescents, and women of childbearing age who do not have a documented history of rubella immunization or laboratory evidence of detectable antibodies. A target of 97% up-to-date coverage (i.e. at least one dose of vaccine) by the second birthday was set for 1997, and it is estimated that 95% coverage was, in fact, achieved. Compared with the target of 99% coverage by the time of school entry in that year, the estimated coverage compared well, at 97%.

CRS became a nationally notifiable condition in 1979. As well, active surveillance of CRS is carried out through the IMPACT sentinel system, a network of 12 tertiary care, pediatric hospitals representing > 85% of Canadian tertiary care beds for children. Since 1996, these hospitals have reported information on cases of

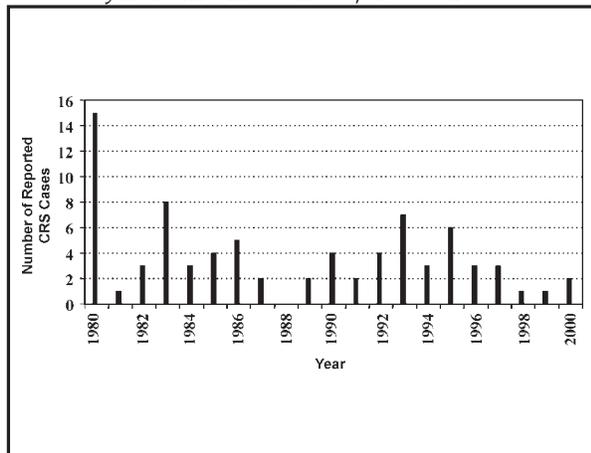
CRS to the Canadian Paediatric Surveillance Program (CPSP). Pediatricians surveyed in the CPSP are also asked to report congenital rubella infection (a laboratory confirmed case with no clinically compatible manifestations). The objective is to gather incidence and epidemiologic data, particularly maternal risk factors, on these cases. The CRS case definitions used are shown in Table 2.

Figure 3 shows the reported number of CRS cases from 1980 to 2000, a pattern that mirrors closely the number of rubella cases over this period (except for the rubella epidemic in 1997, for which there was no corresponding peak in CRS rates). From 1996 to 2000 there have been just one or two cases of CRS per year, for a total of seven. Of the five cases on which there is information, two were born to immigrant women, one to an Aboriginal Canadian and two to non-Aboriginal Canadians. One of the latter two women had previously given birth to a healthy child. She reported that she did not remember having been immunized against rubella at any time, even at postpartum discharge from hospital with the first child, nor had she undergone rubella screening; she was unaware of any contact with a rubella case during her pregnancy.

**Table 2: Confirmed case definition for congenital rubella syndrome**

<b>Live birth</b>	Two clinically compatible manifestations (any combination from Groups A and B, below) and laboratory confirmation of infection.
<b>Still birth</b>	Two clinically compatible manifestations (any combination from Groups A and B, below) and isolation of rubella virus from an appropriate clinical specimen.
<b>Group A</b>	Cataract or congenital glaucoma, congenital heart defect, sensorineural hearing loss, pigmentary retinopathy.
<b>Group B</b>	Purpura, hepatosplenomegaly, microcephaly, microphthalmia, mental retardation, meningoencephalitis, radiolucent bone disease, developmental or late onset conditions such as diabetes, progressive panencephalitis and any other conditions possibly caused by rubella virus.

Figure 3: Reported cases of congenital rubella syndrome in Canada, 1980-2000



The low incidence of CRS in recent years suggests that Canada is very close to the goal of elimination of indigenous rubella infection in pregnancy. Several strategies may help to achieve elimination:

- (a) Ensure that all women without documented proof of rubella immunization receive the vaccine.
- (b) Review, in particular, the immunization records of women from regions with poor coverage, especially the records of immigrant women.
- (c) Carry out routine rubella antibody screening prenatally, and immunize all

susceptible women in the immediate postpartum period.

- (d) Institute standing orders for immunization of susceptible women before hospital discharge.
- (e) Investigate/follow up all infants born to mothers with confirmed or suspected rubella infection during pregnancy, even if the infants have no obvious abnormalities on examination.

**Discussion from the floor:** It was noted that although information on whether reported cases have been laboratory confirmed is often not available through the national case reporting system, refinements in diagnostic techniques over the years have made inaccurate diagnosis less likely. Another point was made that, in Ontario, about half the mothers of infants with CRS have been found to come from countries with no rubella immunization. Even though they may have been in Canada for many years, opportunities for immunization have evidently been missed. There was discussion about the extent to which therapeutic abortions, carried out when rubella infection is detected early in pregnancy, have kept the number of CRS cases at a low level.

## Rubella Overview and the UK/WHO Situation

Dr. Jenny Best

A comprehensive overview of rubella can be found in *Principles and Practice of Clinical Virology*<sup>(2)</sup>. When rubella is acquired in the first 12 weeks of pregnancy, the virus nearly always crosses the placenta, and congenital abnormalities result in more than 75% of cases. After 12 weeks the risks decline fairly rapidly, and between 13 and 16 weeks the risk of congenital abnormalities, consisting mainly of deafness and retinopathy, is about 17%. CRS can be prevented by immunization. Attenuated strains of the virus were developed in the 1960s, and nowadays most vaccines contain the RA27/3 strain, which is attenuated by passage in W1-38 human fibroblasts at 30° C to 35° C. The vaccine induces long-lasting immunity. Joint symptoms occur in up to 40% of postpubertal females, but these resolve within a few days.

Although immunization is contraindicated during pregnancy, therapeutic abortion is not required if the vaccine is administered inadvertently. Pooled data from follow-up studies conducted in the U.K., U.S., Germany and Sweden on mothers who were inadvertently given vaccine during pregnancy revealed that in only 13 of 417 children (3%) was there laboratory evidence of rubella infection<sup>(2)</sup>; one of the 13 children had an abnormality consistent with CRS. (However, these overall figures may be misleading, since only 135 of the women had been immunized during the high risk period, of 1 week before to 6 weeks after conception.)

At present, the rubella immunization program in the U.K. consists of a first vaccination at 12 to 15 months of age for all infants and a second at

school entry. Surveillance data are obtained from the following sources:

- (a) laboratory reports and case notifications;
- (b) estimates of rubella susceptibility among pregnant women obtained from the Public Health Laboratory Service (serologic surveillance);
- (c) number of congenital rubella births (National Congenital Rubella Surveillance Program);
- (d) number of rubella-associated therapeutic abortions (Office of National Statistics);
- (e) vaccine coverage estimates (COVER program).

Rubella incidence during the 1990s peaked in 2 years — 1993 and 1996 — mainly as a result of infection among young men, as was the case in Canada. From 1987 to 1995 the proportion of women found to be susceptible during their first pregnancy was 2%, and among women with a previous pregnancy the proportion was 1%. Results from three laboratories indicated a clear difference during 1994-95 in susceptibility among Asian and non-Asian women, at 4.4% versus 1.3% respectively. This difference, particularly marked among women aged 15 to 19 (12.7% Asian versus 1.3% non-Asian), was felt to be a result of the Asian women entering the U.K. after the age of immunization. This is clearly a group that needs to be targeted for immunization, possibly through well women

and family planning clinics. Of some concern are the data from the COVER program showing that there was a drop in MMR vaccine coverage from the end of 1994 to 1999 (down to 72% in some areas of the country), which is felt to be due to the unwarranted adverse publicity that MMR vaccine has received.

The number of CRS cases and rubella-associated terminations of pregnancy decreased considerably after 1978-79 with intensification of the rubella immunization program<sup>(3)</sup>. In 1996, after the increase in rubella incidence, there were 12 CRS cases and nine rubella-associated terminations, whereas in the last 2 or 3 years there have been only seven cases of CRS. From 1991 to 1995, 15 of the 19 cases of CRS occurred in infants of women born outside the U.K.; in the outbreak of 1996, four of the 12 women were foreign born. Overall, a quarter of the infections reported between 1991 and 1996 were acquired outside the U.K.

Laboratory techniques for antibody screening include the semi-automated enzyme immunoassay (EIA), microparticle EIA (automated), latex agglutination and single radial hemolysis. Ideally, serum is tested by means of the main assay in use at the particular laboratory, and in the case of negative or equivocal results there is re-testing with a different technique, possibly latex agglutination. Regular proficiency testing as well as quality control on the assays should be performed.

A diagnosis of rubella infection can be achieved with two assays through demonstration of a rise in IgG levels, using serum taken from the acute stage of infection and again from the convalescent stage, and of IgM antibody; or through a finding of positive results for IgG and IgM from one serum sample with confirmation from a second sample. Techniques for detecting IgM in saliva have proved useful for testing children. Virus isolation and polymerase chain reaction

(PCR), though more complex, may also be used diagnostically.

Reliance on rubella-specific IgM antibodies as an indicator of rubella infection is not without problems. Different assays vary with respect to sensitivity and specificity, and there may be as many false positives as there are true positives when the incidence of rubella is low. Cross-reacting IgM antibodies can give rise to false positive results, for instance in patients with recent Epstein Barr virus infection. Furthermore, some women have IgM antibodies that persist for a year or more after rubella infection or immunization. IgM antibodies may also suggest re-infection. Re-infection is most frequently detected in women with vaccine-induced immunity who have prolonged exposure to rubella virus. It is generally asymptomatic and is defined as an immune response seen in an individual with previous immunity, as determined by a reliable technique. Re-infection should be distinguished from primary infection in pregnancy, since in re-infection the risks to the fetus of CRS are considerably lower, at < 5% according to prospective studies.

Tests for rubella IgM antibodies are not indicated unless there is a history of rash in a pregnant woman or contact with a rubella-type rash. Unnecessary tests for rubella IgM may lead to problems in interpretation, and the positive predictive value of IgM results tends to be low when the prevalence of rubella is low. Interpretation of positive results should be based on as much information as possible about rash illness, contact with rash, and previous immunization and antibody screening. A variety of assays to detect IgM should be available in a reference laboratory, including direct (capture) and indirect (antigen-coated plate) techniques, together with rubella IgG avidity EIA, which will indicate whether the infection is recent (low avidity) or not. Immunoblot techniques may be

useful for the diagnosis of postnatal and congenital rubella. PCR is useful for prenatal diagnosis.

With regard to the rubella and CRS status internationally, data collected during the mid-1990s showed a high rate of susceptibility to rubella among females of childbearing age in the Caribbean islands, in parts of South America, parts of Southeast Asia, and parts of Africa; in some countries, more than 25% of women were susceptible. Epidemics were found to occur every 4 to 7 years in developing countries. Rates of CRS were similar to those in developed countries before rubella immunization had been established, for instance, 1.7 per 100,000 in Jamaica, 2.2 per 100,000 in Panama.

In January 2000, the World Health Organization recommended that developing countries with high rates of rubella and CRS should consider introducing rubella immunization<sup>(4)</sup>. Whichever system of immunization is introduced, whether selective immunization or universal childhood immunization, it is important that females of childbearing age be screened and immunized if necessary, since susceptibility will increase in this group as young children acquire immunity through immunization and rubella is no longer circulating in the community.

Recent data indicate that many of these countries, specifically in Central and South America and the Caribbean, now include rubella in their immunization programs. There are still gaps in immunization, mainly in Africa, Southeast Asia and some of the Eastern European countries.

**Discussion from the floor:** A concern was raised that MMR immunization may occur quite often in girls and young women who do not know they are in the early stages of pregnancy or who are not pregnant but have not been warned to avoid pregnancy for a period of time. In response, it was stated that although the data on inadvertent immunization in pregnancy are few, more studies (in Costa Rica and Brazil) following up the effects of such immunization are in progress. Another point was made that it is sometimes difficult to be sure of a diagnosis of re-infection in women previously immunized: results from avidity testing may not always be helpful, and there is the possibility that the finding of IgM antibodies is a result not of rubella but of another virus. Dr. Best emphasized that this is why information from as many sources as possible is necessary, i.e. from the obstetrician, the patient, and the family practitioner.

## **Rubella in the U.S. and PAHO**

*Dr. Susan Reef*

Detailed background information on rubella activities in the U.S. can be found in the MMWR<sup>(5)</sup> and Reef et al<sup>(6)</sup>. The national rubella immunization program was introduced into the United States in 1969, initially targeting vaccination of male and female infants from  $\geq 1$  year of age to puberty. At the same time, a surveillance system for CRS (the National Congenital Rubella Syndrome Registry) was established at the U.S. Centers for Disease Control and Prevention. The result of the childhood immunization strategy was a substantial decrease in rubella incidence, particularly among those aged  $< 15$  years, from 57,686 in 1969 to approximately 12,000 within 4 to 5 years. The number of CRS cases also declined, from 67 cases annually in 1970 to  $< 10$  in the mid to late 1990s. As a result of outbreaks of rubella observed in older adolescents and young adults during the 1970s, the Advisory Committee on Immunization Practices recommended in 1977 that postpubertal and adolescent females also be immunized. Other groups that have since been targeted for vaccination include college students, health care and day care professionals, and individuals in the military. In the early 1990s, most rubella cases occurred in people aged  $< 20$ , but from the mid-1990s people aged  $\geq 20$  have accounted for the majority of reported cases. Only 21 cases of rubella have been reported so far in 2001. The goal is to eliminate indigenous rubella and CRS by the year 2010.

By the mid to late 1990s, most rubella outbreaks occurred among foreign-born Hispanic adults. By 1997, the country of birth was being collected as a part of the national surveillance system, and data from the beginning of 1998 to the end of 1999 indicate that 41% of rubella cases were from Mexico, 26% from Central

America and the Caribbean, and in 26% the country of birth was the U.S. or Puerto Rico.

Since 1997, approximately 40% of infants with CRS had mothers exposed to infection outside the U.S. Overall,  $> 80\%$  of the mothers are foreign born, 75% being of Hispanic origin. The best strategies for ensuring immunity in these susceptible women are being considered, including enhancing postpartum rubella immunization throughout the country and developing methods for targeting foreign born men and women.

Molecular typing of rubella isolates, another aspect of the U.S. surveillance system, was undertaken with the goal of identifying the virus strains circulating in the country, their origin and geographic characteristics, and whether they are endemic to the U.S.<sup>(7)</sup> Three distinct genotypic groups have been found, all with similar demographic characteristics. Furthermore, two different groups may be circulating geographically close to each other, suggesting an importation of the rubella virus.

With regard to the work of PAHO, a Technical Advisory Group has recommended incorporating measles and rubella or MMR vaccine into childhood immunization schedules, reducing the number of rubella-susceptible women of childbearing age, and initiating surveillance that integrates rubella surveillance (with measles surveillance) and CRS. By the end of 2001, about 90% of countries in the PAHO region will have established MMR or MR as part of their childhood immunization programs. Immunization of susceptible women of childbearing age, a more recent objective, is already established in Canada, the U.S., Cuba, Chile, Cost Rica, Panama and Uruguay. Other countries in Latin

America are planning to initiate postpartum vaccination.

PAHO strongly believes in the importance of laboratory confirmation of suspected cases (of rubella and measles) in the surveillance of these diseases. In 1998 there were 135,000 cases, of which cases in Argentina, Mexico and Venezuela made up 92%. In 1997, a Technical Advisory Group to PAHO advised that for countries wishing to control CRS rapidly, immunization campaigns for females 5 to 39 years needed to be conducted; for rapid control of rubella as well as CRS, males and females in this age group would need to be targeted for immunization. Caribbean countries have been among the first to institute mass campaigns for

adults. Adult mass campaigns have been conducted in Chile and Costa Rica.

**Discussion from the floor:** There was a query about progress in Asia and Africa in terms of immunization, since there are a high proportion of immigrants to Canada from these regions. The response was that some African countries are showing interest in beginning rubella immunization, but only 2% of the countries in Africa have incorporated rubella into their national programs. In terms of the sensitivity and validity of the surveillance system in the U.S., problems have become apparent and will be studied further.

## Rubella Laboratory Diagnostics

Graham Tipples

Additional discussions on rubella laboratory diagnostics can be found in the previous sections by Drs. Eleni Galanis and Jenny Best. Rubella laboratory testing is necessary for confirming postnatally acquired rubella, for confirming prenatally acquired rubella (both for prenatal diagnosis and the diagnosis of postnatal congenital rubella syndrome or congenital rubella infection), for rubella antibody serostatus screening, and for testing of pregnant women exposed to a possible rubella case. Rubella infections can be laboratory confirmed by virus isolation, demonstration of a significant rise in rubella antibody titre, or by detection of rubella-specific IgM antibodies in a serum sample. Hospital and provincial public health laboratories in Canada carry out routine rubella antibody screening (serostatus) and rubella IgM

antibody testing (confirming active rubella cases). The National Microbiology Laboratory coordinates the rubella serologic proficiency testing program as well as providing selected reference services, including rubella antibody avidity testing and reverse-transcriptase PCR<sup>(8,9)</sup>.

A genotyping method for rubella virus has been established but is not currently used in Canada<sup>(7)</sup>. Rubella virus can be isolated and detected in saliva samples up to 7 days after the appearance of rash. It should be possible to incorporate rubella genotyping into a closely linked measles/rubella enhanced surveillance program, since nasopharyngeal specimens are required to be collected for suspected measles cases. Genotyping data for rubella would be

Table 3: Commercial rubella serology kits used in Canadian laboratories in 2000

<b>IgM Serology</b>		<b>IgG Serology</b>	
<b>Commercial Test</b>	<b>No. of Laboratories</b>	<b>Commercial Test</b>	<b>No. of Laboratories</b>
Abbott AXSYM	5	Abbott AXSYM	18
Behring Enzygnost	6	Behring Enzygnost	4
Vidas Rubella IgM	1	LA Becton Dickinson	2
Abbott IMX	2	Rubascan	3
Beckman Access	1	Abbott IMX	3
		Beckman Access000	1
		HI – Behring	1
		HI – Biowhittaker	1
		Bio-Merieux Vitek Vidas	1
		DiaSorin	1
		Meridian Premier	1
		Roche Cobas Core	
<b>Total no. of laboratories</b>	<b>15</b>	<b>Total no. of laboratories</b>	<b>34*</b>

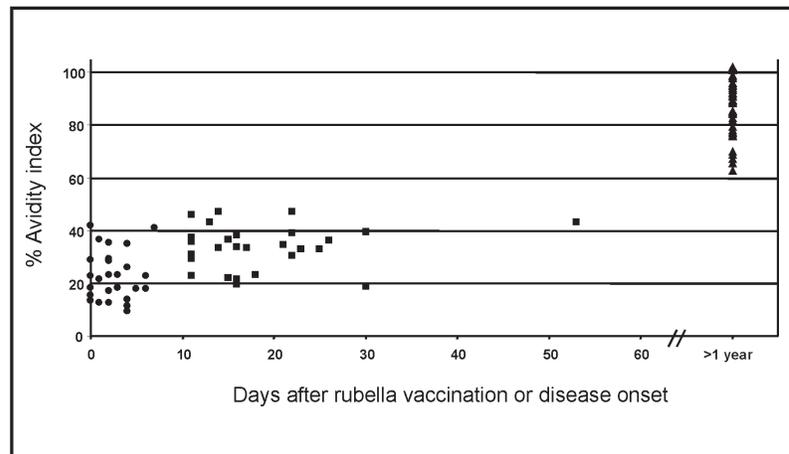
*\*Some laboratories use more than one test.*

useful for tracking transmission pathways and differentiating vaccine from wild-type strains.

Of the laboratories participating in the rubella serology proficiency testing program, 15 test for rubella IgM and 34 for rubella IgG (Table 3). There is variability in the performance of the different commercial assays, and it would be useful to evaluate these assays more thoroughly in terms of sensitivity, specificity and predictive values, using well-defined panels of sera.

Several suspected rubella cases in pregnant women have been referred to the National Microbiology Laboratory. Positive IgM serology is considered indicative of a recent rubella infection and thus has important implications for the management of the pregnancy. However, when disease incidence is low, as is the case with rubella in Canada, the positive predictive value for IgM testing is low, and thus there is a real risk of a false positive result. It is therefore imperative in these situations to confirm the positive IgM result using an alternative test. Avidity testing may prove useful in this regard<sup>(10)</sup>. Avidity is a measure of the overall binding strength between antigen and antibody, and testing relies on the fact that over time the avidity strength increases<sup>(11)</sup>. Thus, low-avidity antibodies indicate recent infections and high-avidity antibodies indicate past infections. A rubella antibody avidity test has been established at the National Microbiology Laboratory for confirming IgM positive results<sup>(12)</sup>. A well-defined panel of paired sera from rubella cases has been used to assess this avidity assay (Figure 4).

Figure 4: Maturation of rubella-specific antibody avidity



The avidity index of rubella-specific antibodies was determined in acute (●) and convalescent (■) sera from recent rubella infections, and in sera from past (> 1 year) rubella infection/vaccination exposure (▲). An avidity index of 60% appears to be a reasonable cut-off for differentiating recent (low avidity, < 60%) from past (high avidity, > 60%) infections

In conclusion, the development of laboratory guidelines is necessary for rubella serologic testing in pregnant women. Avidity testing is a useful assay for differentiating primary infection from re-infection or previous exposure. Lastly, surveillance (epidemiologic and laboratory) of rubella should be more closely linked with measles surveillance.

**Discussion from the floor:** One participant suggested that maternal immunologic responses are complicated by pregnancy and that serology results in pregnant women must therefore be interpreted with caution. Canadian laboratories' use of HI (hemagglutination inhibition) tests for rubella IgG antibody detection was questioned because of the tests' high false-positive rates; as well, there was concern that the IgM tests were almost all indirect assays, also likely to give false positive results. Dr. Tipples responded that in the case of measles, comparison of the capture assay with indirect assays has shown that some of the latter gave results equally as good as the former. Decisions about the best tests to use should be based on investigation and careful evaluation of individual assays.

## Waning Immunity to Rubella

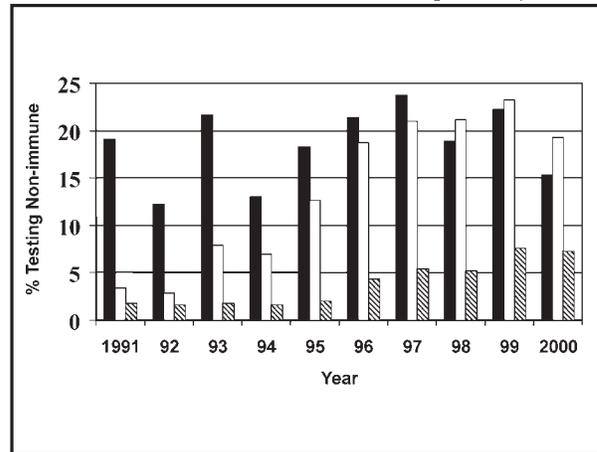
Sam Ratnam

Cohort and cross-sectional studies carried out in Newfoundland on MMR vaccination strategies have indicated that rubella is the most immunogenic component of the vaccine, with the initial serologic response at nearly 100%<sup>(13,14)</sup>. The rubella protective immunity, as defined by the presence of rubella antibodies at > 10 international units, is sustained in over 90% of vaccinees up to 6 years after immunization<sup>(15,16)</sup>. The proportion with protective antibodies decreases thereafter, dropping to < 80% by 13 years after immunization<sup>(15)</sup>. The implication is that over 20% of women over 14 years of age may be entering the childbearing years without protective antibodies against rubella.

This observation has been substantiated by the Newfoundland prenatal rubella screening program (the provincial rubella immunization program began in 1971 with a centralized rubella prenatal screening program commencing in 1972). Rubella immunity was > 90% among pregnant women during the 1970s and 1980s, indicating a widely prevalent, naturally induced immunity at that time in this age group<sup>(17)</sup>. However, during the past decade the proportion of those susceptible increased from about 5% to almost 14%; this was most striking in the age group 20-24 years, which registered an increase from 3% in 1991 to 23% in 1999 (Figure 5)<sup>(18)</sup>. More specifically, the age group 15-19 years accounted for over 70% of all those testing susceptible in 1991, and by the end of the 1990s the age group 20-30 years represented 75% of those testing susceptible, this being attributable to the compounding age cohort effect. It is important to note that the vast majority of women in this group had been vaccinated against rubella.

It is clear that a significant proportion of those born in the postvaccine era and given a single

Figure 5: Newfoundland rubella screening program, age group distribution of rubella susceptibility



Solid bars represent ages 15-19, open bars represent ages 20-24, and cross-hatched bars represent ages 24-34 years

dose of MMR vaccine are likely to exhibit waning immunity to rubella over time, as the absence of circulating wild virus means that there is no longer a natural booster effect. Although a two-dose MMR vaccine strategy was introduced in 1995-96 across the country, with the second dose given either at 18 months or school entry, the impact of this on long-term immunity against rubella remains to be seen. Whether the waning immunity, as defined by the absence of protective rubella antibody, necessarily means susceptibility to rubella infection in previously vaccinated populations has not been established.

The conclusions from the presentation are as follows:

- (a) A significant proportion of those born in the postvaccine era and given a single dose of MMR vaccine are likely to exhibit waning immunity to rubella over time. This is attributable in part to a lack of natural booster effect, as the wild rubella virus has not been in circulation for more than a decade.
- (b) Although a two-dose MMR vaccine strategy was introduced in 1995-96 across the country, the impact of this on long-term immunity against rubella remains to be seen.
- (c) There is a continuing accumulation of rubella susceptible women who are of prime reproductive age. The public health significance of this is not known.

**Discussion from the floor:** The question was raised of whether undetectable or low levels of rubella antibody many years after immunization necessarily implies susceptibility to infection. In the U.S., declining antibody titres among immunized populations have also been observed, but outbreaks among unvaccinated foreign-born populations have not spread to the vaccinated resident U.S. population. It is possible that in the previously vaccinated susceptible population, anamnestic response could be triggered to mount an effective defence when challenged with the wild virus. It was pointed out that the *Canadian Immunization Guide*<sup>(19)</sup> states that if a woman has documentation of prior rubella immunization and is not pregnant there is no indication for rubella immune status testing. Another point made was that in the age groups of concern, i.e. the late 20s and early 30s, the risk of exposure to the wild virus is likely to be lower than in younger age groups in school or campus settings.

## Effectiveness of Standard Postpartum Orders for MMR vaccination

Dr. Erica Eason

According to the Canadian Paediatric Surveillance Program, half of all babies reported to have CRS in Canada are born to mothers who have previously given birth, which means that half could have been prevented with postpartum rubella immunization after the previous birth. Since there is probably substantial under-reporting, nationally, of CRS cases, the number of affected cases that could be avoided with postpartum immunization is likely higher than it would seem from the number of reported cases.

The usual procedure when a pregnant woman is found to be susceptible to rubella is that she is told to go to her doctor or to a public health clinic for immunization after the delivery. However, in a review carried out at 16 hospitals it was reported that in a total sample of 2,551 pregnant women, of the 8.4% who were susceptible only 27% were immunized in hospital, and by the end of 3 months after discharge a further 2% had been immunized<sup>(20)</sup>. Although standing orders for immunization of susceptible women are recommended in hospitals there has been no evaluation of whether such orders are effective.

A cohort study was undertaken to determine whether a set of printed, postpartum orders would be more effective than the existing handwritten orders in increasing postpartum rubella immunization rates in one hospital<sup>(21)</sup>.

Printed standing orders were introduced in the hospital in July 1997 and included the statement: "MMR vaccine 0.5 mL SC if not rubella immune. If no result available, do titre, to be sent to attending staff." The cohorts consisted of randomly sampled women who had delivered babies in the 1 year period before and after July 1997 (excluding the 6 months before and after this time).

Table 4 shows the results of the study: a statistically significant increase in the proportion of postpartum vaccinations and decrease in the proportion for which immunization status was missing. The proportion of women who had a previously missed opportunity for postpartum immunization was 56.8%. There was no difference in the immunization rate for women with negative antibody titres and those with equivocal titres (84.1% versus 75.0% respectively). Parity, maternal age and gestational age at delivery did not predict rubella immunity. However, mean gestational age was significantly lower (35.2 weeks) among women whose serologic status was unknown than women whose status was known (38.5 weeks). For 31 women with missing serostatus in 1998 a titre was submitted after delivery, and one-third of these 31 were found to be susceptible to rubella. Because of this high proportion the standing orders have been changed, so that women with

Table 4: Results before and after introduction of printed, postpartum standing orders (2,065 charts reviewed, 118 rubella susceptible)

<b>Immune Status</b>	<b>Before</b>	<b>After</b>	<b>Statistical Significance</b>
Rubella susceptible	4.9%	6.7%	Not significant
Status missing	11.3%	5.3%	p < 0.001
Vaccinated	12.1%	81.7%	p < 0.001

missing serostatus are now immunized. An audit of the system in March-April 2001 indicated that of 10 rubella susceptible women sampled all had been immunized, so the effects of the standing orders appear to be durable.

The effectiveness of printed standing orders may have been partly due to physicians' and nurses' acceptance of the evidence that MMR immunization can prevent CRS and the recommendations contained in the *Canadian Immunization Guide*<sup>(19)</sup>. Involvement of the hospital staff before the change was implemented was likely another contributing factor. Furthermore, replacing the handwritten orders meant that physicians did not need to spend as much time searching through records and deciding whether to write out individual orders.

Since family physicians in Canada rely on the Society of Obstetricians and Gynaecologists (<http://sogc.medical.org>) for guidelines on the necessary procedures for pregnant women, it is important that the Society include in its guidelines that postpartum immunization should be carried out in hospital and the steps that should be taken if a woman's serologic status is missing. The Canadian Task Force on Preventive Health Care (<http://www.ctfphc.org>) does not mention postpartum rubella (MMR) immunization at all, and this is a gap that should

be filled. A final point is that if a large proportion of susceptible, pregnant women are of foreign origin, perhaps a national policy of immunizing all immigrants as they enter the country would help reduce the number of cases of CRS.

**Discussion from the floor:** The need to immunize newly arriving immigrants was endorsed. Rubella-susceptible immigrants may pose a risk to Canadians in two ways: in terms of the Canadians they may give birth to in the future, and by their tendency to form a highly susceptible, closely clustered population at risk of giving rise to an outbreak. The problem is that federal legislation dealing with health requirements for new immigrants to Canada focuses on the potential harm that might be caused to the resident population. Thus, chest radiography to detect TB and syphilis tests are carried out so that infection is not passed on to Canadians already here. Once new arrivals are established in a province their health care becomes the responsibility of that province. In some provinces with large immigrant populations, local efforts are often made to reach immigrant families through the children's school immunization requirements. However, there is no formal process.

## **Review of a “Survey of Late Emerging Manifestations of CRS in Canada”**

*Dr. Eleni Galanis*

Although the effects of rubella infection during early pregnancy are usually evident at the time of the infant’s birth and classified as congenital rubella syndrome, there can be late manifestations that only become evident after several years. Some of these may be due to vascular insufficiency or possibly autoimmune disorders; the pathology is poorly understood. About 20% of children with CRS go on to develop diabetes, and about 5% develop thyroid disease; there may be varying levels of deafness and ocular disorders arising after birth; vascular defects may occur as a result of stenosis of the arteries; and progressive rubella panencephalitis may develop, with behavioural problems, seizures, and eventually death.

In 1997, Human Resources and Development Canada provided funds to a past-president of the Canadian Deaf Blind and Rubella Association (CDBRA) to conduct a survey of late manifestations of CRS (“A Survey of Late Emerging Manifestations of Congenital Rubella in Canada, 1999”). One hundred people (or their parents/caretakers) between the ages of 5 and 65 responded to the survey. The survey results include, among other things, the following: (a) 21% developed glaucoma after the age of 6; (b) in 24% there was a change in the ability to hear; (c) 23% reported some aggressive behaviour; (d) 23% had seizures after the age of 6; (e) 10% developed thyroid disorders; and (f) 12% developed diabetes.

The survey attracted interest, since few data have been published on the issue. The past-president has contacted the Division of Immunization, Health Canada, in the last year for help in analyzing the data and publishing the results in a peer reviewed journal as well as for funds to continue further studies.

A number of criticisms were raised about the survey. There was selection bias, in that specific service institutions (e.g. CDBRA, Canadian National Institute for the Blind) were contacted as sources for the data, but physicians, hospitals or the Canadian Paediatric Surveillance Program were not. Only 200 of the 2,000 people the author estimated to be suffering from late onset manifestations of CRS were approached, and only half responded. There was no independent clinical or laboratory information to support the self-reported diagnosis of CRS and related conditions. The questionnaire was 23 pages long and often used medical jargon rather than enquiring about symptoms in easily understood terms; some of the conditions generally considered to be a part of CRS were not addressed. Finally, data entry and analysis were problematic.

Despite the need for research and data in this poorly understood area it was felt that, because of the methodologic flaws and questionable validity of the survey responses, the manuscript in its present form could not be used as the basis for a peer-reviewed article. Moreover, the Division has limited funds at present to support further research. If there is interest from Canadian epidemiologists, researchers, or international partners to explore this database and pursue the research, they should contact Eleni Galanis at the Division of Immunization, Health Canada. Suggestions from attendees included asking IMPACT to keep a database of CRS cases identified and to perform follow-up assessments to monitor late onset manifestations.

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