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Rubella in the Russian Federation: epidemiological features and control measures to prevent the congenital rubella syndrome

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SUMMARY

A review of the epidemiology of clinical rubella in the Perm region of the Russian Federation from 1979–97 showed that the incidence was about 220 cases per 100000 population. Congenital rubella syndrome (CRS) accounted for 15% of birth defects and for about 3·5 cases of CRS per 1000 live births per year. Surveys of the seroepidemiology of rubella infection revealed that the susceptibility rate among pregnant women (i.e. rubella virus antibody haemagglutination-inhibition (HAI) assay titres < 10) was 16·5%. As serum rubella antibody HAI titres $\geqslant 10$ both prevented infection in pregnant women and protected their foetuses, serological testing has been introduced into the routine antenatal services. Pre-existing rubella antibodies were found not to interfere with the immune response to vaccination, so selective immunization was provided to girls approaching puberty and to women of childbearing age. A programme of epidemiological surveillance is being developed to define tactics for the widescale introduction of rubella vaccination.

INTRODUCTION

The urgent need to study rubella infection in the Russian Federation is driven by several factors [1]. Foremost is the elevated incidence of clinical rubella (i.e. 150000 to 500000 cases are registered annually) [2, 3]. Furthermore, the current system of rubella surveillance focuses only on the clinically manifest forms of infection that become registered as cases, which is an underestimation. For example, 30–70% of rubella infections in adults have been found to be subclinical [4, 5].

In the Russian Federation there also has been an increase over the last decades in the rates both of congenital pathologies and of those developmental abnormalities that become apparent during infancy [6]. In particular, the sentinel parameter of congenital malformations increased from 103·0 per 10000 new-borns in 1973 to 235·0 per 10000 new-borns in 1997. Given the absence of routine rubella prenatal immunization in the Russian Federation, rubella virus infection poses a particular danger to the foetuses of pregnant women [6–8].

This paper describes an ongoing study of the surveillance and the prevention of rubella and congenital rubella syndrome (CRS) in the Perm region of the Russian Federation. It also reports on the evaluation of a rubella vaccination programme targetted to prepubertal girls and to women of childbearing age [10]. A number of foreign-manufactured

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rubella vaccines that contain the rubella virus strain Wistar RA 27/3 are registered for use in the Commonwealth of Independent States (CIS) [7, 11–13]. The reactogenicity and immunogenicity of these rubella vaccines when used in public health programmes of mass vaccination in the Russian Republic remained to be elucidated [14, 15].

This study was driven by four goals: first, to define the basic directions for seroepidemiological research that are needed to establish a surveillance system for rubella infection; second, to elaborate the role of rubella virus infection in the presentation of congenital pathologies; third, to demonstrate the immunogenicity and safety of a rubella vaccine given to prepubertal girls and women of childbearing age in the Russian Federation; and fourth, to establish a regional programme for the prevention of CRS.

Although data on congenital rubella syndrome are unavailable from most of the CIS, in 1984 the European Regional Bureau of the WHO had included CRS in the list of diseases subject to eradication by the year 2000 [16].

METHODS

Study population

The studies were conducted in Perm, a large industrial region of the western Urals in the Russian Federation. (Particular study populations are described in detail under "Epidemiology of clinical rubella", "Seroepidemiology of rubella infection", "Congenital rubella syndrome", and "Rubella vaccination".)

Epidemiology of clinical rubella (1979–97)

Official data were obtained for the incidence of clinical rubella in Perm over a 16-year period (1979–97). Only history and physical examination were used to register rubella cases.

An evaluation of annual and long-term rubella incidence dynamics for the total population, as well as for distinct age and social groups, was carried out using the technique described by Belyakova and colleagues [17], as modified by Rjikushin for airborne infections [7].

Seroepidemiology of rubella infection (1992–6)

More than 7000 serum samples were collected in 1992 from children and adults, and the humoral immune status measured by rubella antibody haemagglutination-inhibition (HAI) assays. A group of 98 healthy girls aged 12–13 years who had never been diagnosed with clinical rubella also were screened to prepare for a rubella vaccination programme. In subsequent years, other serum samples were obtained in response to specific rubella outbreaks.

The rubella diagnostic kits that were used were produced by the Pasteur Scientific Research Institute of Epidemiology and Microbiology (St. Petersburg, Russian Federation) and by the Tarassevich State Research Institute of Standardization and Control of Biological Preparations (Moscow, Russian Federation). The assay runs incorporated a rubella virus specific international standard antibody, with a hyperimmune serum sample serving as a control.

To enable testing of the small quantities of serum and to interpret the reaction results, the standard methods were modified according to the Instructions on the use of the rubella diagnostic kit (source: Russian Ministry of Health, 1990) [15]. (The serum HAI assays described used methods similar to those described by Liebhauber [18], Haukenes [19] and Bradstreet [20].) In addition, selective use of the detergent Unithiol allowed determination of the presence of rubella IgM antibodies in the umbilical cord blood samples. If the cord blood HAI reaction was due to IgM antibodies, the measured titre from an aliquot treated with Unithiol was at least fourfold less than the HAI titre for a saline-diluted aliquot.

The assays were performed as follows. Serum samples were diluted by adding 0·1 ml of serum to 0·4 ml of isotonic saline solution (1:5 proportion); the detergent Unithiol was diluted in the ratio of 1 ml of Unithiol and 3 ml of saline (1:4 proportion). A serum sample was divided into two equal 0·25 ml aliquots: the first aliquot was further diluted 1 in 2 with isotonic saline solution; the second aliquot was further diluted 1 in 2 with the Unithiol solution. Thus, two serum aliquots were obtained, both at a final dilution of 1 in 10. These were incubated at room temperature for 2 h before determination of the rubella HAI titre values.

Subjects having a serum rubella antibody HAI titre < 10 were classified as rubella virus antibody negative; a rubella antibody HAI titre $\geqslant 10$ being regarded as rubella virus antibody positive. Positive rubella virus antibody responses were further classified: HAI assay titres $\leqslant 32$ were considered as low, titres 64–128 were interpreted as intermediate, and titres $\geqslant 256$ were defined as high. Reinfection among rubella virus antibody-positive persons was defined as a specific antibody titre increase of fourfold or more.

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Congenital rubella syndrome (1994–6)

A serological survey was carried out between 1994 and 1996, both of 126 infants clinically diagnosed with CRS (aged 0–3 months) and of their mothers. Suspected CRS was confirmed in a newborn baby by the presence of rubella virus-specific IgM antibody in an umbilical cord blood sample or confirmed in an infant by elevated titres of specific IgG antibodies in a serum sample [21]. Rubella virus IgG titres $\geqslant 160$ were classified as being elevated for the analysis of CRS used in this study. As a control, serum samples from 60 healthy newborn children and their mothers were tested. Additional blood samples were drawn from 112 of the children in the first 3 months of life, and 112 paired maternal serum samples were obtained.

Rubella vaccination (1996)

An evaluation of the immunogenicity of a rubella vaccine was carried out in 1996, within the ongoing study of the surveillance and the prevention of rubella and CRS, among 5025 pre-pubertal girls and women of child-bearing age (16–30 years old) who had no history of clinical rubella. The upper age limit of 30 years for vaccination of women was based on the seroepidemiological observation that 97% of women in the 35- to 45-year old age group were rubella virus antibody positive (i.e. serum HAI titres $\geqslant 10$). In addition, by 30 years of age 85% of mothers had given birth to their children.

A live-attenuated rubella virus vaccine [Rudivax™; Aventis Pasteur (formerly, Pasteur Mérieux Connaught), Lyon, France] was used for immunizations. This lyophilized vaccine contains an attenuated rubella virus (strain Wistar RA 27/3 M). Each dose has not less than 1000 $CCID_{50}$ of the virus, as well as containing human albumin (23 mg), lactose (56 mg), and an excipient for freeze drying; vaccine is reconstituted with 0·5 ml of sterile water. Injections were given by the intramuscular route in the deltoid region [22, 23].

Preceding vaccination, and 30 days later, a blood sample was taken to detect rubella virus antibodies in serum. Reactogenicity of the vaccine was established within the 30 days after inoculation. Each vaccine recipient was asked to select from a chart any signs and symptoms occurring 5–18 days after vaccination. A comparison group was formed, consisting of 60 patients with an active rubella infection who had not been vaccinated.

Statistics

Rubella virus antibody HAI titres were expressed as the inverse of dilution, converted to $\log_2 x$ values; the geometric mean titre (GMT) values were then calculated. The significance of between-group differences was determined using the Student's t-test based on the Poisson distribution (with $P < 0{\cdot}05$ taken to be significant) [24].

RESULTS

Epidemiology of clinical rubella (1979–97)

A study of the incidence of rubella from 1979–97 in Perm City, a large, densely populated metropolitan centre, revealed repeating cycles of increased rubella infection, each lasting 3–5 years (data not shown). For each rubella epidemic to appear, the accumulation of enough susceptible persons required an inter-epidemic period of 2–3 years. During these inter-epidemic years, no rubella cases were listed in the registries as occurring among children younger than 24 months of age. When an epidemic cycle began again, however, up to half of the younger children became infected. In rural Perm (i.e. sparsely inhabited regions with a population less than 200000) epidemic peaks persisted for 4–6 years. Inter-epidemic years were characterized by an absence of rubella cases among children between 1 and 9 years of age.

Throughout Perm, the seasons for greatest risk of infection during high-incidence years were the winter and spring (data not shown). The seasonal increase began in January, reaching its maximum in April (when there were about 100 cases per 100000 population), and by June the incidence returned to its initial level. In inter-epidemic years, the infection risk rose during the months of March, April, and May.

A preliminary analysis of the distribution by age of disease incidence suggested that children less than 1 year old infrequently became ill (6·1 per 1000). Closer examination, however, revealed that the risk of infection increased sharply after 5 months of age (7·5 per 1000). In particular, the incidence rate in children aged 6–12 months (6·8 per 1000) was three times greater than in children aged 0–6 months (2·2 per 1000).

The greatest incidence (50·4 per 1000) was in the 2- to 3-year-old age group. Disease activity was particularly marked among children attending pre-school establishments (PSEs). Outbreaks in PSEs occurred repeatedly, with periods persisting for at least 3 years,

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Table 1. *Geometric mean rubella virus antibody titres (GMT) in different social groups within the region of Perm, Russian Federation, 1992*

Group	Percentage with rubella virus antibody titres < 10	GMT $\pm$ S.D.* ($\log_2 x$)	*t*-test value†	Level of significance, *P*
Blood donors‡	10·2	4·49 $\pm$ 0·21	—	—
Pregnant women	16·5	7·13 $\pm$ 0·26	2·42	$< 0{\cdot}05$
Pre-school personnel	17·0	6·76 $\pm$ 0·27	2·00	$< 0{\cdot}05$
Healthcare staff	17·6	6·76 $\pm$ 0·27	2·17	$< 0{\cdot}05$

* S.D., standard deviation of the mean.
† Compared to the control group (blood donors).
‡ Samples were chosen primarily from women, 20–25 years of age.

during which time more than half of any group of children was affected. The overall incidence among those younger than 14 years of age was 12·9 per 1000.

Analysis of the age structure among adults in epidemic years revealed an increased rubella incidence among certain age groups. In particular, women 20–29 years of age showed a 200% increase: from 2·0 per 1000 during inter-epidemic years to 4·0 per 1000 in epidemic years, which was significantly more than the incidence among men during epidemic years (1·0 per 1000) ($P < 0{\cdot}05$). Among all women with clinical rubella, employees in PSEs and paediatric health care facilities represented 60·8% of the cases.

Rubella incidence among pregnant women could be estimated based upon the finding of one pregnant woman with rubella per 1000–1200 cases of rubella.

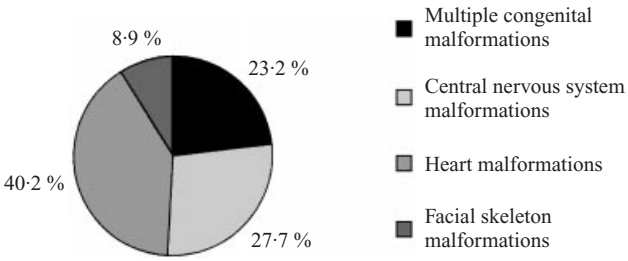

Fig. 1. Distribution of the clinical presentations among 112 infants (0–3 months of age) born with CRS in the region of Perm, Russian Federation (1994–6).

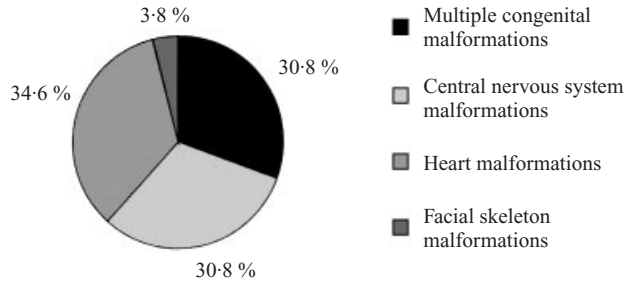

Fig. 2. The mothers identified post-partum as having had serum rubella IgG HAI titres $\geqslant 160$ who had given birth to infants (0 to 3 months of age) with CRS. Distribution of the clinical presentations of their 26 infants.

Seroepidemiology of rubella infection (1992–6)

The results of the seroepidemiological study of rubella immunity in the population, using the HAI assay method, showed that about 70% of young children were susceptible to rubella infection. Rubella virus antibody negativity was observed in 65·6% of children aged 1–3 years, in 48·0% of the 3- to 6-year-old group, and in 10·2% of adults. On the other hand, specific antibodies to rubella virus were found in 77·6% of girls at the age of puberty, which included low titres ($\leqslant 32$) in 5·3%, intermediate titres (64–128) in 14·2%, and high titres ($\geqslant 256$) in 58·1% of these young women.

Overall, 16·5% of pregnant women were rubella virus antibody negative (18·0% at the age of 18–20 years, 3·5% by the age of 35–45 years). Personnel employed at PSEs and at health care facilities also were at notable risk of infection: their level of susceptibility was 17·3% (Table 1).

The number of rubella virus antibody-negative persons (i.e. percentage with an antibody titre < 10) at the beginning of an epidemic of rubella varied from 16·2–20·8%. In an inter-epidemic period, the proportion of rubella virus antibody-negative persons averaged 6·7%, ranging from 3·8–9·7%.

Reinfection among rubella virus antibody-positive persons (i.e. an increase of fourfold or more in the level of specific antibodies) was recorded only in those who had initial antibody titres between 10 and 40; nevertheless, there were no clinical manifestations. Reinfection occurred in 45·6% of pre-school children, in 12·2% of students, and in 6·6% of adults ($t = 10{\cdot}42$, $P < 0{\cdot}001$).

Serological investigations were prompted by rubella outbreaks in organized collectives (e.g. PSEs, schools,

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Table 2. *Systemic adverse reactions reported after administration of a live-attenuated rubella virus vaccine containing the Wistar RA 27/3 M strain [Rudivax™; Aventis Pasteur (formerly, Pasteur Mérieux Connaught), Lyon, France)] to 5025 pre-pubertal girls and women of childbearing age (16–30 years old) who had no history of clinical rubella, observed 5–18 days after immunization, as compared to the symptoms of natural rubella virus infection within a control cohort of 60 patients with acute clinical rubella who had never been vaccinated, in the region of Perm, Russian Federation, 1996*

	Number of reports (%)	
Reactions	Acute clinical rubella	Post-vaccination
Catarrh symptoms	8 (13·3)	704 (14·0)
Asthenia	6 (10·0)	648 (12·9)
Fever ($\leqslant$ 38 °C)	4 (6·7)	352 (7·0)
Lymphadenopathy	3 (5·0)	302 (6·0)
Peptic disorders	2 (3·3)	291 (5·8)
Salivary gland swelling	1 (1·7)	100 (2·0)
Joint pain and swelling	0	100 (2·0)
Insomnia	0	100 (2·0)

boarding schools, or military barracks). In response to one particular rubella outbreak, emergency serological testing of pregnant women revealed a susceptibility rate of 9·6%. Rubella infection was registered in 26·6% of those rubella virus antibody-negative pregnant women who had been in contact with an ill person: manifest forms of the disease in 6·6%, and asymptomatic ones in 20·0%. Among the pregnant women with an initial rubella virus antibody titre $\geqslant$ 10 who had had contact with a person with rubella, reinfection occurred in 6·7% of cases, which was significantly less than the rate of primary infection among rubella virus antibody-negative pregnant women ($t = 6{\cdot}63$, $P < 0{\cdot}001$). The data suggested that an HAI antibody titre $\geqslant$ 10 prevented rubella virus infection in pregnant women. (Of note, no medical abortions resulted from this outbreak, and no instances of CRS were registered following 1 year of surveillance.)

Congenital rubella syndrome (1994–6)

Specific IgM antibodies to rubella virus were detected in cord blood samples of 15·0% (19/126) of newborn infants with congenital malformations consistent with CRS: 8 had multiple defects (6·3%); 5 had heart abnormalities (4·0%); 5 had central nervous system disorders (4·0%); and 1 had defects of the facial skeleton (0·7%). Specific IgM antibodies were not found in the cord blood of healthy children.

Additional blood samples were obtained from 112 infants in the first 3 months of life: 22 of these infants had rubella virus IgG antibody titres $\geqslant$ 160. This included 26·9% of infants with multiple defects (7/26), 22·0% of children with congenital defects of the central nervous system (7/31), 15·6% of children with heart abnormalities (7/45), and 10·0% of children manifesting skeletal defects of the face (1/10) (Fig. 1). In the same group of 112 infants, elevated rubella virus IgG titres ($\geqslant$ 160) were found in the mothers of 26 of these infants: 30·7% (8/26) of the mothers of children with multiple defects; 25·9% (8/31) of mothers of children with congenital defects of the central nervous system; 20·1% (9/45) of mothers of children with defects of the heart; and 10·0% (1/10) of mothers of children with defects of the facial skeleton (Fig. 2). By contrast, only 5·0% of mothers (3/60) who gave birth to healthy children had such elevated antibody titres. The greater frequency of detection of high rubella virus IgG titres in women who gave birth to children with multiple malformations, with defects of the heart, and with defects of the central nervous system, compared to those who bore healthy children, was statistically significant ($t = 4{\cdot}0$; $P < 0{\cdot}001$).

Rubella vaccine immunization (1996)

In 1996, immunization with live-attenuated rubella vaccine was studied in Perm for pre-pubertal girls and

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for women of childbearing age (16–30 years old). Prevaccination and follow-up serum samples of the 5025 vaccine recipients were obtained 30 days after immunization. All rubella virus antibody-negative girls and women (i.e. serum HAI titres < 10) were found to have seroconverted. At day 30, the GMT of rubella HAI antibodies reached 7·50. Among all initially rubella virus antibody-positive girls and women, 15·6% showed a fourfold increase of antibody titres after immunization. In women who had low serum rubella antibody HAI titres ($\leqslant 32$) before receiving vaccine, the GMT increased significantly, from a value of 4·50 before immunization to 5·30 afterwards ($t = 2{\cdot}0$, $P < 0{\cdot}05$). On the other hand, among initially rubella virus antibody-positive subjects who had intermediate or high titres ($\geqslant 64$) before immunization, no significant increases of antibody titres were noted after immunization, with the GMT of 9·20 before vaccination becoming 9·30 subsequently.

No local reactions were observed following vaccination. Generalized reactions, such as catarrh symptoms (e.g. rhinitis, cough, conjunctivitis, and sore throat) were registered in 14·0% of vaccine recipients; a mild fever ($\leqslant 38$ °C) was observed in 7·0% of subjects (Table 2). These signs and symptoms were transitory, and none required special treatment, as has been reported following other investigations with the RA27/3-strain rubella virus vaccines among preadolescent girls [25, 26] or adult men and women [27]. Overall, vaccine-associated reactions and natural rubella infection-related reactions appeared to occur with the same frequency.

DISCUSSION

Accurate clinical diagnosis of rubella is difficult [28]. The presenting maculo-papular rash and fever cannot be distinguished clinically from many other similar exanthematous diseases such as infection by human herpes virus-6 in children between the ages of 5–12 months [29] or human parvovirus B19 infection among older children and adults [30]. This may confound epidemiological investigations [31–33]. Therefore, establishment of a rubella surveillance system in the Perm region of the Russian Federation was based upon serological monitoring of the population, emergency serological testing during outbreaks, and timely identification of rubella infection in pregnant women. Serological monitoring was used to investigate the presence of rubella virus antibodies in various age and social groups in order to appreciate the level of rubella virus circulation in the population. This revealed groups at risk, and territories and periods of time associated with increased incidence, as well as allowing prediction of the course of an epidemic process. This emergency serological testing also disclosed subclinical forms of the infection. Emergency serological testing was carried out for the differential diagnosis of clinical rubella and to evaluate the seroprotective status of persons, particularly pregnant women, who had been in contact with a person with rubella [34]. Considering that 85% of pregnant women with rubella were unaware of the danger this infection posed to their unborn child, pregnant women who had had contact with a person diagnosed with rubella were strongly advised to consult an obstetrics clinic.

The incidence of clinical rubella in a population during an epidemic could be correlated with the rubella virus antibody negativity rate in pregnant women aged 20–25 years (unpublished observations). Therefore, the recommendations that were formulated in Perm were aimed at prevention of CRS: in particular, susceptibility rates over 15% in a population of pregnant women were considered as an unfavourable prognostic sign. Due to the observation that in epidemic years the largest increase in rubella incidence in adults was among women of childbearing age, it was imperative to identify rubella virus antibody-negative pregnant women from within groups particularly at risk of infection, such as medical personnel and the staffs of PSEs and schools. (Although no data were available concerning the percentage of women in the population who work in PSEs and paediatric health care facilities, the fact remains that a large percentage of women who contracted rubella were employed in these institutions.)

A consultative-diagnostic prenatal centre was established in Perm for pregnant women. This centre, the first of its kind in the Russian Federation, provided close interactions between obstetrics clinics, paediatric clinics and State Sanitary services, which also enhanced epidemiological surveillance for CRS.

Perm had an elevated incidence of clinical rubella (220·8 cases per 100000 population versus 200·0 cases per 100000 population for the Russian Federation, overall). CRS accounted for 15% of congenital malformations, and about 3·5 cases of CRS per 1000 live births. Although the birth rate in the Russian Federation is declining, there continues to be a high incidence of rubella and a marked increase in the

number of cases of CRS. The rate of CRS per 1000 live births that was revealed in Perm is among the highest reported in the literature. For example, a recent review prepared for the World Health Organization [35] underscored that the pre-vaccination incidence in industrialized countries fell between 0·1 and 4 cases of CRS per 1000 live births. A forecasted increase from 1998 to 1999 in rubella incidence and in the fraction of rubella virus antibody-negative pregnant women (from 16·2% to 20·8%) made the Perm region an at-risk territory. Providing protection to the foetuses of pregnant women from rubella virus infection could be achieved by a selective vaccination strategy of girls approaching puberty and of women of childbearing age [36, 37]. This initiative would ensure protection of all women of childbearing age [38, 39]. These factors led to the decision to provide selective immunization in this region of Russia for girls approaching puberty and for women of childbearing age.

A level of rubella virus antibody positivity for a population that is above an 85% threshold, as determined by serological monitoring, should provide protection within a given age group [37]. A childhood vaccination strategy would ensure a rapid fall in incidence among the general population, while further reducing the risk that a rubella virus antibody-negative pregnant women becomes infected [37]. As the protective efficacy of the RA27/3-strain rubella virus vaccine during natural epidemics is between 90 and 95% [40, 41], mass immunization ought to begin next among children from 12 months old up until the age of school entry, the population most susceptible to infection.

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