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Prevalence of antibodies against rubella virus in the Netherlands 9 years after changing from selective to mass vaccination

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SUMMARY

A two-dose mass vaccination programme with a combined vaccine against measles, mumps and rubella (MMR) was adopted in the Netherlands in 1987, replacing the selective schoolgirl vaccination strategy introduced in 1974. To obtain insight into the effect of mass vaccination and the population's immunity, the antibody levels against rubella were studied in the general Dutch population and in religious groups refusing vaccination. In the national sample, we observed a high prevalence (96·5%) for rubella antibodies in vaccinated cohorts as well as in the older unvaccinated cohorts. No indications of rapidly waning immunity after vaccination were found. There are indications of low virus circulation in the last few years. The very high seroprevalence in women at childbearing age is consistent with the few reported cases of congenital rubella syndrome (CRS) at present. However, individuals in the age group of 1–9 years who are not vaccinated for religious or other reasons have a considerably lower seroprevalence and thus there is a potential risk of a CRS outbreak in the future.

INTRODUCTION

Selective vaccination offered to girls at the age of 11 years was introduced in the Netherlands in 1974. This strategy attempted to eliminate the risk of rubella infection amongst women of childbearing age only to prevent congenital rubella syndrome (CRS). However, mathematical models showed that a universal two-dose vaccination schedule would be more effective [1, 2]. In contrast to selective vaccination, this strategy might interrupt rubella virus transmission and eventually be more effective in reducing the incidence of CRS. Therefore, since 1987, a combined vaccine of measles, mumps and rubella (MMR) has been given to boys and girls at the age of 14 months and 9 years. A catch-up campaign during the first 3 years with MMR for 4-year-old girls and boys was carried out [3]. For years, the coverage for the MMR at 14 months, as well as at 9 years, has been 94% [3].

Although the success of vaccination is evident from the fact that the number of reports of rubella infections and CRS in the post vaccination era have decreased considerably [4], universal vaccination may cause paradoxical effects in the long term. Due to the decrease in virus circulation, the mean age of infection of those susceptible may increase. If the infection is delayed until childbearing age, this could result in an even higher CRS rate. In the Netherlands, this may particularly be possible for groups who refuse vaccination on religious grounds and who are clustered geographically and sociodemographically. Herd immunity could be inadequate in these communities.

Natural infection by wild virus might induce higher antibody levels and a decrease in these levels seems to be smaller than in vaccine-induced antibody levels

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[5–7]. Therefore, in combination with less natural boostering opportunities due to less virus circulation immunity might not persist life-long [5–7].

To obtain an insight into the population's immunity, the levels of antibodies against rubella were studied in the general Dutch population and in religious groups refusing vaccination.

SUBJECTS AND METHODS

Within each of five geographical regions in the Netherlands with similar population sizes, eight municipalities with a probability proportional to their size were sampled. Within each municipality, an age-stratified sample (0, 1–4, 5–9, to 75–79 years) of 380 individuals was randomly selected. Subjects were requested to give a blood sample, to fill out a questionnaire and to bring their certificates from the national immunization programme (NIP).

Similarly, individuals from eight municipalities with a low vaccine coverage (62–84%) were sampled in order to assess the immunity in geographically clustered orthodox reformed groups that refuse vaccination. The data were collected between October 1995 and December 1996. Details of the study design have been published elsewhere [8, 9].

Serum samples were analysed by a standard ELISA as described earlier [10]. The IgG antibody concentrations were measured against rubella virus (strain HPV77). The mean of two independent, arithmetic measurements with a serum dilution of 1:200 was determined. International unitage was calculated relative to the second International Standard for Antirubella Serum (WHO) for which the four parameter fit method in Kineticalc (KC4) with a BioTek plate reader (EL312e, BioTek Instr., USA) was used.

The results from each plate were accepted if the WHO reference revealed the original amount (1000 IU/ml) in the linear part of the curve $\pm 10\%$, and the two control sera were within their predetermined 95% confidence interval (CI). The minimum level of detection was 1·0 IU/ml. Sera with unitage below this level were not observed. The cut-off value was 10·0 IU/ml in agreement with international standards [11].

The data were analysed in the Statistical Package SAS. A statistical significance level of 5% was used in testing differences between proportions. Seronegative samples were included in the calculation of geometric mean titres (GMTs). The proportions and GMTs were adjusted for the age-stratified sampling and cluster sampling. Therefore, the frequencies and GMTs within each municipality were weighted by the proportion of the age group in the population. The weighted frequencies and GMTs were averaged over the 40 municipalities. For the low vaccine coverage sample, frequencies and GMTs weighted proportionally to the age distribution in the municipality were averaged and weighted by the population size of the municipality [8].

RESULTS

Response

The participation rates for blood sampling and questionnaire data amounted to 55% and 53% in the national sample and the low vaccine coverage municipalities respectively. This rate is unknown for the orthodox reformed group within these municipalities, since we did not have data on religion for non-participants. Data on age, gender, marital status, kind of reminder (by telephone, by mail or otherwise), nationality, region and degree of urbanization of the municipality were available for all participants and non-participants. In our non-response study, an association with non-participation was found for these variables. However, adjusting for participation rate, the effect on the overall estimates on seroprevalence of rubella was less than one standard error in both samples (data not shown). Therefore, no correction was performed in our analyses.

For the subgroup of non-participants who had filled out a questionnaire, data on religion and on participation in the NIP were available. Within the age group 1–19 years (the age group roughly eligible for general vaccination) 97% of the participants in the national sample reported to have participated in the NIP in comparison with 93% of the non-participants who filled out a questionnaire. For the same age group of orthodox reformed individuals within the low vaccine coverage sample these figures amounted to 44% and 27%. As this information was not available for non-participants who did not fill out a questionnaire the effect on seroprevalence estimates is unknown, and no correction could be carried out.

National sample

The overall seroprevalence of antibodies against rubella in the national sample was 96·5%, and the

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Table 1. *Rubella seroprevalence and geometric mean titres (GMTs) in the general Dutch population and among orthodox reformed in the low immunisation coverage sample; 95% confidence interval is shown in parentheses*

	Number	Seroprevalence (%)	GMT (IU/ml)
National sample			
Overall	8295	96·5 (96·1–96·9)	67·7 (64·3–71·4)
Men	3916	95·9 (95·0–96·8)	64·1 (59·6–68·9)
Women	4379	96·8 (96·2–97·4)	67·7 (63·4–72·3)
Orthodox Reformed			
Overall	255	91·4 (85·6–97·2)	70·6 (55·2–90·4)
Men	128	85·3 (73·9–96·8)	56·2 (34·4–91·8)
Women	127	94·0 (89·1–99·0)	73·3 (62·4–86·0)

overall GMT was 67·7 IU/ml (Table 1). There were no significant differences between the sexes. The age-specific seroprevalence and GMT in the national sample are shown in Figure 1*a* and 1*b*. A decrease in the GMT was observed after birth, and after the first 2 months of life the seroprevalence declined sharply from 27·7 IU/ml (95% CI 22·1–34·7) to 4·0 IU/ml (95% CI 3·0–5·3). The seroprevalence increased after the first vaccination (at 14 months) and was over 95% from 17 months of age onwards in both boys and girls. The seroprevalence remained at this level in all the age groups studied except for girls at the age of 22 months and 7 years, at which ages a statistically non-significant dip in the seroprevalence was observed. A significant decline in GMT (from 75 to 30 IU/ml) for 2–8-year-olds was noticed. The seroprevalence showed a small, statistically non-significant elevation in seroprevalence after 9 years of age, the age at which a second vaccination is offered, whereas the GMT showed a statistically significant rise up to the age group of 15 to 19-year-olds (110 IU/ml). Thereafter, the GMT declines slightly to a non-significant lower level of about 70–90 IU/ml and is sustained to very great ages.

Men of 19–34 years who had never been vaccinated, were compared with women in this age group who were eligible for selective vaccination (Fig. 1*a*). The women had a slightly, but not significantly, greater seroprevalence (96·8%; 95% CI 95·2–98·3) than the men (94·1%; 95% CI 92·1–96·1). The GMT in the age group 19–29 years was similar for men and women. In the age group 30–79 years, men had a significantly higher GMT than women (86·7 IU/ml; 95% CI 82·1–91·5 and 73·0 IU/ml; 95% CI 69·0–77·2 respectively), whereas in the 40 to 79-year-old group the seroprevalence also was slightly, but statistically significant, greater for men (99·7%; 95% CI 99·4–100·0 and 98·3%; 95% CI 98·3–98·4 respectively).

The seroprevalence of women at childbearing age (15–45 years) was 97·9% (95% CI 96·9–98·8).

Low vaccine coverage sample

The small difference in seroprevalence between the low vaccine coverage sample (95·0%) and the national sample (96·5%) could be ascribed entirely to the orthodox reformed individuals within the low vaccine coverage sample (Table 1). Therefore, only age-specific results of these orthodox reformed individuals are presented. The overall seroprevalence and GMT within this group were 91·4% and 70·7 IU/ml, respectively, and not significantly different from the national sample estimates (Table 1).

The seroprevalence and GMT for the age group of 1–4 years were significantly lower than those in the national sample. This was also true for the 5–9-year-old orthodox reformed group but this was not statistically significant (Fig. 2*a*, *b*). There was no statistical difference in seroprevalence and GMT for the older age groups compared with the national sample. The seroprevalence of the orthodox reformed women at childbearing age (15–45 years) was 98·9% (95% CI 93·8–100·0).

DISCUSSION

The high seroprevalence in our nation-wide study (above 95%) indicates a high level of protection against rubella in the Dutch population [5, 12, 13]. No effect of socio-demographic variables on the overall seroprevalence was observed in spite of their association with non-participation in both samples.

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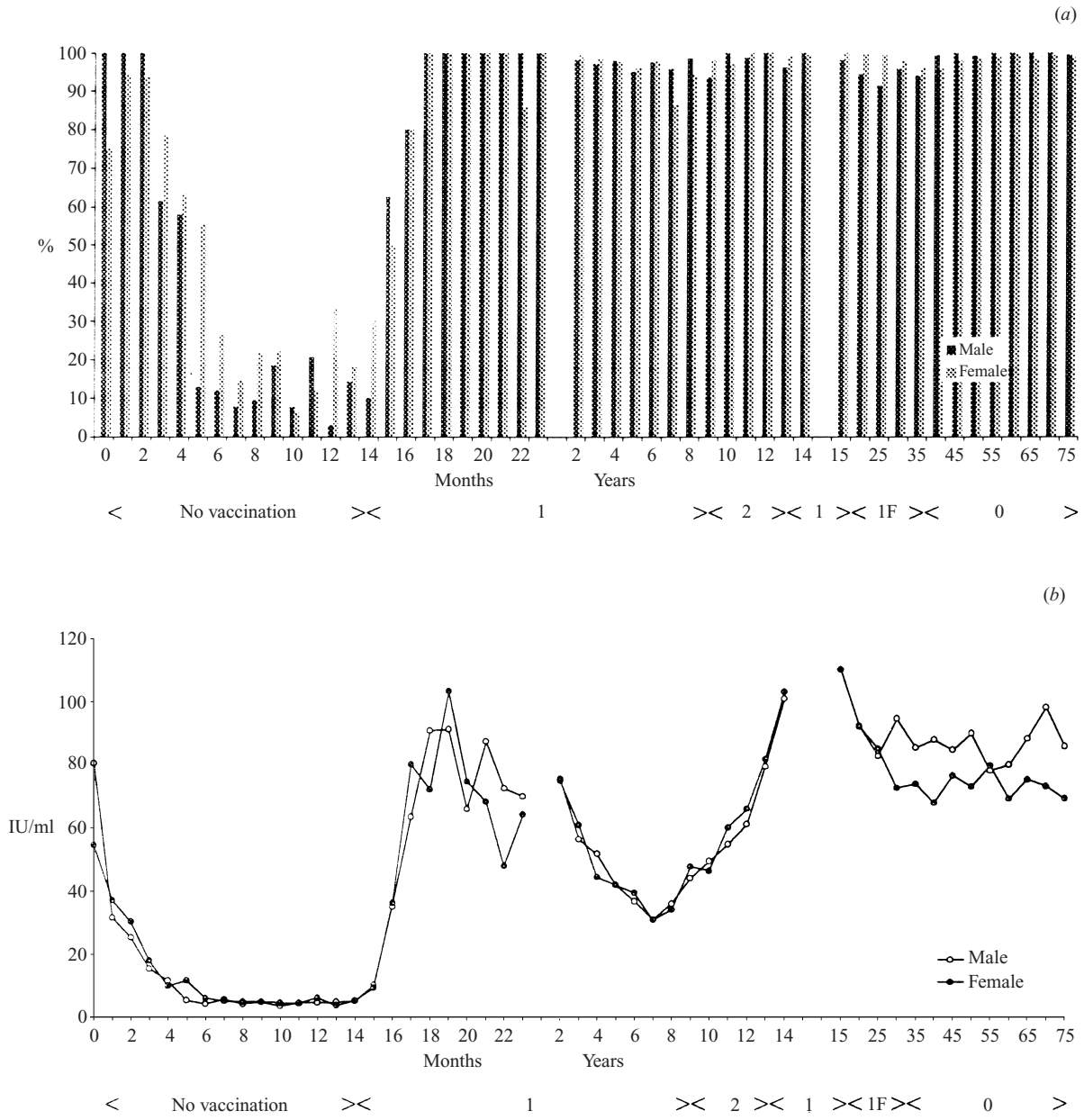

Fig. 1. Age-specific rubella seroprevalence (*a*) and geometric mean titres (*b*) in the national sample amongst 0–79-year-old men and women (age in months for those less than 2 years of age, in years for those aged 2–14 years and in age classes for 15–19, 20–24 to 75–79 years). The number of doses of rubella vaccine offered through the routine vaccination programme is given; 1F is one dose for females only.

Vaccination status may also be expected to play a role in response but could not be corrected for because we did not have information on this for all non-participants. However, given the small difference in self-reported participation in the NIP between 1 to 19-year-old participants and non-participants with a questionnaire (97 and 93%) within the national sample, and the vaccination coverage for MMR in our country (94%), we do not expect a considerable effect on national seroprevalence estimates. The orthodox reformed non-participants who had filled out a questionnaire reported less frequently to have participated in the NIP than participants of this religious group (44 and 27%). As no information on religion was available for non-participants who did not fill out a questionnaire, the true non-participation bias is unknown. Thus, the estimated seroprevalence and GMT may not reflect the true values in this religious group, and these data must be interpreted with caution.

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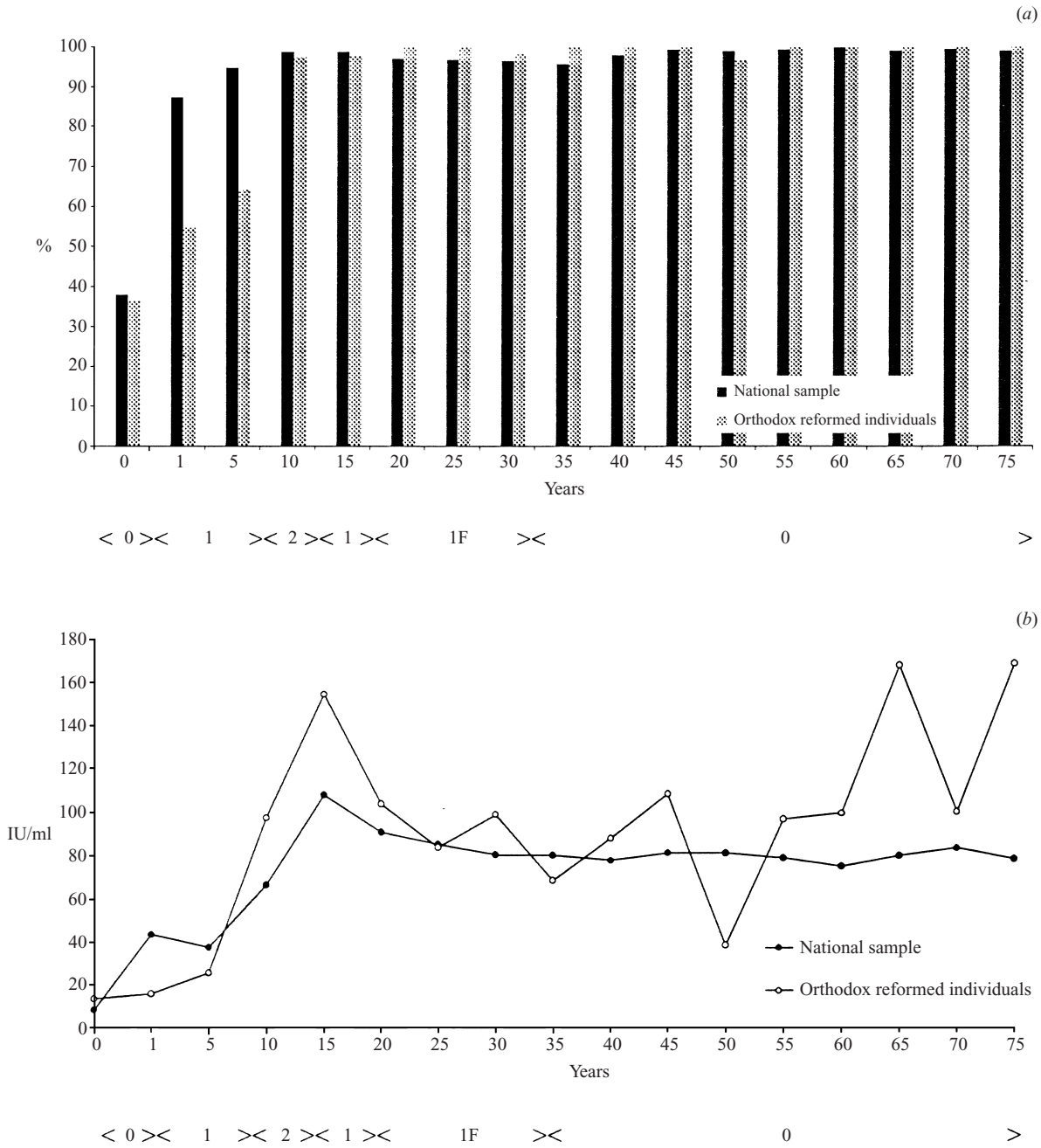

Fig. 2. Age-specific rubella seroprevalence (*a*) and geometric mean titres (*b*) in the national sample compared with the orthodox reformed individuals in the low vaccine coverage sample. The number of doses of rubella vaccine offered through the routine vaccination programme is given; 1F is one dose for females only.

Amongst orthodox reformed individuals, who are socio-geographically clustered in the Netherlands, a gap in immunity was observed for 1 to 9-year-olds (children born after the introduction of general vaccination). Their seroprevalence resembled that in young individuals before the introduction of mass vaccination in other West European countries [21–23, 27]. However, the GMT in this group was lower than that of young individuals in the pre-vaccination era. This indicates that some of the young orthodox reformed subjects have vaccine-induced immunity rather than naturally acquired immunity, which is consistent with their self-reported participation in the NIP.

The gap in immunity in the young orthodox reformed population may pose a threat for the future. The clustering of susceptible individuals can lead to transmission of the rubella virus once it is introduced

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into this population because of insufficient herd immunity. This could result in an increase of cases of rubella and, more importantly, CRS. This scenario was observed in a largely unimmunized Amish community in the United States, in which 20% of the women at childbearing age were susceptible. A rubella outbreak in 1991 led to a high rate of CRS (22 reported cases compared to 6 reported cases between 1970 and 1991) in this community [14].

The seroprevalence in women at childbearing age was above 97% both in the general population and in orthodox reformed individuals. Nevertheless, extrapolation shows that approx. 73500 women at childbearing age (2·1% of 3500000 women aged 15–45 years in the Netherlands) may be expected to be susceptible to rubella infection although most of them are probably protected by herd immunity. This is consistent with the few reports of rubella infections and CRS in recent years [4].

The risk of reinfection and CRS for seropositive women is very small, no matter whether rubella antibodies are naturally acquired [15, 16] or vaccine-induced [6, 15–20]. In 1996, only 5% of the reported rubella patients in the Netherlands had been vaccinated, and they may represent primary or secondary vaccine failures [4].

It should be noticed that this is not a longitudinal, but a cross-sectional study: not only effects of aging, but also cohort effects are observed. Because the two-dose vaccination schedule was implemented in 1987, only individuals up to the age of 8 years may reflect the effects of this adaptation of the vaccination policy in 1987.

A high seroprevalence and GMT are observed after the first vaccination. The GMT decreased in the years after the first vaccination for both men and women. This is consistent with other reports [7, 21, 22]. An explanation could be a lack of boosting of immunity owing to limited virus circulation in the last few years. This is in accordence with the low number of reports of rubella and CRS [4]. Because of the short time after the introduction of universal vaccination in the Netherlands, the time window was too small to study the persistence of rubella antibodies for a longer period of time. Seroprevalences of 95–98% 11–17 years and of 85% 23 years after a one-dose vaccination have been reported in the literature [5, 23–25].

The age group to whom two vaccinations were offered (9–13-year-olds) showed higher GMT than the 8-year-olds. However, the GMT did not reach the high levels obtained after the first vaccination (18–23-month-olds) or after natural infection (35–79-year-olds). This is consistent with observations in the literature that the second vaccination particularly improves the antibody level of those with low levels of vaccine-induced antibodies and primary vaccine failure [23, 24, 26].

The seroprevalence in the cohort with two vaccinations (9–13-year-old individuals) and the cohort with one vaccination (14–18-year-olds) was over 95%. For the cohort eligible for two vaccinations this may probably be explained by the slight over-representation of vaccinated individuals. Individuals aged 14–18 years were offered their first vaccination at the age of 9 years. However, the increase in the GMT with age in this group probably indicates a greater chance of natural infection before vaccination, particularly if they were born longer before 1987 (the force of infection was probably higher in the 1980s than in the 1990s).

The decreasing seroprevalence and level of GMT in young infants in the first few months of life is ascribed to loss of maternal antibodies (passive immunity). No information on the vaccination history of their mothers was available but it seems probable that most mothers were in the age group vaccinated at the age of 11 years and that they therefore had a mixed natural and vaccine-induced immunity. Possibly children of mothers with only vaccine-induced immunity will have a shorter duration and a lower level of maternal antibodies. Whether such an effect is present cannot be studied for years, since the first children born of mothers raised in the mass vaccination era are not expected to be born before at least 2003, when the oldest of this group will reach the age of 15 years.

The seroprevalence amongst women 20–34 years old was slightly, but not significantly, greater than amongst men. This is consistent with the history of selective vaccination of women aged 19–33 years. However, mathematical models indicate that if there was neither wild virus circulation, nor subclinical reinfection of vaccinated individuals nor import of virus, the difference in seroprevalence between men and women in this age group would have been larger than we observed [28]. According to the seroprevalence, fewer men than women in the group aged 20–34 years are immune to rubella. Nonetheless, the level of the GMT for this age group is higher for men than for women. The group of women aged 20–34 years who were offered vaccination at the age of 11 years had mixed natural and vaccine-induced immunity. Men of the same age only have naturally

acquired immunity which could explain their higher GMT.

The GMT and seroprevalence in the older female age group was lower than in the male group. Some of the women aged 34–60 years could have been vaccinated in anticipation of a future pregnancy but this probably does not sufficiently account for the difference, since most adult women are expected to have been immune. Another explanation for the higher GMT in men 20 years and older could be a greater immune response in males to rubella virus infection, but so far this has not been reported in the literature.

In conclusion, we observed a high seroprevalence for rubella in vaccinated cohorts, as well as in the older unvaccinated cohorts. No indication of rapidly waning immunity after vaccination was found. There are indications of low virus circulation in the last few years. The very high seroprevalence in women at childbearing age is consistent with the few reported CRS cases at present. However, individuals in the age group of 1–9 years who are not vaccinated for religious or other reasons seem to have a considerably lower seroprevalence, and thus there is a potential risk of a CRS outbreak in the future. In the coming years, serosurveillance studies should focus on high-risk populations such as young individuals who are unvaccinated because of religious objections.

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