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Seroprevalence of rubella antibodies in The Netherlands after 32 years of high vaccination coverage

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ABSTRACT

Here we present rubella virus specific antibody levels in a large cross-sectional population-based serosurveillance study performed in The Netherlands in 2006/2007.

In the nationwide sample, seroprevalence was high (95%). Higher levels of rubella specific antibodies were observed in the naturally infected cohorts compared with the vaccinated cohorts. After both vaccinations, the geometric mean concentration of rubella specific antibodies remained well above the protective level. However, antibody concentrations decreased faster after one than after two vaccinations. Infants too young to be vaccinated were a risk group in the nationwide sample. In the orthodox protestant group, individuals younger than 6 years of age were at risk for an infection with rubella, consistent with a small local outbreak that recently occurred at an orthodox protestant primary school.

The general Dutch population is well protected against an infection with rubella virus. However, monitoring the rubella specific seroprevalence remains an important surveillance tool to assess possible groups at risk.

1. Introduction

Rubella is a generally mild disease during childhood. However, infection in early pregnancy can result in fetal growth retardation, abortion, and congenital rubella syndrome (CRS). Infants with CRS may have sensi-neural deafness, mental retardation, heart defects or ocular abnormalities [1].

Between 1974 and 1987, 11-year-old girls in The Netherlands were offered a single dose of rubella vaccine to prevent CRS. In 1987, a combined measles, mumps and rubella (MMR) vaccination was implemented in the national immunization program (NIP) [2,3], with a catch-up campaign targeting the 1983–1985 birth cohorts [4]. Since 1987 MMR-vaccination coverage has been high. In 2012 a coverage of 96% and 93% was reported for, respectively, both vaccine administrations at 14 months and 9 years of age [5] thus exceeding the herd immunity threshold of minimal 85% necessary to prevent transmission of rubella [6].

The most recent rubella epidemic occurred in 2004–2005 among a subgroup of the population with low vaccination coverage (LVC). A total of 387 cases were reported, which is presumably a vast underestimation of the real incidence of infection, since rubella virus infection is often asymptomatic and at the time of the outbreak only laboratory confirmed rubella virus infections were notifiable. Rubella in pregnancy among those cases resulted in 2 fetal deaths and 14 children with congenital infection [7]. In the LVC communities up to 40% of the inhabitants, the strictly orthodox protestant group, refuse MMR vaccination due to religious reasons. This orthodox protestant minority consists of about 213,000 persons, which is about 1.3% of the Dutch population. About 75% of this strict religious group lives in a geographically clustered area often referred to as the "bible belt" region [8]. The epidemic demonstrates that high vaccination coverage in all regions is important to contain incident cases and to prevent transmission of rubella virus.

To monitor protection against vaccine preventable diseases included in the Dutch NIP, large cross-sectional population-based serosurveillance studies have been performed in 1995/1996 and in 2006/2007 (the Pienter1 and Pienter2 study, respectively) [9,10]. Two large serum banks representative for the Dutch population were assembled.

Here we present the sero-epidemiological analyses of rubella specific IgG antibody levels assessed in the Pienter2 study for both the general Dutch population and the population living in LVC areas. Results are compared with those obtained 11 years ago in the Pienter1 study and are discussed in view of the potential for future epidemics.

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2. Materials and methods

2.1. Study population

A cross-sectional population-based serosurveillance study, which was approved by the local ethics committee, was carried out in The Netherlands between February 2006 and June 2007 (ISRCTN 20164309). This so called Pienter2 study had a similar design as a previous study performed in 1995–1996 [9–11]. The Netherlands were divided into five geographical regions of approximately equal population size. Within those five regions, eight municipalities were randomly selected with a probability proportional to their size. From the 40 municipalities an age-stratified sample of 380 individuals was drawn from the population register. A total of 6383 samples were available from the nationwide sample and 1517 samples from the LVC sample. Participants signed an informed consent prior to participation and donated a blood sample. In addition they were asked to fill in a questionnaire at home and to bring their vaccination certificates. Demographic data were available from all invited individuals. Vaccination history was confirmed for 80% of the total number of participants eligible for the NIP.

2.2. Laboratory methods

Serum samples were stored at −80 °C until use. From each sample, 5 μl serum was used to determine the IgG antibody concentration against the rubella HPV-77 strain [GenWay, San Diego, CA]. The fluorescent bead-based multiplex immunoassay (MIA) using Luminex technology was performed as described before [12]. Briefly, serum samples were diluted 1/200 and 1/4000 in phosphate buffered saline containing 0.1% Tween 20 and 3% bovine serum albumin. The international rubella standard (RUBI-1-94), controls and blanks were included on each plate. Antibody concentrations were obtained by interpolation of the mean fluorescent intensity (MFI) in the reference curve using a logistic-5PL regression type and expressed in international units per ml (IU/ml). An antibody concentration of ≥10 IU/ml was considered protective and was used as cut-off for the calculation of the seroprevalence [13]. For a proper comparison between the Pienter1 (measured with ELISA) and Pienter2 study (measured with the MIA), antibody concentrations below 3 IU/ml were set at 1.5 IU/ml due to the difference in lower limit of quantitation (LLOQ) between the MIA and ELISA (0.004 and 3 IU/ml, respectively) [12].

2.3. Data analysis

2.3.1. Seroprevalence and GMC

Data were analyzed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) and R [14]. The study design was taken into account for all analysis. Seroprevalence and geometric mean concentrations (GMC) in the nationwide sample were estimated by weighting age, gender, ethnicity and degree of urbanization. This was done to match the Dutch population distribution as to that of the 1st of January 2007. Seroprevalence and GMCs in the LVC sample were weighted by age and gender. Denominations in the LVC sample were classified into two groups based on vaccination coverage defined by Ruijs et al. [8]. The first group consisted of the orthodox protestant individuals and the second of the non-orthodox protestant individuals.

Differences in seroprevalence between years or age groups were determined by first estimating the parameters of the beta distribution for both seroprevalences using the method of moments [15]. Next, the risk ratios, their corresponding 95% confidence intervals, and p-values were estimated by Monte Carlo simulations of both seroprevalences. Differences in the GMC between years or age groups were identified by calculating differences in to natural log converted concentrations and tested by using the t-test. p-values of <0.05 were considered statistically significant.

2.3.2. Waning immunity in the nationwide sample

We performed linear regression analyses of natural log transformed antibody concentrations to study rubella concentrations by time since MMR vaccination in our cross-sectional sample. Persistence of rubella ln IgG antibody concentrations after the first MMR vaccination was studied in participants of Dutch origin, 2–8 years of age who had received one MMR vaccination at the age of 13–16 months. Persistence of rubella ln IgG antibody concentrations after the second MMR vaccination was studied in participants of Dutch origin, 9–20 years of age who had received their MMR vaccinations at the age of 13–16 months and at 8 or 9 years of age, respectively.

2.3.3. Risk factors in the nationwide sample

We used logistic regression to study risk factors for rubella susceptibility among individuals in the nationwide sample. The following determinants were studied: age, gender, ethnicity, degree of urbanization and the number of rubella vaccinations. Backward selection was used to identify determinants of rubella susceptibility. A determinant remained in the model if the p-value was <0.1. The crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

3. Results

3.1. GMCs in the nationwide sample

The overall GMC in the nationwide sample was 67 IU/ml (95% CI: 65–70) (Fig. 1), with a GMC of 66 IU/ml (95% CI: 62–70) and 69 IU/ml (95% CI: 66–72) for males and females, respectively. After 3 months of age, maternal antibody levels rapidly declined to 1.1 and 0.3 IU/ml in the 6–9 and 10–13 months cohort, respectively. A clear rise in GMC to 108 IU/ml (95% CI: 71–163) in the age group of 17–23 months was induced by the first vaccination at the age of 14 months. Thereafter GMC decreased to 36 IU/ml (95% CI: 29–47) in the 5 years age cohort and remained stable until the age of 8 years. The second vaccination induced a small increase in GMC to 58 IU/ml (95% CI: 48–70) in the 9 years age cohort, followed by an almost steady level of 40 IU/ml up to 20 years of age. From the age of 21–23 years onwards, in the not (fully) vaccinated cohorts, GMC increased and fluctuated thereafter around 90 IU/ml.

3.2. Seroprevalence in the nationwide sample

The overall seroprevalence in the nationwide sample was 95% (95% CI: 94–96) (Fig. 1). In the first three months of life, seroprevalence was just below 80% and decreased to very low levels of 21% and 2% in the 4–5 and 6–9 months age groups, respectively. Seroprevalence in the 10–13 months age group increased to 6% due to early vaccinated children. After as well the first as the second vaccination, seroprevalence in the age cohorts of 10 year and older remained above the herd immunity threshold of 85%. Importantly, women in childbearing age had a seroprevalence level >95%. A significantly higher seroprevalence was observed in females compared to males born in 1975–1976 ($p = 0.005$), just after introduction of rubella vaccination for 11 year-old girls.