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ORIGINAL INVESTIGATION

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Antibodies against vaccine-preventable diseases in pregnant women and their offspring in the eastern part of Germany

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Abstract Maternal and cord blood samples of 290 pregnant women in the eastern part of Germany with a mean age of 28 years (16–41 years) were analyzed for antibodies to vaccine-preventable diseases. Both mothers and infants had detectable levels of antibodies to mumps in 96% and to tetanus in 93% of cases. Detectable levels to poliomyelitis, diphtheria, measles and rubella varied from 55% to 91%. Cord blood samples had a significantly higher prevalence of antibodies to pertussis (61%) and diphtheria (81%) in comparison to maternal samples (pertussis 37%, diphtheria 70%) as well as significantly enhanced antibody concentrations to diphtheria. In conclusion, the prevalence of antibodies to pertussis (61%), diphtheria (81%), poliomyelitis (55–59%) and measles (85%) is suggested to be insufficient in newborn infants to protect them against these infectious diseases.

Keywords Vaccination antibodies · Pregnant women · Cord blood · Maternal antibodies · Placental antibody transfer

Introduction

Vaccinations are one of the most important and effective preventative measures for the protection against infectious diseases and their complications. They provide individual protection, interrupt chains of infections, and can lead to world-wide eradication of infectious diseases [5]. Serious side-effects of active immunizations are rare. The high benefit-cost ratio of immunizations reduces public health costs.

The world-wide revival of infectious diseases, the increasing ease of travel and population migration, and concerns about insufficient herd immunity have lead to intense discussions about vaccination programs in Germany. The population of the former East Germany had high immunity levels to vaccine-preventable diseases as the consequence of strict immunization measures during childhood and adolescence. Since re-unification of Germany in 1990 the immunization rate to, for example, measles has declined [12].

Immunity acquired by vaccination or natural infection not only protects pregnant women and their fetuses against serious infections, but also their newborn infants for the first months of life [13]. The age of primigravida has increased from the end of the second decade to the second half of the third decade in the eastern part of Germany since 1990. As immunity wanes with time, the question arises as to whether today's elderly primigravidae and their offspring are less well protected from vaccine-preventable diseases.

The objective of the present study was to examine the prevalence and concentrations of antibodies to vaccine-preventable diseases in pregnant women of the former East Germany. The findings are compared with their vaccination history and the newborn infant's antibody levels.

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Materials and methods

Patients and serum samples

Healthy unselected women ($n = 290$) aged 16–41 years (mean 28 years) who delivered at the District Hospital Rudolstadt, Germany, consecutively between 1995 and 1996 and their newborn infants were enrolled. Of the infants, 254 (87.6%) were delivered

spontaneously, 20 (6.9%) by vacuum extraction, and 16 (5.5%) by cesarean section at a gestational age of 34–42 weeks (median 41 weeks). All women grew up in the German Democratic Republic (GDR) and were vaccinated according to the legally binding vaccination guidelines. The vaccination records in the Central Vaccination Archives of the district of Rudolstadt were checked for determination of immunization history against tetanus, diphtheria, pertussis, measles, mumps, rubella, or poliomyelitis.

Sera were stored at –20°C until investigated. IgG class antibodies to tetanus toxin, diphtheria toxin, *Bordetella pertussis*, measles virus, mumps virus, rubella virus, and polioviruses serotypes 1–3 were quantitatively measured in the paired samples from mother and child.

Serological testing

IgG class antibodies to tetanus toxin, diphtheria toxin, and *B. pertussis* were detected using the commercially available SERION ELISA classic (Virion Serion, Germany). As *B. pertussis* antigen, highly purified acellular components of pertussis toxin and filamentous hemagglutinin were used. The tests were performed manually as directed by the manufacturer's protocol and evaluated automatically using SERION easy base 4PL software. Tetanus and diphtheria antitoxin levels were expressed in international units (IU) and were classified according to the international standards [29]. Concentrations of >0.1 IU/ml indicated full protection. Results of pertussis ELISA were expressed in Food Drug Administration Units (FDA U). Here, antibody levels of >30 FDA U/ml are referred to as pertussis antibody positive. The methods applied in the present study can be regarded as internationally accepted assays for immunological proof of immunity to tetanus [29] and diphtheria [32]. The ELISA technique has also been used in several seroepidemiological studies of *B. pertussis* [9]. However, antibordetella antibodies can not to be considered a protective correlate for pertussis. All assays were validated by testing control sera corresponding World Health Organization (WHO) and FDA standards, respectively.

In-house indirect immunofluorescence tests were used to measure IgG to mumps and measles. Vero cells infected with measles virus (prototype strain Schwarz) or mumps virus (prototype strain Jeryl Lynn) were prepared on microscopic glass slides as antigens. Titers greater than or equal to 1:10 were considered positive. The assays were validated by testing control sera of the Institute for Standardization and Documentation in Medical Laboratory (INSTAND), Düsseldorf, Germany.

Rubella virus-specific IgG was quantitatively analyzed using the microparticle enzyme immunoassay IMx Rubella IgG 2.0 (Abbott, Germany) registered by the Paul-Ehrlich Institute, Langen, Germany. The test was performed automatically using the IMx analyzer with the IMx system modules version 6.0 and version congenital diagnostics 7.0 as software. Results were expressed in Center for Disease Control and Prevention units (CDC U). According to the manufacturer's recommendations concentrations of >10 CDC U/ml were referred to as rubella IgG positive; 2 CDC U correspond to approximately 1 WHO U and >15 WHO U/ml indicate full protection against rubella. The assay was calibrated using the international WHO standard.

Polio virus-specific IgG class antibodies were measured by quantitative microneutralization assay using standardized technique [38]. The prototype strains Sabin of the poliovirus serotypes 1–3 were propagated in HEp-2 cells. These cells were maintained in a mixed culture medium consisting of 50% lactalbumin hydrolysate and 50% Leibovitz's L15 medium supplemented with 2 mM L-glutamine, 10% fetal calf serum, 100,000 IU/l penicillin and 0.1 g/l streptomycin sulfate. Virus-specific antibodies of 50 µl serum diluted from 1:5 to 1:640 were neutralized with 50 µl 10^2 $TCID_{50}$ (tissue culture infective dose 50%) per 100 µl of poliovirus at 36°C for 1 h. The mixture was incubated on HEp-2 cell monolayers for 5 days. Each serum dilution was tested eight times. The neutralizing antibody titer corresponded to the highest serum dilution showing a complete inhibition of the cytopathic effect. Serum samples were considered positive if neutralizing antibodies were present with titers of 1:10 and above [33].

Statistical analysis

Relative frequencies were computed within both groups of mothers and newborns as number of vaccinated or seropositive cases divided by the number of patients enrolled. Differences between immunization history and seroprevalence were analyzed by means of the Yates chi-square test. Antibody prevalences and mean antibody concentrations were compared using the Fisher's exact test and the Student's *t*-test, respectively. Correlations between antibody concentrations and factors such as maternal age, gestational age, and mode of delivery were studied using the Kruskal-Wallis test. *P* values were subject to a significance level of 5%.

Results

Based on documented data on vaccination history, immunity to mumps and rubella had to be expected in about 30% and 38% of the pregnant women enrolled (Table 1), whereas the vaccination rate to tetanus, diphtheria, pertussis, measles, and polio was estimated as 82–85%. For all diseases, apart from measles, the number of mothers with detectable antibody levels was significantly at variance from their vaccination history. There were more mothers with antibodies than expected for mumps, rubella, and tetanus toxin and fewer than expected for *Bordetella pertussis*, polioviruses, and diphtheria toxin.

Comparing the seroprevalences in mothers with that of their offspring no significant differences were found

Table 1 Vaccination history in comparison to prevalence of antibodies to tetanus, diphtheria, pertussis, mumps, measles, rubella, and poliomyelitis in pregnant women ($n = 290$)

Infectious agent/toxin	Vaccination history		IgG-positive pregnant women		Statistical analysis
	n	%	n	%	
Tetanus toxin	245	84.5	269	92.8	Significance
Diphtheria toxin	244	84.1	203	70.0	Significance
Bordetella pertussis	245	84.5	107	36.9	Significance
Mumps virus	86	29.7	279	96.2	Significance
Measles virus	237	81.7	230	79.3	No significance
Rubella virus	109	37.6	251	86.6	Significance
Poliovirus type 1	245	84.5	181	62.4	Significance
Poliovirus type 2	245	84.5	186	64.1	Significance
Poliovirus type 3	245	84.5	185	63.8	Significance

for tetanus toxin, mumps, measles, rubella, and polio (Table 2). In contrast, IgG class antibodies to diphtheria toxin and *B. pertussis* were detected more frequently in the umbilical cord blood than in maternal samples. Antibody concentrations to diphtheria toxin were significantly enhanced in newborn infants if compared with their mothers (Table 3). The highest antibody concentrations, 11- to 17-fold above the positive cut-off of the assays used, were measured for tetanus antitoxin as well as IgG to rubella in both maternal and neonatal sera. Diphtheria toxin and *B. pertussis* antibodies were measured 3- and 5-fold, respectively, above the cut-off values, while antibody titers to mumps, measles, and polioviruses were on average 2-fold above the detectable levels.

Antibody concentrations against measles in cord blood sera were found to increase significantly with maternal age. There was also a significant correlation between gestational age and concentrations of *B. pertussis* antibodies in cord blood. The mode of delivery had no effect on antibody concentrations of the newborns.

Discussion

This study shows that a vaccination uptake of more than 90% in the former East Germany led to protective immunity against tetanus in pregnant women and their offspring. Neonatal tetanus, a feared disease, has nearly disappeared in Germany. Among women without a documented vaccination history more than 50% were found to have protective immunity against tetanus (Table 1). These inaccuracies in some cases show carelessness in taking the history of vaccinations and in handling of certificates of vaccinations. Regular booster injections are an important pre-condition for the high protection level against tetanus [28]. Although the vaccination rate in the group of pregnant women was the same for tetanus and diphtheria, the immunity rate to diphtheria was, with 70%, comparatively low. The majority of women had apparently never received a booster dose to diphtheria after completion of the basic block of immunizations. These findings are consistent with studies in Saxony, where 33% of 41–50 years olds have been found to lack protective antibody levels against diphtheria, and in Mecklenburg-Vorpommern where the figure is 52% [15]. To achieve herd immunity, at least 80% of the population should have protective levels of antitoxic antibodies [8]. The STIKO (current vaccination committee) of the Robert Koch Institute in Germany, therefore, recommends a booster vaccination every 10 years throughout life preferably as a combined diphtheria-tetanus vaccine to achieve reliable protection [28]. In view of the increasing risk of importing these diseases from Eastern Europe, there is an urgent need for the existing gaps in the immunity level to be closed.

Newborn infants had a 10% higher protection level to diphtheria and significant higher antibody concentrations than their mothers. A possible explanation is the

Table 2 Prevalence of IgG antibodies against tetanus, diphtheria, pertussis, mumps, measles, rubella, and poliomyelitis in pregnant women and their newborn infants ($n = 290$)

Infectious agent/toxin	IgG-positive pregnant women		IgG-positive newborns		Statistical analysis
	n	%	n	%	
Tetanus toxin	269	92.8	272	93.8	No significance
Diphtheria toxin	203	70.0	234	80.7	Significance
Bordetella pertussis	107	36.9	176	60.7	Significance
Mumps virus	279	96.2	281	96.9	No significance
Measles virus	230	79.3	245	84.5	No significance
Rubella virus	251	86.6	265	91.4	No significance
Poliovirus type 1	181	62.4	158	54.5	No significance
Poliovirus type 2	186	64.1	172	59.3	No significance
Poliovirus type 3	185	63.8	167	57.6	No significance

Table 3 Mean concentrations or titers of antibodies to tetanus, diphtheria, pertussis, mumps, measles, rubella, and poliomyelitis in pregnant women and their newborns ($n = 290$) (*FDA* Food Drug Administration, *CDC* Center for Disease Control and Prevention)

IgG antibodies to:	Mean concentrations or titers		Statistical analysis
	Pregnant women	Newborns	
Tetanus toxin	1.5 IU/ml	1.7 IU/ml	No significance
Diphtheria toxin	0.4 IU/ml	0.6 IU/ml	Significance
Bordetella pertussis	79.2 FDA U/ml	93.2 FDA U/ml	No significance
Mumps virus	1:20	1:21	No significance
Measles virus	1:18	1:19	No significance
Rubella virus	113 CDC U/ml	174 CDC U/ml	No significance
Poliovirus type 1	1:16	1:19	No significance
Poliovirus type 2	1:18	1:20	No significance
Poliovirus type 3	1:19	1:19	No significance

existence of an active placental transfer of maternal IgG during the third trimester of pregnancy [19, 20, 31] first reported by Kohler and Farr [14]. This phenomenon has been described for antibodies to measles, mumps, rubella, and parainfluenza viruses as well as tetanus antitoxin [3, 21, 26, 34]. The results of this study suggest active placental transfer of IgG to diphtheria toxin and *B. pertussis*. The fact that cord blood samples showed a higher prevalence and concentration of all antibodies, with the exception of polioviruses, is in line with this observation (Tables 2, 3). A higher prevalence of antibodies in the cord blood sera can be the consequence of actively transported antibodies if maternal concentrations are below the detectable levels of the methods used. Although a specific receptor-mediated binding of the Fcγ portion of IgG at the maternal surface of the placenta has been proposed [11], the detailed biochemical and biophysical mechanisms of transplacental IgG transport are still unknown.

Routine active immunization against pertussis was already introduced into former East Germany in 1964 [8]. The low antibody prevalence of 37% among pregnant women with an immunization history of about 85% in this study is probably caused by waning humoral immunity over time. In addition, anti-bordetella antibodies do not necessarily correlate with protective immunity to pertussis [16]. Our results suggest that pertussis immunization in early childhood does not protect adults adequately against the disease [22]. Since 1991 there has been a noticeable steady increase in pertussis cases from a considerably lower incidence rate in the eastern part of Germany than in the western part of the country [24]. Despite high immunization levels, an increasing number of pertussis cases has been reported in adolescents and adults in the USA [4] and in Germany [27] for some years. These groups are a significant source of exposure for young children without protection [37]. Consequently, booster immunizations for children and adults using acellular pertussis vaccines which have a lower side-effect risk in comparison to the conventional whole-cell vaccine [36] should be given high priority [18]. Since 2000, the STIKO of the Robert Koch Institute in Germany recommends one booster vaccination with acellular vaccine for infants and adolescents (aged 11–18) with complete basic immunization. The resulting immunity levels would also be of benefit to newborn infants.

The 97% prevalence of detectable antibodies to mumps in both mothers and newborn infants is mainly the result of previous maternal infections. Mumps vaccination was only offered to selected groups of the populations in the former GDR [8]. In contrast, measles immunization was compulsory for children from 1970. Thanks to an immunization level of more than 90%, only 17–199 measles cases per year were recorded between 1986 and 1990 [1]. The antibody prevalence of about 80% in mothers and 85% in neonates found in this study is lower than the 95% reported in adults above 20 years of age in all Germany [12] and the 97% in newborn infants in Switzerland [6]. The lower levels in our study could result from methodological differences. However, measles outbreaks in both children and adults [2] indicate insufficient herd immunity in the eastern part of Germany. Since the measles contagiosity has been calculated to be nearly 100%, a significant reduction of the circulating virus and its transmission can not be achieved unless the herd immunity is 95% or more. The fact that maternal antibody titers increase with age in the present study could be the result of re-expositions to circulating wild virus.

The high seroprevalence of rubella virus is mainly due to natural infection. Of women at the child-bearing age in the Eastern part of Germany 10% were found to be susceptible to rubella in 1990 [25] and this has probably reduced to 0.8–3% up to 1998 [30]. The relatively low rate (38%) of pregnant women with a history of rubella vaccination reflects the fact that in the former GDR, rubella immunization was only offered to seronegative young girls with occupational risk factors. The primary objective of rubella immunization is the prevention of the congenital rubella syndrome (CRS). In Germany, at least 50 live born infants with CRS per year have to be expected [30]. The goal of the WHO to eradicate mumps, measles and congenital rubella in Europe by the year 2000 has not been achieved in Germany. Compared with other European countries, Germany has one of the lowest immunization rates against these three illnesses [23].

Despite a high level of vaccination uptake for poliomyelitis, only 62–64% of pregnant women in this study had detectable antibody levels at the time of delivery. For the interpretation of these findings it has to be considered that the protective level of anti-poliovirus antibodies detected by the neutralization assay is 1:8, whereas we used a cut-off value of 1:10. The prevalence rates found in our study are considerably lower than was reported, with 78–95% in both parts of the re-united Germany in 1993 [7]. In comparison, a limit value of 80% would be necessary to prevent the circulation of a wild-type virus [10]. Generally lower immunity rates against polioviruses have been found in the eastern as opposed to the western part of Germany that reflects the different vaccination policies before 1990 [29]. The pregnant women who grew up in the former GDR and received complete basic immunizations with monovalent and subsequent trivalent oral poliovirus vaccines (OVP) had their last vaccinations 8–33 years ago. To achieve adequate protection, booster vaccinations with inactivated poliovirus vaccine at 10-yearly intervals have been recommended for everybody who is at an increased risk of exposure to poliovirus such as travelers into endemic regions and for health-care workers [28].

The seroprevalence of all three poliovirus serotypes in newborn infants was only a little lower than in their mothers, which is in accordance with previous studies [17]. In contrast, premature infants have been found to have a significantly reduced placental transfer of poliovirus-specific antibodies [17]. The antibody-negative

young babies could be at risk of infection from the wild virus, especially from serotype 1. Immunization with live attenuated OVP has eliminated poliomyelitis caused by wild poliovirus in Germany for about 10 years. This and the risk for vaccine-associated paralytic poliomyelitis (VAPP) led to the introduction of inactivated poliovirus vaccine (IPV) in 1998. Although no autochthonous poliomyelitis case has been reported in the European countries for 2 years since 1999, the severe diseases of paralytic poliomyelitis in newborn infants could occur again because of decreasing vaccination levels and because of the risk of importing the wild virus from South-East Asia and Africa. Few months ago, three polio cases caused by type 1 wild virus imported from India were reported in Bulgaria [39]. Therefore, a monitoring system to immediately identify and respond to any occurrence of polio infection is required in all countries [35].

In summary, pregnant women and their newborn infants in the eastern part of Germany have a high prevalence of antibodies to tetanus and mumps. The antibody prevalence to pertussis, diphtheria, poliomyelitis, and measles is suggested to be not sufficient for an effective protection. Whereas in the case of measles this might be due a low vaccination rate, the observed decreasing antibody prevalence to pertussis, diphtheria, and poliomyelitis may be due to the increasing time interval from the last immunizations. This effect may be relevant for pregnant women who are now older than in the past. Mature newborn infants have enhanced immunity levels as a result of active placental transfer of IgG class antibodies during late pregnancy. Despite high immunity rates to rubella, the risk for CRS is not eliminated. Strict implementation and further improvement of current immunization guidelines are necessary to protect pregnant women and their offspring from serious infectious diseases.

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