

Review article

**Reduced measles and varicella passive immunity and susceptible infants in the 21ST century.
Myth or reality?**

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Abstract

Vaccination against measles has substantially decreased child mortality worldwide. The recent introduction of varicella immunization has significantly reduced the associated disease burden. However, there exists a period of elevated disease susceptibility among infants secondary to the diminishment of maternal passive immunity. This article reviews recent studies on transplacentally transferred antibodies against measles and varicella.

Recent Findings

Both MMR and varicella vaccines are usually administered in children, aged older than 12 months, since it has been established that co-existing maternal antibodies interfere with vaccine immunogenicity. Currently, a notable proportion of infants are susceptible to measles due to the diminishment of transplacentally acquired passive immunity. The most plausible explanations of this phenomenon include the replacement of the reproductive population by vaccinated women, as opposed to those having undergone natural measles infection, and the decrease of natural boosting effect of the wild type virus.

Summary

The window of susceptibility to measles has increased in infants, as it might also happen for varicella in the near future. In order to progress towards the diseases' eradication and, more importantly, to protect those population groups, including young infants, with high morbidity rates attributed to the diseases, it is evident that further investigation will be conducted for the immunization against measles and varicella at an earlier age.

Keywords

Measles; varicella; passive immunity; maternal antibodies; immunization

Introduction

This article reviews the evolution of measles and varicella vaccination policies, the occurrence of a window of susceptibility for infection during late infancy, extending from the loss of passively acquired maternal antibodies through the first dose of recommended vaccination as well as studies about potential solutions to this problem.

Measles

Measles is a highly contagious, acute viral infection caused by measles virus, a negative strand RNA virus in the Morbillivirus genus of the Paramyxoviridae family [1]. It is transmitted by either direct contact or droplet spread [2]. Severe disease complications may occur, including otitis, pneumonia, hepatitis, encephalitis, subacute sclerosing panencephalitis and could potentially be fatal [3].

Globally, due to the implementation of measles vaccination policies, the mortality rate attributed to measles has decreased between 2000 and 2008 by 78%. During 2008, there were 164,000 deaths attributed to measles globally, which account for approximately 450 deaths per day or 18 deaths per hour. More than 95% of measles deaths occur in low-income countries with insufficient health care

infrastructures. During 2008, approximately 83% of the pediatric population globally received one dose of measles vaccine by their first birthday through routine health services, which is observed to be notably increased from the respective rate of 72% during 2000. Approximately 700 million children aged from 9 months to 14 years, residing in high risk countries, were vaccinated from 2000 to 2008 [4].

In most industrialized countries high levels of immunization have been achieved, leading to a marked diminishment of the incidence rate of measles. Routine measles vaccination coverage in Europe and Central Asia has increased to 93%, thus resulting steadily in <1000 deaths per year from 1999 to 2004. During the same period, the most significant reduction in deaths has been observed in the Sub-Saharan African region (from 530.000 to 216.000 deaths per year), which has also been attributed to the increase of measles vaccination coverage (from 49% to 65%) [5]. However, sporadic cases of measles, as well as outbreaks, continue to occur in countries where endemic transmission has been interrupted, depicting the major obstacles to its eradication, phenomena which are directly associated with the effects of globalization, including enhanced travel and migration of population groups [6,7,8]. Although, for instance, measles has been declared eradicated in the US [9], import-associated outbreaks of measles continue to occur sporadically due to the persistence of endemic measles globally and the high volume of

international travel. However, no nation currently requires measles vaccination for travel and US international travel recommendations regarding vaccination depend upon voluntary compliance [10, 11].

Varicella

Varicella is caused by a double-stranded DNA human alpha-herpesvirus, varicella zoster virus (VZV), and primarily occurs during the first decade of life. Most Central and Northern European countries report that >90% of children contract chickenpox before entering adolescence, whereas data from Southern European countries report a slightly lower incidence rate during childhood [12-15].

VZV is transmitted by direct contact from droplet or airborne spread of vesicle fluid or respiratory tract secretions of patients with chickenpox, as well as the vesicle fluid of patients with herpes zoster [16]. Although it is observed to develop as a mild disease in otherwise healthy children, varicella can cause complications in both previously healthy and immunocompromised hosts [17, 18]. Moreover, primary VZV infection in pregnant women prior the 20th week of gestation may develop as severe congenital varicella syndrome [17]. Furthermore, a primary maternal infection may cause severe neonatal varicella [19].

During the 5-year period prior to vaccine licensure in 1995, in the US 4 million cases of chickenpox occurred each year, primarily among children younger than 15 years of age, while 11,000 hospitalizations and an average death rate of 103 children were reported annually [20-25].

In Germany, it was estimated that prior to the implementation of universal vaccination, 739,000 cases of chickenpox, 5740 hospitalizations, and 22 deaths attributed to the disease occurred annually [20,26]. Unfortunately, since in most European countries reporting of varicella is not obligatory, reliable data regarding the incidence rate of varicella is not available.

Vaccines

The measles virus was first isolated in 1954 [1]. Measles vaccination was incorporated in the routine childhood immunization schedule in US and Canada in 1963 and 1965, respectively (Edmonston B strain) [27, 28]. One of the initial vaccines was a formalin-inactivated vaccine that provided only short-term immunity and primed the recipient for a more severe disease, atypical measles. When this vaccine was withdrawn, a live attenuated vaccine (LAV) was developed by passage of the original isolate of Edmonston virus through cell culture, primarily in chicken cells. Further passage of the Edmonston virus resulted in further viral attenuation and the well-tolerated vaccines is commonly used to date [1]. The combined live attenuated measles-mumps-rubella vaccine (MMR), administered at 12 months of age, was introduced in the U.S.A. in 1982 [28]. In Europe, the MMR was introduced in 1988 and has been included ever since in WHO's Expanded Program on Immunization [29]. Currently, in European countries the first dose of the MMR is administered between 12-18 months of age. In certain countries, including France, an early start is recommended for children attending day-care (first dose at 9 months, followed by second dose at 12-15 months). In addition, in most countries vaccination is recommended prior to travelling to regions known for the endemicity of the wild-type virus; the first vaccination dose is administered at 9 months of age while the second dose is usually administered 3 to 10 years later. In Germany, following the introduction of

the MMRV vaccine, both doses are administered during the second year of life [30].

Varicella vaccines based on the attenuated Oka-strain of VZV have been marketed and available since 1974 [4,18]. The vaccine has been proven safe and effective, and universal vaccination has been implemented in several countries [18]. US were the first country to implement universal vaccination against varicella in 1995 [20,31]. In 2006, the Advisory Committee on Immunization Practices issued a recommendation for two doses of varicella vaccine to be administered universally to children [20]. According to the American Academy of Pediatrics, the first dose should be administered at 12-15 months of age and the second at 4-6 years of age, respectively, whereas in Germany, as previously noted, both doses are administered during the second year of life, with a time interval of 3 months in between doses [32].

Passive transplacental immunity

IgG antibodies are transferred from the mother to the fetus by an active transport mechanism beginning at approximately 17 weeks of gestation and most often following the 28th week of pregnancy. Cord blood values are similar to maternal titres at approximately 33 weeks of gestation and are observed to be 1.5-2 times higher at term [33].

Infants are protected against measles and varicella by maternally acquired antibodies. However, as shown from previous studies, these antibodies impede the response to measles and varicella vaccination during infancy [34]. The interval between the loss of protection due to the diminishment of maternal antibodies and the protection provided by vaccination should be as brief as possible, particularly secondary to the potential risk of early infection [35-37].

Until recently, maternal measles antibodies transferred via the placenta to the fetus referred to mothers among whom either immunity was acquired by natural infection or had repeated natural boosters through contact with the circulating wild-type virus [34].

In a prospective cohort study among 218 women Leuridan et al [38] concluded that 10% of naturally infected women and 20% of vaccinated women had no detectable measles IgG antibodies at childbearing age. While mean antibody levels were not differentially associated with participants' age, naturally infected women had significantly higher antibody levels than vaccinated women.

In another prospective study of a cohort consisting of 118 children, Klinge et al [34] provided evidence indicating that only 5% of German infants older than 9 months of age had detectable antibodies against measles. In a more recent study, Leineweber et al [33] evaluated prospectively a cohort consisting of 71 full term and 101 preterm infants. Between 6 to 12 months of age less than 20% of the infants born after 32 weeks of gestation had detectable measles antibodies. In contrast, all of the infants born prior to 32 weeks of gestation were found to be negative for the presence of measles antibodies. In a study conducted among 138 infants, Jo et al reported that the seropositivity rates, as well as the measles specific IgG level, decreased rapidly following 3 months of age [39]. Moreover, Pinquier et al, found a significant decline of maternal measles neutralizing antibodies among infants who were consequently no longer protected against measles between 6-12 months of age [40]. This is also supported by a prospective study of maternal measles immunity in a cohort of 147 newborns, conducted in Bangladesh by Shilpi et al. Only 25.5% of the newborns examined had protective levels

of measles antibodies between 2-5 months of age and none had protective levels from 5 months onwards [41].

This situation is similar, if not direr, in developing countries where infants lose maternally acquired antibodies more rapidly than those in developed countries. It is noteworthy that infants in developing countries may lose maternally acquired antibodies at as early an age as 5 to 6 months [42]. In a study conducted in Nigeria, Hartter et al showed that only 17% of the 4-month-old Nigerian infants were protected against measles. The overall prevalence of measles antibodies of 206 infants up to 9 months of age was 45%. Moreover, the prevalence of measles antibodies was limited to 32% among infants aged 3 months and 2% among those aged 6-9 months [42].

Similar principles of passive transplacental measles immunity apply to maternal IgG antibodies against varicella. Specific antibodies can be detected in fetuses following the age of 13 to 15 weeks of gestation. Between the 26th and 28th week of gestation the transplacental transfer increases and at approximately the 34th week the parity of maternal and cord IgG levels is achieved. By term, fetal antibody levels may exceed the respective maternal levels [43]. In a prospective study conducted by Leuridan et al, concerning kinetics of maternally acquired antibodies against varicella in infants, it was depicted that the mean duration of protective titres of maternal IgG antibodies is 2.4 months of age [44].

In another study conducted among approximately 300 children aged 9-10 months, Goh et al found that only 1.4% of the study population had detectable maternal IgG varicella antibodies [45]. Moreover, Gagneur et al provided evidence indicating that infants aged older than 6 months are most likely no longer protected against varicella by maternal antibodies. This may potentially explain the serious forms of chickenpox disease observed among 6-24 months child old [46].

In another study, Wutzler et al investigated the seroprevalence of natural immunity against varicella in 4602 people aged from 0 to >70 years of age. The seroprevalence was observed to decline from 79.4% during the first 3 months of life to 8.6% by the conclusion of the first year of life, thus indicating a diminishment of passively acquired maternal antibodies [19].

In a similar study conducted in Swiss children in order to assess the seroprevalence of VZV IgG antibodies Heininger et al observed a seroprevalence rates of 89.5% and 38.3% among infants aged less than 3 months and 3-6 months, respectively. In contrast, among children aged 6-12 months, none of the 47 children examined had detectable IgG VZV antibodies [17].

In conclusion, secondary to the marked diminishment of antibody levels among infants during the first year of life, a reconsideration of the recommended immunization schedule concerning measles and varicella may be necessary among this particular population group.

Susceptible infants and earlier vaccination

Earlier immunization against measles and varicella may potentially minimize the duration of the period between the loss of maternal antibodies transferred via the placenta and the administration of the recommended measles and varicella vaccination for infants. However, there exist potential barriers to the adoption of earlier immunization schedules, including the inherent immaturity of the immune system of young infants, as well as the potential interference by maternal antibodies.

Several studies concerning these obstacles have been conducted. In a study in the US, Gans et al prospectively assessed a cohort consisting of 248 infants aged 6-9 months who were immunized with live measles virus vaccine. All infants consequently received the MMR-II dose at the age of 12 months. When the 9-month-old infants were immunized in the absence of passive antibodies, their immune response was observed to be equivalent to those of the 12-month-old children, thus indicating that the former have no intrinsic impairment of B-cell function. However, the capacity of the infant immune system to generate humoral response to the measles vaccine was markedly diminished among infants aged 6 months old [47].

On the other hand, in another more recent study carried out in São Paulo by Zanetta et al, although the striking majority (94%) of children were seronegative at six months of age, regardless of the cause of maternal immunity, vaccination or natural infection, the response to measles vaccination was observed to not exceed 54% at 8 months of age and depleted throughout 9 months of age. The optimal age of vaccination proposed was that of approximately 15 months of age [48].

Moreover, a prospective study conducted in Canada by Carson et al, involving 300 infants' response to early measles vaccination, confirmed that vaccine strains AIK-C and CLL could successfully prime young infants, particularly those born to vaccinated mothers [49].

As aforementioned in developing countries it is imperative that more drastic measures regarding vaccination are taken. Specifically, it is suggested that a two-dose measles vaccination policy, with a first dose of monovalent vaccine administered at 6 months of age, may be implemented in Nigeria [42].

Finally, in a study conducted by Martins et al, in the area of Bandim Health Project (Guinea-Bissau) among 1333 children assessed, 441 children were vaccinated at the age of 4.5 months using the Edmonston-Zagreb vaccine and 892 children were vaccinated at the age of 9 months. It is noteworthy that whilst 28% of children tested at 4.5 months, prior to vaccination, had protective levels of maternal antibodies against measles, 92% of the children vaccinated had measles antibodies by the age of 9 months. Moreover, it was shown that efficacy of early vaccination for children with serologically confirmed measles and definite clinical measles was 94%. Hence, measles outbreaks may be curtailed by vaccination using the Edmonston-Zagreb vaccine at as early as 4.5 months of age [50].

With regard to varicella, current vaccination recommendations differ between countries. In most countries there is no official recommendation for routine varicella vaccination of healthy children aged less than 12 months. Moreover, in other countries varicella vaccination is recommended only among high-risk groups. However, several studies concerning vaccination with combined MMRV have shown that administering the vaccine in infants at as early an age as 9 months, with a second dose administered at 12 months of age, results in good immunogenicity. Therefore, the vaccine can be used in circumstances where early protection is needed [20].

The main determinant of maternal antibody-mediated inhibition of immune responses is represented by the titre of maternal antibodies present at the time of immunization, or rather by the ratio of maternal antibodies to vaccine antigen administered. It is thus obvious that late immunization is more efficient than early immunization even in the presence of maternal antibodies. However, such a strategy would fail to prevent early cases of infection, which are concomitantly most often of greater severity.

There are two possible explanations for the aforementioned observation: 1) trace amounts of maternally transferred neutralizing antibodies are not detected with the commonly used serological methods and interfere with the seroconversion; and, 2) the immune system of 6 month old infants may not be mature enough to mount a sufficient antibody response to vaccination.

DNA vaccines that express viral proteins could potentially serve as the solution to providing adequate protection among newborns and young infants from severe illness during the period of elevated disease susceptibility. This would still allow for a boost immunization with the live attenuated measles virus vaccine, as recommended, after 9 months of age. In a study in the U.S.A. regarding neonatal mice born to naïve and measles-immune mothers, Capozzo et al demonstrated that Sinbis virus replicon-based DNA vaccines elicited antibody levels above the protective threshold and cellular immune responses, despite the presence of passively acquired antibodies [51]. Similar research efforts are necessary for varicella as well.

Discussion

Unfortunately, vaccination against measles and varicella in one generation increases the possibility of infection in the next. As time passes, the proportion of vaccines in the population increases, with the latter gradually replacing individuals with lifelong protection acquired from natural infection [52]. Infants become more susceptible as passively acquired maternal antibodies become less and are catabolized earlier [53]. This is directly linked to the fact that vaccine-induced immunity is less robust and less durable than immunity conferred by natural infection. Moreover, it is possible that the diminishment of antibodies is accelerated in the absence of re-exposure to wild-type virus and, therefore, lack of natural boosting immunity [51]. It is also important to refer to the continuously increasing age of parity in the western population, with an increased interval between childhood vaccination and childbirth. As a result, a decrease in transmitted maternal protection is observed [35].

A more comprehensive understanding of measles immunity in infants would enhance the use of already existing live attenuated measles virus vaccines and their administration to younger infants [49], the design of novel vaccines that provide adequate protection, the potential elimination of period of disease susceptibility among infants, and consecutive gradual global eradication of both diseases [54].

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