Loss of Passively Acquired Maternal Antibodies in Highly Vaccinated Populations: An Emerging Need to Define the Ontogeny of Infant Immune Responses

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Protection against infectious diseases is provided to young infants by passive immunity through the transplacental transfer of immunoglobulin G during pregnancy and through immunoglobulin A in breast milk [1–7]. Despite the obvious benefits of these antibodies to the youngest infants, their levels wane over time, necessitating the development of active immunity through vaccination. The timing of primary vaccination is complex, driven by the need to provide protection prior to a time when the infant is likely to be exposed to disease, by the possibility of interference with vaccine-induced immunity by passively acquired maternal antibodies, and, finally, by considerations of the developing infant immune system [7–9].

The titers of transplacentally transferred passive antibodies (PA) provided to infants are, in part, determined by antibody titers present in the mother during pregnancy. These maternal titers are affected by her nutritional and immune status, and evidence demonstrates that antibody titers induced by vaccination are typically lower than titers induced by natural disease [3, 5, 6, 10]. After decades of vaccination against childhood diseases, it is clear that successful vaccine programs have resulted in dramatic decreases in morbidity and mortality. However, the increasing prevalence of vaccine-derived maternal antibodies has also led to unexpected outcomes. This is most evident in the emergence of measles susceptibility in young infants living in highly vaccinated populations where the measles vaccine has been in use for decades [11–14]. Historically, in developed nations protection against measles among infants <12 months of age was provided by a combination of PA and herd immunity, supported by high population immunization rates. However, this barrier has been disrupted, to a certain extent, by global importation of measles and, paradoxically, by the success of the measles vaccine programs, as vaccine-induced PA wanes earlier in infants as compared to PA derived from maternal natural infection [4, 8, 15, 16]. Measles outbreaks in countries with high measles vaccine coverage have demonstrated a shift in measles incidence to children <12 months of age [17–19], before primary measles vaccination commences in most developed countries.

Further, the number of susceptible infants aged <12 months is expected to increase among highly vaccinated populations as the majority of women in child bearing years have vaccine-induced immunity to measles, with recent studies showing 99% of infants born to vaccinated mothers lacking detectable antibodies to measles by 6 months [3, 4].

Waaijenborg and colleagues eloquently highlight this phenomenon in this issue of the *Journal* by comparing titers of antibodies against measles, mumps, and rubella in 2 distinct populations in the Netherlands, one with high vaccination rates and one with opposition to vaccination and, thus, low vaccination rates and presumably higher rates of immunity induced by natural disease. As with previous studies, the authors note significantly lower measles antibody titers in infants born to women from the highly vaccinated populations in comparison to those born to mothers with presumed naturally induced immunity. In addition, the authors also compared mumps and rubella titers in the 2 populations, showing higher rubella titers in mothers from the population with low vaccination rates and low levels of mumps titers in both groups. Varicella was used in this study as a "control" disease because it is caused by a naturally circulating virus in both populations and because varicella

vaccination is not used in the Netherlands; antibody titers were found to be equivalent in the 2 infant groups. As the authors correctly conclude, their findings support the importance of surveillance to define changing epidemiologic shifts resulting from national vaccine policies.

The significance of the findings of Waaijenborg et al is vital for the control of measles in young infants, whereas mumps and rubella are not typically seen in young infants and, outside of congenital rubella, are generally not as severe. Despite fairly low antibody titers to mumps in infants, there has not been a reported increase in disease in this age group [20, 21]. Varicella is infrequently seen in neonates, and while the severity of disease is higher than in older age groups, mortality is not [22]. This latter phenomenon may change as vaccine immunity replaces naturally induced immunity for varicella in pregnant woman and will require future monitoring. This is in contrast to measles, which remains the leading cause of vaccine-preventable childhood mortality globally, with 164 000 deaths annually and the highest fatality rates occurring during the first year of life [17, 23, 24]. This high mortality rate and the recent epidemics in the United States, where 21% of reported cases and 26% of measles hospitalizations occurred in children aged <12 months [25], have created a renewed interest in an early primary measles vaccine dose.

The newly emerging epidemiologic shift in the early waning of PA among infants described by Waaijenborg et al highlights the evolving susceptibility of young infants in highly vaccinated populations to some vaccine-preventable diseases. This has also created opportunity for studies focusing on the ontogeny of viral vaccine immunity in infants in the absence of PA. The majority of work in this area has centered on measles, given the high infant mortality of this disease in this age group. Mumps has not been targeted for early vaccination because recent outbreaks suggest that, unlike measles and rubella, mumps immunity provided

by measles, mumps, and rubella vaccination may not persist and, therefore, an earlier dose may not be indicated [26]. Measles vaccination of infants as young as 3 months has shown partial success [27–29], with limited immune responses in younger infants attributed to interference from PA and to limitations of the developing immune system [8, 20, 21, 27, 28, 30, 31]. Despite this reduced immunogenicity, an early primary measles vaccination strategy was effective in a measles outbreak in the United States, as well as in countries where measles is endemic [31, 32].

Numerous studies have outlined the challenges surrounding early infant vaccination. In the presence of PA, measles humoral immunity is diminished, but importantly, at least for measles, T-cell responses are induced even in young infants in the presence of PA and serve to boost the humoral responses to antigen reexposure, such as after repeat vaccination. These boosted antibody responses are of high avidity, suggesting an anamnestic response that is likely to be rapidly protective [20, 33, 34]. Additionally, T-cell immunity persists after early measles vaccination [35]. This same PA interference has not been seen with other viral vaccines, specifically mumps, rubella, and hepatitis B [6, 20, 21], but it has been documented with rotavirus vaccine, at least among infants living in developing countries [7]. The interfering effects of PA constitute an area of active research, as the mechanisms responsible for the blunting effects of PA in humans are not completely known and would be important to understand if vaccines that can overcome this obstacle are to be developed.

It is clear that T-cell immunity to viral vaccination is present, even when currently available measurements demonstrate that B-cell immunity may in some cases be lacking, raising the question of what the best correlates should be for measuring vaccine efficacy in infants. The efficacy of early measles vaccination in epidemics in the United States and in the developing world where measles is

endemic supports the viability of early measles vaccination, despite the reports of poor antibody responses under these circumstances. Newer research methods have allowed for more detailed and robust antigen-specific B-cell memory determinations, showing that standard antibody assays may not be predictive of true B-cell memory responses [36], and these new tools will be important for studies in young infants in order to understand the nature of ontogeny and function of B-cell immunity.

Data from early measles and mumps vaccine studies have also highlighted other immunologic findings, such as decreased T-cell production of interferon γ, as well as the immature maturation of the innate immune responses [20, 37, 38]. Studies using measles vaccination in the developing world indicate that early measles vaccination gives a survival advantage not only against measles mortality, but also against all infection-attributable mortality, suggesting a nonspecific priming of the infant immune system [39]. This phenomenon is supported by work using BCG vaccination to boost the responses of other vaccines given simultaneously at birth [40]. Taken together, this work begins to define some of the mechanisms that drive the developing immune system and are important for understanding how best to target the immunologic environment for vaccine development in infancy, such as with the use of adjuvants.

Waaijenborg et al report on the susceptibility of infants resulting from successful vaccine programs in the developed world. Given the high infant mortality from measles, low level but continued measles importations, and the potential for a growing population of infants susceptible to important diseases such as measles at younger ages, early vaccination may be the most effective strategy for protection against vaccine-preventable diseases during the first year of life. Such a strategy must be pursued within the context of better defining the developing infant immune system. In addition, work is needed to determine better correlates of viral vaccine efficacy in

young infants and to delineate both the specific and global contributions that vaccines provide to the developing immune system.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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