Immunological considerations regarding parental concerns on pediatric immunizations

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Abstract

Despite the fundamental role of vaccines in the decline of infant mortality, parents may decide to decline vaccination for their own children. Many factors may influence this decision, such as the belief that the infant immune system is weakened by vaccines, and concerns have been raised about the number of vaccines and the early age at which they are administered. Studies focused on the infant immune system and its reaction to immunizations, summarized in this review, show that vaccines can overcome those suboptimal features of infant immune system that render them more at risk of infections and of their severe manifestations. In addition, many vaccines have been shown to improve heterologous innate and adaptive immunity resulting in lower mortality rates for fully vaccinated children. Thus, multiple vaccinations are necessary and not dangerous, as infants can respond to several antigens as well as when responding to single stimuli. Current immunization schedules have been developed and tested to avoid vaccine interference, improve benefits and reduce side effects compared to single administrations. The infant immune system is therefore capable, early after birth, of managing several antigenic challenges and exploits them to prompt its development.

Key words: vaccine; children; heterologous effect; pediatric immunization.

1. Introduction

Despite the fundamental role of vaccines in the decline of infant mortality [1], the decision of vaccinating one's own children is often made with some anxiety [2]. Concerns are varied and include the safety of single vaccine components, the age at first immunization (i.e. too early) or the number of vaccines (i.e. too many) [2]. Severe adverse reactions are extremely rare [3], but parents may have more general worries regarding the capacity of such a young immune system to bear immunizations. The aim of this review is to summarize key concepts of human immunology and vaccinology to understand the reaction of the early age immune system to vaccines.

2. Vaccine-specific immune responses in children

2.1 Development of vaccine-specific immunity

The development of adaptive memory responses, which are the primary target of immunizations, needs the initial triggering by innate cells such as professional antigen presenting cells (APC). However, this step is defective in early age [4]: newborn antigen presenting cells are low in number, immature, respond poorly to activation via Pattern Recognition Receptors (PRR) and provide modest co-stimulation [Reviewed in 5, 6]. As a consequence, primary CD8 and CD4 responses may be weaker [Reviewed in 7, 8] and show a bias toward a Th2 phenotype [Reviewed in 7, 8], which is then reverted through booster doses and adjuvants [9, 10]. Nevertheless, the development of a memory pool is not prevented, even in subjects with undetectable effector responses [11].

The immaturity of secondary lymphoid organs [12, 13] limits the development of humoral responses at early age, which are lower in magnitude and shorter in duration [Reviewed in 14]. Nonetheless, the development of memory B cells is not compromised and may occur even in subjects with low antibody titers [15, 16]. In addition, infants below the third month of age are unable to generate antibody responses against those

antigens that do not require T cell help (e.g. polysaccharides) [17, 18], a problem overcome through their conjugation with proteins [19].

The overall immaturity of infant immune system (summarized in Fig. 1 and Table S1), which was necessary to ensure maternofetal tolerance [18], results in lower vaccine responses than those developed in adults [20], save some relevant exceptions [21-23]. However, the primary aim of pediatric vaccines is not to develop adult-like immune responses (which will be reached through boosting doses [24, 25]), but rather to induce protective immunity, and data show that protective antibody titers may be elicited in more than 90% of children at 7 months of age against individual immunogens such as Polio, diphtheria-tetanus-pertussis (DTP), haemophilus influenzae type B (Hib), Hepatitis B virus (HBV) and Pneumococcal conjugate vaccine (PCV) [26]. Indeed, newborns can still develop innate and adaptive responses against the enormous number of microorganisms met since the delivery or even in utero [27-29] and vaccine-specific B and T immune responses already within hours after birth [30, 31], demonstrating that even if some immune functions may be suboptimal in early age, they are sufficiently developed to mount protective responses and generate effective memory cells [11, 15, 16], the final targets of vaccines. In addition, adjuvants and formulation efforts may help an immature immune system to develop vaccine-specific responses that would not be elicited by natural infections [19].

2.2 Indirect effects of vaccine-specific immunity

The importance of vaccine-specific responses goes beyond the simple prevention of the infections targeted by the immunization (Table 1). For instance, vaccine-induced epitope-specific responses towards one virus may show cross protection against other viral genotypes [32] or viruses of the same family [33]. Prevention of heterologous infections also occurs by avoiding the immunosuppressive effects exerted by pathogens such as varicella, influenza or measles [34-36]. Vaccine-preventable infections are often involved in other pathologies; for instance, respiratory infections and Bordetella pertussis contribute to sudden infant death syndrome (SIDS) [37-39]. Indeed, whilst several modifiable (e.g. sleeping position, type of bed and bedclothes) and non-

modifiable (e.g. genetic) risk factors are associated with SIDS [38], its incidence is lowered after vaccination against DTP, Hib and pneumococcal bacteria [39-41].

3. Non-specific immune responses elicited by vaccines

Several studies have shown that exposure to infectious agents may alter the immune response to unrelated infections [42]. Consistently, vaccines have been shown to affect, on a long term temporal frame, innate immunity (that has recently shown memory-like properties referred to as “trained immunity”) as well as adaptive immunity toward unrelated antigens [43, 44].

3.1 Adjuvant effect

Bacillus Calmette–Guérin (BCG) vaccine induces a strong polyclonal stimulation, boosts APC and lymphocyte functions [44-46] and increases responses toward vaccines administered at the same moment [47] or even later [48, 49]. In addition, BCG vaccine is used as an immunotherapeutic treatment against cancer and has been shown to prevent lymphoma and leukemia [45, 50].

3.2 Effect towards heterologous infections

BCG and, most likely, measles-mumps-rubella (MMR) vaccines favor the development of macrophage and monocyte functions [44, 51, 52] as well as lymphocyte responses [44, 48, 52, 53]. This has been associated with a lower incidence of infections [54-56], particularly at the level of the respiratory tract [57-59]. Conversely, alum-adjuvanted DTP vaccines induce preferentially Th2-responses [60, 61] and are associated with increased susceptibility to infections [54, 55, 62]. However, this effect is controversial, as some studies found a protective role or a lack of association [57, 63, 64].

3.3 Effect on atopic disorders and autoimmune diseases

Historically, vaccines have been proposed to be involved in the development of allergies, asthma and other atopic disorders [65]. However, while this association has not been confirmed [66-68], it has been shown that

protection towards heterologous respiratory infections through direct and indirect mechanisms may decrease the risk of asthma, in particular with MMR [69, 70] and BCG [71, 72] vaccines. Moreover, as atopic disorders are associated with Th2-type responses [73], vaccines favoring a Th1 phenotype (such as BCG or MMR) might be protective [72]. Conversely, although some studies found also a protective role for inactivated vaccines [68, 74], others reported lack of association or even a negative effect [75, 76].

Vaccines have also been considered as potential causes of autoimmune diseases (AIDs), in particular due to adjuvants responsible for the "autoimmune/inflammatory syndrome induced by adjuvants'' (ASIA) [77, 78]. This topic is quite controversial: while case reports were published [77, 78], cohort studies showed a lack of association between vaccinations and AIDs [79].

3.4 Effect on overall mortality

The capacity of some vaccines (i.e. BCG [80-82], MMR [80, 82], Smallpox [83] and Polio [84] vaccines) to prevent unrelated infections results in a lower mortality rate. Conversely, it has been proposed that DTP vaccine might be associated with a higher mortality rate, although results are not consistent between studies [56, 80, 82, 85-90]. WHO concluded that evidence is insufficient to support any association of DTP vaccine with overall mortality [82].

4. Concerns leading to "personalized" immunization schedules

The fear that infant immune system may be weakened by vaccines leads to "personalized" immunization schedules where vaccines against those diseases believed not so harmful or easy to contract are delayed or avoided. This attitude jeopardizes the health of children for all their lifetime [91, 92], as well as of the community where they live [93], including the grandparents [94], newborn siblings [95] and the mother herself [92].

4.1 Are vaccines weakening the immune system?

The above reported scientific evidence (summarized in Tables 1 and S2) argues against a deleterious effect of vaccines on the infant immune system, showing rather that vaccines behave as other environmental factors (microbes or nutrients), in accordance with the hygiene hypothesis, favoring the development of the immune system [96, 97]. Indeed, children with complete vaccination coverage show, compared to unvaccinated or poorly vaccinated pairs, a lower mortality rate and a general better health status [98-102].

4.2 My child is so young, should I delay vaccinations?

Current vaccination schedules, although they may vary between countries, recommend immunizations directly after birth with HBV and BCG vaccines (and eventually oral polio vaccine, OPV), and at 2 months with DTP, Hib, PCV, rotavirus vaccine (RV) and inactivated polio vaccine (IPV). Often parents prefer to postpone immunizations to wait for a "more mature" immune system [103]. This may leave children unimmunized for years. Indeed, while the immune system rapidly develops some functions at the time of first dose, i.e. two-three months after birth [18, 104, 105], other properties (such as balanced IgG1 and IgG2 production) may reach adult-levels at 1 year [104, 106, 107] or even during adolescence, as in the case of IL12 production [104, 108, 109]. In addition, the suboptimal features of the infant immune system that may argue against early life vaccination are the same that render infants more susceptible to infections [6, 110]: natural infections induce, in infants, poor Th1 and T-independent antibody responses which are instead elicited by vaccines [10, 19, 111]. Thus, postponing the first dose of vaccines: i) may have low to no effect on immunogenicity [112]; ii) may increase the risks of adverse events [113], of never completing the vaccination course [103, 114] and of modifying the order of immunizations with possible negative health outcomes [57, 115]; iii) and, most of all, will leave children unprotected in a very risky period. For instance, a delay in initiating the diphtheria-tetanus-acellular pertussis (DTaP) immunization program may double hospitalizations [116-118] as the first dose administered at 2 months of age already confers considerable protection (from 50% to 75% or more) [118-120].

4.3 Are multiple immunizations overwhelming the immune system?

Co-administration of vaccines is possible in two ways: combined vaccination (several antigens formulated in one single vaccine) and simultaneous administration (more than one vaccine is administered concurrently but at different anatomic sites). Simultaneous administration may be less compliant [121] compared to combined vaccination, but it lowers the risk of interference between vaccines [122]. The latter may be positive, as for vaccines comprising antigens and adjuvants at the same time [21, 47, 123], or negative, as was shown with the combination of MMR and varicella vaccines (MMRV) [124]. This specific problem was later solved, mostly by changing the doses of single components, to achieve for MMRV vaccine administration the same level of immunogenicity as when MMR and varicella vaccines are administered separately [125]. Vaccines may interfere at the level of the formulation or, when injected, at the level of immune responses, for instance through polyclonal stimulation by one component or competition for cross-specific responses. It has been proposed that live vaccines should be administered with a minimum of 28 days of time gap [122] to avoid negative interferences [126]; however, this concept has been challenged in some studies [127, 128]. Conversely, negative interferences seem not to affect inactivated vaccines [129, 130].

Current immunization schedules are tested to avoid vaccine-specific interactions and show that infants may efficiently respond to up to 10 vaccines (each of them composed of several antigens) at the same time [131, 132]. This demonstrates that multiple vaccinations do not exhaust immune resources, and are a safe practice [133]. This concept is proved in children with mild diseases that have comparable vaccine responses as healthy pairs [134-136]. Indeed, the huge repertoire of B- and T- cell specificity renders the immune system capable of recognizing and facing different threats at the same time. It has been assumed that as much as 11 vaccines given at the same time will exploit only the 0.1% of the B cell response [137].

5. Conclusion

The tremendous benefits that immunizations have on children's health may be undermined by personal risky choices (not doing or delaying vaccinations) driven by some misconceptions such as: i) underestimating life threatening diseases or the functionality of an early age immune system; ii) overestimating vaccine side effects. Complete and reliable lists of adverse events connected to immunizations may be easily found (Box 1) to inform parents. Conversely, the understanding of the interaction between the early age immune system and vaccines is a more complex issue that involves several notions of immunology and vaccinology, and inadequate answers to parents' doubts on these topics may have deleterious effects on immunization programs. Parents should be reassured by current evidence demonstrating direct and indirect benefits of vaccines, such as a decrease in overall morbidity and mortality from pediatric age, and a positive role in the development of the immune system (Table 1). The knowledge of these indirect effects, the awareness of the threats that some vaccine-preventable diseases pose especially in early age, and a correct understanding of infant immunity may thus provide the basis to avoid the counterproductive decision of underimmunization (such as delaying vaccinations or avoiding multiple immunizations, see Table 2). This decision, although taken with the good intention to safeguard one's own children, may easily put at risk their life and the health of surrounding people.

Conflict of interest statement

None.

Acknowledgements

This work was supported by the French Agence Nationale de la Recherche (ANR; projectANR-14-CE14-0030-01). We would like to thank Justin Frere for editorial assistance.

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Figure Legends

Fig. 1. Early age antigen-specific immune response.

Newborns have few APCs, which display an immature phenotype (1) and a low response to some TLR ligands (2). This results in suboptimal antigen presentation ("signal 1", 3) and co-stimulation through surface receptors ("signal 2", 4), as well as secretion of cytokines ("signal 3", 5), in particular IL-12. Understimulated $CD4^+$ T cells show therefore a poor effector response, biased towards a Th2 type (6). B-cell responses are also impaired: T-cell independent humoral responses develop only several months after birth (7) and even T-cell dependent ones are weak due to a low expression of co-stimulatory molecules (8) and a limited development of T follicular helper cells (9). The IgG production is limited as plasmacells are poorly functional (10), and produced antibodies show reduced affinity maturation and shorter lifespan, in addition to be mainly constrained to the IgG1 subclass (11). Defects at the level of APCs and $CD4^+$ T-cell activation result in lower effector CD8 responses against some antigens (12), also due to higher levels of suppressive populations (13). Further details and literature references are presented in Table S1. Abbreviations: APC: antigen presenting cell; TLR: toll like receptor; PAMP: Pathogen-associated molecular pattern; PRR: pattern recognition receptor.

535 **Table 1**

536 Immune-related heterologous effects of vaccines. Proposed mechanisms and literature references are shown

537 in Table S2

Factor	Effects
Susceptibility toward unrelated infections	BCG and MMR vaccines have been associated with lower risk of infections. DTP vaccine has been associated in some studies with an increased susceptibility to enteropathogens in girls but showed a protective effect against respiratory infections.
Adjuvant effect	BCG vaccine has been shown to improve responses toward vaccines administered at the same moment or later, and is used as immunotherapeutic against cancer.
SIDS	Some vaccines, and in particular DTP, have been associated with a reduced incidence of SIDS.
AIDs	Clinical and cohort studies failed in finding an increased prevalence of AIDs in subjects exposed to vaccines or adjuvants, suggesting that AIDs and ASIA are not generalized phenomena. Further studies are necessary to assess frequency and mechanisms of the reported cases.
Atopic disorder	MMR and BCG vaccines have been shown in some studies to decrease the risk of asthma. Conflicting results have been shown for DTP vaccine.
Overall mortality	BCG, MMR, Smallpox and oral Polio vaccines have been associated with a lower mortality rate. DTP vaccine has been associated with either increased and decreased non-specific mortality. However, current evidence is insufficient to support either of these conclusions.

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Table 2

Common questions regarding interaction between vaccines and early age immune system

Questions	Reasons of Parents	Answer
May I decide to do only part of recommended vaccinations?	Some vaccine-preventable-diseases believed not so harmful or easy to contract	This choice may have different harmful consequences: • Leave children unprotected for underestimated dangers. • Reverse the vaccination schedule with detrimental effects on heterologous immunity. • Weakening of the herd immunity → negative consequences for relatives (e.g. grandparents, siblings too young to be vaccinated, pregnant mothers) and immunocompromised persons.
Are vaccines weakening the immune system?	Fear of immunosuppressive effects of vaccines	• Vaccines, in particular if administered on time and according suggested immunization schedules, favor the development of the immune system, enhancing protection not only against infections targeted by the immunization, but also to unrelated microbes.
My child is so young, should I delay vaccinations?	Fear that early age immune system may be too frail	• The immune system of infants, although not fully mature, may easily bear the stimuli provided by vaccines, which are relatively weak if compared to the natural infections. • Innate and adaptive immunity in young children lack some specific functions that render them more susceptible to infections that, for the same reason, display high morbidity and mortality rate at early age. Vaccines are the only strategy to improve protection against these threats. • For some vaccines, children may display adult-like immune responses, even in early age.
Are multiple immunizations overwhelming the immune system?	Fear of overstimulating the immune system	• The immune system may develop strong and competent antigen-specific immune response to hundreds of unrelated antigens at the same time. • All licensed combined vaccination and simultaneous administration of vaccines are always tested to assess that the co-administration is not inferior to administration of single components.