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VIEWPOINT

One vaccine for life: Lessons from immune ontogeny

Sam Brophy-Williams,[1] Mario Fidanza,[2] Arnaud Marchant,[3] SingSing Way[4] and Tobias R Kollmann[2]

[1]Department of Infectious Diseases, Perth Childrens Hospital, Child and Adolescent Health Service, [2]Systems Vaccinology, Telethon Kids Institute, Perth, Western Australia, Australia, [3]Institute for Medical Immunology, Université libre de Bruxelles, Charleroi, Belgium and [4]Center for Inflammation and Tolerance, Cincinnati Children's Hospital, Cincinnati, Ohio, United States

There remains a general misconception that the immune status of the fetus and neonate is immature or insufficient. However, emerging research in immune ontogeny prompts reconsideration of this orthodoxy, reframing this period instead as one of unique opportunity. Vaccine responses (qualitative and quantitative) vary between individuals, and across demographic cohorts. Elements of baseline immune status and function predict vaccine response – some of these factors are well described, others remain a subject of ongoing research, especially with the rapidly expanding field of 'omics' research, enabled by development of highly granular immune profiling techniques and increasing computational capacity. Age is one of the strongest predictive factors associated with variability in the response to vaccination; and predictable variation in response to vaccination is a key to identify the crucial underlying mechanisms. Specifically, circulating maternal antibody in the young infant can modulate immune response to vaccination, acting as an 'undercover adjuvant' that, counter to current dogma, may offer a pathway to longer lasting, higher quality immune response to vaccination. Exciting avenues for novel research in this area have the potential to dramatically alter how we protect the world's most vulnerable population – the very young.

Vaccine responses are variable and that this variability can, to some extent, be predicted by immune baseline, that is, the immune status at time of vaccination.[1] Differences in immune baseline may be static or dynamic, inducible, genetic, single or multifactorial. Some markers of these baseline immune differences are known and defined: pre-vaccination levels of activation-induced cytidine deaminase, which is a well-established serum correlate of B-cell immunoglobulin class switching, predict serum antibody response to flu vaccine[2]; and elevated pre-vaccination inflammation makers (higher levels and/or increased activation of pro-inflammatory innate immune cells and a transcriptomic profile dominated by pro-inflammatory proteins) predict age-related hyporesponse to hepatitis B vaccination.[3,4]

Vaccine responses are the result of complex interactions between many cells and molecules in different parts of our body. Defining and comparing this complexity captured in the concept of an 'immune baseline' thus requires an approach with capacity to incorporate information covering this complexity; an 'omics' approach made possible with the development of highly granular multiplex immune profiling (including transcriptomics, genomics, flow cytometry and cytokine and antibody profiling) and computational modelling (machine learning, artificial intelligence) to handle these multi-dimensional data sets.[5] This approach breaks open the black box, revealing clinically important predictors of vaccine response.[6]

Baseline Predicts Outcome: Beyond Vaccination

This concept can be simply summarised under the immunological premise that *baseline predicts outcome*. This is evident in vaccination response, and in other areas of infectious diseases and immunology. Risk for hospitalisation from severe infections over the first year of life in HIV exposed but uninfected infants can be predicted from baseline innate immune phenotypes characterised by higher CD40 expression in non-classical newborn monocytes measured at birth.[7] Immune signatures at baseline predict not only the response to malaria vaccination but also clinical outcomes of acute infection with better outcomes in individuals with an immune 'signature' of B cell enrichment, upregulation of Th1 and Th2 pathways, interferon responses, and p53 activation.[8] 0.5% of HIV-infected people are 'elite controllers' who maintain undetectable viraemia in the absence of antiretroviral therapy – these individuals demonstrate specific cytotoxic T lymphocyte activity predicted by their HLA haplotype.[9]

Shifting the Baseline

In realising that baseline predicts outcome (of vaccination or disease) – we are prompted to ask: can we alter that baseline to optimise vaccine response – can we turn everyone into a 'good responder'? And how might we do that?

Altering the immune baseline, and thus response to, for example vaccination, can be achieved through well designed and appropriately timed adjuvants, the administration of other immune modulators before, after, or with vaccination, or by timing vaccine delivery during specific periods in immune ontogeny.

Correspondence: Dr Sam Brophy-Williams, Department of Infectious Diseases, Perth Childrens Hospital, Child and Adolescent Health Service, WA 6009, Australia. email: sam.brophy-williams@health.wa.gov.au

Sam Brophy-Williams and Mario Fidanza contributed equally as joint first authors.

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Adjuvants

Adjuvants have been used to modify host responses to vaccination since Gaston Ramon injected tapioca starch to cause sterile abscesses at injection sites in horses to increase yield of tetanus and diphtheria anti-sera in the early twentieth century.[10] The field has progressed from those early discoveries, and now more than 30 licenced human vaccines from different manufacturers contain adjuvants (including human papillomavirus, influenza and *DTPa*-hepB-*IPV*-Hib vaccines used in Australia).

Immune modulators

Immune modulators other than those classified as adjuvants have more recently been shown to have an effect on vaccine response. Administration of the mTOR inhibitor Rapamycin with influenza vaccine has been shown to induce improved cross-strain protection through inhibition of B cell class switching. This yields an antibody response skewed towards conserved hemagglutinin elements, rather than subtype variant epitopes.[11,12]

Capitalising on natural variation in immune ontogeny

In addition to modifying immune baseline through external manipulation (adjuvants), natural variation in baseline can be used to optimise outcomes, and to protect those most vulnerable. Variation in immune baseline has been described across intrinsic demographic parameters like age.[13–15] The evidence shows that with the same vaccine, and the same immunomodulation, predictably and consistently different effects are seen at different ages, reflecting underlying different stages along the immune ontogeny pathway. This is seen between adults and children, but the most dramatic differences are observed in the neonate.[16]

Neonatal Vaccination

Newborns are undoubtedly at high risk of infection causing clinical disease. However, the negative perception of neonatal immune 'immaturity' is at odds with existing data.[17] More precisely, the highly adaptable nature of the newborn immune system to the rapidly changing challenges incurred during the first days of life highlight the immense capacity of the newborn immune system.[17,18] While only some of the relevant mechanisms that allow such a feat to be accomplished are known, what is known indicates a superb system of fine-tuned balance and counterbalance, that is a system focused on resilient homeostasis.[19,20]

This raises the obvious question of the efficacy of newborn vaccination. While vaccinologists most commonly measure peak antibody titres as the sole outcome of vaccination (as 'correlate of protection'), clinical protection itself is the key target, yet protection is not commonly assessed in newborn vaccine trials.

In global practice, only the Bacillus Calmette-Guérin (BCG), hepatitis B virus (HBV) and polio vaccines are recommended at birth. Neonates do mount an antigen-specific interferon gamma response to BCG vaccination.[21,22] HBV vaccination with alum-adjuvanted hepatitis B surface antigen induces antibody and T cell responses to HBV in neonates, though these are distinct from adult responses.[23,24] However, this vaccine is protective even when only 30–50% of newborns reach 'protective' anti-HbS titres after a single dose,[25] which implies that other mechanisms (i.e. not just antibody titres) might be responsible for effective vaccine responses. Thus existing data from routine newborn vaccination (see above) as well as trials of experimental newborn vaccinations (reviewed in[6]) indicate that newborns are very much capable of mounting protective immune responses to vaccination.

Furthermore, birth is the most reliable point of contact with health services, offering an opportunity for high vaccine coverage compared to the 6–8 week mark when the next EPI vaccines are routinely given.[26] Thus, why are we not giving more vaccines at birth? After all, globally, the newborn period is very dangerous. Approximately 2 million infants die in the first week of life, accounting for 32% of under-5 mortality; a quarter of these deaths are from infectious causes.[27]

Safety considerations

Safety is of paramount importance when considering a prophylactic intervention, including newborn vaccination. Outside of the few newborn vaccines currently in widespread use, other vaccines approved for use in older infants have generally been shown to be safe for use within the first days of life. These include existing preparations of acellular pertussis, Hib and pneumococcal conjugate vaccines.[28,29] Influenza vaccination has been shown to be safe and immunogenic down to 6 weeks of age, but to our knowledge has not been tested in newborns.[30] Of interest, PCV-10 uses a Haemophilus outer membrane protein and may confer protection against other invasive Haemophilus including non-typeable *Haemophilus influenzae*, invasive disease with which is commonest in the first month of life[31]; however, more work is needed with larger studies in this area.

Maternal antibody – Hurdle or helper?

The fetal and neonatal immune system is unique for the presence of maternal antibodies (matAb) – which play an important role in functional immunity, and specifically in vaccine response. The presence of high titres of circulating matAb has been demonstrated to suppress antibody titres in response to newborn vaccination,[20] but this focus on humoral immunity measured as antibody titres, as the sole correlate of protection misses the *qualitative* differences in other aspects of immune response. Vaccination under the cover of matAbs could be not only protective but superior, inducing a response characterised by a broader B-cell repertoire and more robust immunological memory.

Circulating matAb does not inhibit neonatal B cell activation, though does alter differentiation into plasma cells and memory B cells. In a murine model, vaccinated newborns with circulating vaccine induced matAbs responded with quantitatively lower titres compared to newborns of naïve mothers, but exhibited qualitatively broader B cell *repertoire*. This is likely explained by matAb binding to the immunodominant epitopes and leaving the infant's own immune system to mount a memory response to non-immunodominant epitopes, which for some pathogens may elicit more broadly neutralising antibodies with useful cross-reactivity.[32,33]

Looking beyond initial antibody response – infants vaccinated with measles vaccines in the presence of matAbs did not produce antibodies to the first vaccine dose, but responded to a booster dose later in childhood with a higher antibody titre than controls, again supporting the hypothesis that memory B cell induction is not inhibited by matAbs.[34] Clinical impact of this is supported by Australian data showing that earlier administration of influenza vaccine (i.e. more likely to be in the presence of matAb) is associated with better protection across several subsequent flu seasons, again suggesting the beneficial broader response induced by infant response to non-immunodominant epitopes.[35]

The same rationale that immune response to vaccination can be modified beneficially by immunising under cover of passive antibody (in this case matAb) has already guided the approach to HIV vaccination efforts.[36] Compared to newly HIV-infected adults, HIV-infected infants born to HIV positive mothers (and therefore challenged with the virus in the presence of matAbs) mount polyclonal, including broadly neutralising antibody responses.[37,38] The presence of broadly neutralising antibody (in these studies given as passive immunisation, but also found as circulating matAb in infants born to HIV-infected mothers) has been shown to improve the neutralisation response to subsequent HIV/SHIV challenge in humans[39] and macaques.[40]

Baseline Predicts Outcome – Guidance for Impact

A general approach is that the use of adjuvants, immune modulators, and timing with respect to immune ontogeny can broadly improve the response of vaccination in nearly all individuals. A specific approach relates to the presence of passive antibody (including matAb) to the vaccine target, that while for some vaccines reducing peak titres to the dominant epitopes, increase breadth of the ensuing immune response and with that possibly increase breadth of protection.

This has massive ramifications in vaccine-preventable disease. While this idea is exciting and possibly transformative, it also still radical, in part because the research is in its infancy. Directions for ongoing and future research include:

1 Consideration of vaccine strategies in pregnancy and early infancy, and how these interact – that is, considering the maternal-newborn unit as one biological system where maternal immunity in part determines the baseline immune status of the newborn.
2 Assessment of adjuvant/immune modulator administration separately from vaccination.
3 Assessment of impact of circulating passive antibody (e.g. maternal) on quality of response to vaccination.

Outlook

To return to our opening premise – the fetal and neonatal immune system is different than that of older infants, children and adults. Different yes, but not necessarily inferior. Perhaps intelligently using age-dependent differences, rather than alteration of vaccine components, adjuvants or external immune modulation, could provide a practical and direct pathway to improve vaccine-mediated protection.

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