As a child, the risk of suffering and dying from infection is higher the younger you are; and higher, the less developed a region you are born in. Childhood vaccination programmes have greatly reduced mortality around the world, but least so for the very young among the very poor of the world. This appears partly owing to suboptimal vaccine effectiveness. Unfortunately, although most vaccines are administered to the newborn and very young infant (less than or equal to two months), we know the least about their host response to vaccination. We thus currently lack the knowledge to guide efforts aimed at improving vaccine effectiveness in this vulnerable population. Systems vaccinology, the study of molecular networks activated by immunization, has begun to provide unprecedented insights into mechanisms leading to vaccine-induced protection from infection or disease. However, all published reports of systems vaccinology have focused on either adults or at most children and older infants, not those most in need, i.e. newborns and very young infants. Given that the tools of systems vaccinology work perfectly well with very small sample volumes, it is time we deliver the promise that systems vaccinology holds for those most in need of vaccine-mediated protection from infection.

Of all forms of inequality, injustice in health is the most shocking and the most inhumane.

Dr Martin Luther King Jr., 1966

1. The problem: the youngest and the poorest are most affected by early life infection

Infectious diseases are the predominant cause of childhood death in the world [1–3]. Most severely affected are the children living in resource-poor areas [3]: a child born in sub-Saharan Africa is 30 times more likely to die before the age of 5 years than a child born in Western Europe [4]. Significant progress in survival of children under the age of 5 years has been made, but inequality has not improved with industrialization and development: today, compared with children in resource-rich countries, children in resource-poor countries are nearly 18 times more likely to die before the age of 5 years, whereas in 1990, this difference was ‘only’ 14 times more [5]. Neonatal infection, in particular, remains a serious problem [1,2,6]. The Child Health Epidemiology Reference Group estimates that 40.3% of 7.6 million deaths among children younger than 5 years of age (i.e. 3.1 million deaths in 2010) occurred in neonates [3]. Infections in neonates, especially those born prematurely, pose enormous healthcare challenges and are responsible for over 1 million of the neonatal deaths every year [1,2,7,8]. The global disparity in childhood deaths, especially neonatal and young infant deaths owing to infection, represents one of most severe forms of injustice in the world today.

Childhood vaccination programmes have greatly reduced demise due to infection [9]. In the US alone, publically funded childhood vaccination has prevented approximately 322 million illnesses, 21 million hospitalizations and 732 000 deaths, with net savings of approximately $300 billion in direct costs and more than $1 trillion in total societal costs over the past decade [10,11]. The World Health Organization expanded programme of immunization, and other regional and national programmes have had similarly profound impact in the rest of the
world [9,12–14]. Vaccination thus undoubtedly represents one of the most cost-effective, life-saving medical interventions in human history [15–17]. However, despite these successes, approximately 3 million children still die every year of infectious diseases that are preventable with presently available vaccines [18]. Most of these vaccine-preventable deaths occur in the newborns and infants of the developing world [1,4]. Several vaccines perform less well in populations based in poorer countries than in wealthier ones, which likely contributes to the increased early life infectious mortality in resource-poor settings [19,20]. Together, the higher risk of suffering and death from infection early in life in the developing world, coupled with the suboptimal response to vaccination represent an unfortunate confluence of disadvantages that amplify each other.

2. The solution: increase insights into how vaccines protect best in early life through systems vaccinology

The obvious solution, improving the neonate’s and young infant’s response to vaccination, is difficult to achieve, because our current understanding of how existing vaccines successfully prevent infection or disease is limited [21]. A key example is the most commonly administered vaccine in the world—neonatal bacille Calmette–Guerin (BCG), the live attenuated strain of Mycobacterium bovis given to newborns to protect against tuberculosis meningitis and miliary TB in infancy [22]. How BCG achieves these protective effects, and why the level of protection afforded by vaccination varies between different populations is not clear [20]. Cellular immunity induced by BCG was thought to provide protection against systemic tuberculosis [13]. In animal models, protective immunity appeared to correlate best with CD4+ T cells that produce cytokines, such as gamma interferon (IFN-γ) [13]. However, when this was analysed in human infants, antigen-specific T cell frequency and cytokine expression profile (including IFN-γ) did not correlate with protection against tuberculosis after BCG vaccination [23]. Moreover, BCG also induces non-specific or heterologous beneficial effects that may be mediated via epigenetic re-programming of monocytes and natural killer cells such that innate immunity is enhanced [24]. However, it is not known if, and if so, how these effects are mediated in newborns. Thus, even for the most commonly administered vaccines, we lack mechanistic insights that could help improve the response of existing vaccines or guide development of new vaccines. This lack of knowledge regarding re-programming the suboptimal immune response of the young and poor to provide effective vaccine-induced immunity represents a key hurdle to overcome the current inequities delineated above.

Systems biological analysis of the host response to vaccination has recently provided unprecedented insights into mechanisms functionally relevant to a protective host response [25]. This ‘systems vaccinology’ employs bioinformatics to computationally model molecular networks and identify signatures of the host response to vaccination [26]. In general, systems vaccinology approaches include ‘OMIC’ measurements, such as genomic, transcriptomic, proteomic, metabolomic and lipidomic, etc. In contrast to traditional techniques, these OMIC approaches share several key features [27]: (i) unlike traditional methods, OMIC approaches are high-throughput, data-driven, holistic and top-down methodologies; (ii) the attempt to understand the cellular response as one ‘integrated system’ rather than as mere collections of different parts by using information of the relationships between many measured molecular species; and (iii) the distinct advantage of a ‘systems approach’ is that it is unbiased (i.e. it does not require a priori selection of the parameters that will be measured but instead encompasses the entire available repertoire). Because all systems biological approaches are hypothesis-generating and merely describe possible associations, to assess potential mechanisms, molecular pathways identified in silico need to be interrogated for cause–effect relationships using in vitro and in vivo (animal) experimentation. Such iterative cycles can then be interrogated in increasingly focused, small human exploratory concept trials [25].

Systems vaccinology has already provided new insights relevant to two major goals in vaccinology: the elucidation of a vaccine’s mechanism of action and the identification of a molecular signature able to predict a subject’s response to vaccination—i.e. biomarkers that indicate whether or not the vaccine will confer protection [25]. Specifically, systems vaccinology has shown that (i) type and duration of immune memory are largely determined by the magnitude and complexity of the innate immune signals induced at the time of vaccination, and (ii) signatures highly predictive of protective responses can be identified for specific vaccines. Furthermore, for vaccines with similar composition, e.g. live attenuated viral vaccines, these signatures share common patterns [28]. Most importantly, given the unbiased approach, systems vaccinology can identify potential involvement of unanticipated pathways in vaccine responses. For example, systems vaccinology tools revealed the entirely unexpected finding that the antibody response (haemagglutination inhibition) to trivalent inactivated influenza virus vaccination is critically influenced by flagellin present on intestinal bacteria that systemically signal via Toll-like receptor 5 to promote plasma cell differentiation and with that antibody production [29].

3. The remaining hurdles: complex OMIC data analysis, optimal study design and harmonization/standardization of operating protocols

Transcriptomics, i.e. RNA expression analyses that measure genome-wide transcript abundances, have been the main focus of systems vaccinology so far [25,30]. It has, however, remained a challenge for the transcriptomic approaches to identify true causal relationships between the ex vivo and in silico generated signature(s) induced by a specific vaccine and their observed biological correlates [31]. It has been increasingly recognized that functional relationships among genes, proteins and metabolites drive biological processes; i.e. a transcriptomic approach alone likely will not suffice to characterize the complexity of the response following vaccination [27]. Ideally, multiple OMIC approaches should be integrated into systems vaccinology studies. Other systems biological fields have already shown how powerful this integrated approach is to successfully unravel regulatory mechanisms governing complex networks [32–34]. Beyond cost, one of the hurdles preventing widespread application of this integrated OMIC approach has been the difficulty in analysing
the complex data; this has, however, more recently begun to be successfully addressed [27,35–38]. Other large-scale profiling technologies, such as multiparameter flow cytometry or multiplex serum protein assays, perfectly complement the systems immunology armamentarium, providing unprecedented capabilities to characterize the human immune response to vaccination down to the single cell level [39,40].

For human systems biological studies to provide the most information, it would be ideal to nest them within larger vaccine efficacy studies [25]. This demands that the larger vaccine trials be set up with systems biological sampling already included in the design; this, in turn, requires rigorous planning from adequate sample size (to ensure sufficient statistical power when applying multidimensional analysis), to standardization (or at least harmonization) of study protocols across sites. The latter point is especially important yet difficult to achieve for trials conducted in resource-poor settings of the world (which is where they should be conducted; see above). For example, the impact of time between blood draw and processing has been shown to be exquisitely sensitive to even minor deviation from standard operating protocols (SOPs) [41–46]. One possible approach to increase such cooperation would be to set up a global systems vaccinology forum with protocols and trial-design advice provided to any group anywhere. As every study site is unique, and SOPs often have to be ‘custom designed’ to fit each individual site, this will be an ongoing challenge, but not impossible if driven by a network of strong yet open collaborators. Such harmonization of trial design and SOPs will be absolutely essential for the third key point to keep in mind: the importance of validation of systems biological findings in an independent study or set of samples prior to drawing firm conclusions or investing precious research resources on translating the in silico derived OMIC signals to molecular cause–effect relationships. These goals are achievable but only with a leadership that has the influence to guarantee such high level yet detailed cooperation between study sites and groups.

4. The promise: apply systems vaccinology to the youngest and the poorest

Most systems vaccinology studies published hitherto have focused on adults [25,47]. The few systems vaccinology studies that included paediatric subjects enrolled infants older than 12 months of age. In fact, we could find only one child under 1 year of age (six months to be precise) that had been studied using systems vaccinology tools [48]. So far as we know, not a single systems vaccinology study focused on adults [25,47]. The few systems vaccinology studies that included paediatric subjects enrolled infants older than 12 months of age. In fact, we could find only one child under 1 year of age (six months to be precise) that had been studied using systems vaccinology tools [48]. Most systems vaccinology studies published hitherto have focused on adults [25,47]. The few systems vaccinology studies that included paediatric subjects enrolled infants older than 12 months of age. In fact, we could find only one child under 1 year of age (six months to be precise) that had been studied using systems vaccinology tools [48].

So far as we know, not a single systems vaccinology study is subjected to the highest morbidity and mortality from vaccine preventable diseases (see above), and most vaccines in the world are administered to the newborn and young infant populations [49].

There are several reasons that have likely prevented, to date, the application of systems vaccinology to those most in need: (i) comparatively little is known about neonatal immunology to guide data interpretation; (ii) the early-life immune system is a rapidly moving target; (iii) obtainable sample volumes (e.g. blood) are relatively small when compared with adult study subjects; and (iv) a general bias in biopharmaceutical development toward older individuals and adults. However, most of these hurdles have been sufficiently lowered over the past few years, such that from a technical point of view, a focus on the neonatal and young infant immune response to vaccination is entirely feasible.

(i) Our current knowledge of neonatal immune responses has significantly expanded, and is ‘coming of age’ [50].

(ii) The rapid changes affecting the immune system in the first hours and days of early life are not random, but rather appear to follow specific developmental trajectories [51,52]; such clearly defined differences are in fact key for systems vaccinology to identify possible signatures [25,53].

(iii) Although these OMIC technologies have so far only been applied to study the response to early-life infection, not vaccination, several OMIC platforms applied to even the smallest of newborns demonstrate that sample volume is not a limiting factor [54,55].

Systems vaccinology is now poised to feasibly deliver the promise it holds to those most in need of vaccine-mediated protection from infection, the youngest among the poor. ‘How the disadvantaged around the world fare is what will clearly determine the destiny of us all’ [56]. It is up to all of us to now deliver on this promise.

Funding statement. N.A. and the Kollmann laboratory benefit from the generous support of the BC Children’s Hospital Foundation and grants from the Canadian Institute for Health Research (CIHR). T.R.K. is supported in part by a Career Award in the Biomedical Sciences from the Burroughs Wellcome Fund and a Michael Smith Foundation for Health Research Career Investigator Award. O.L.’s laboratory is supported by Global Health (OPPGHS294) and Grand Challenges Explorations (OPP1035192) awards from the Bill and Melinda Gates Foundation, NIHR grant 1R01AI100135-01 (and Administrative Supplement PA-14-027) and Adjuvant Discovery Programme contract BAA-NIAID-DAIT-NIHAI2013168, as well as sponsored research agreements with 3M Drug Delivery Systems, Crucell, and MedImmune.

Authors’ contributions. N.A., O.L. and T.R.K. all provided substantial contributions to conception and drafting the article, revised it critically for important intellectual content, and provided final approval of the version to be published.

Conflict of interests. We have no competing interests.

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