Decoding the immune response to successful influenza vaccination

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Systems immunology identifies molecular and cellular signatures associated with adverse clinical events and antibody response to a vaccine against H1N1 influenza virus.

A 2013 report from the World Health Organization estimates that vaccines prevent 2.5 million deaths annually (http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/). Despite such unqualified success, the battle against seasonal and pandemic influenza still has a way to go. Each year, influenza virus causes between 250,000 and 500,000 deaths worldwide (http://www.who.int/mediacentre/factsheets/fs211/en/). Because of antigenic drift, it is the only microorganism that requires annual vaccination, and vaccine-induced protection rates vary widely on the basis of a person's age and immunological history. Although novel vaccine formulations are being tested to address these challenges[1], exactly which immunological factors lead to effective responses to vaccination remains unclear. In this issue of *Nature Immunology*, Sobolev *et al.* compile immunological and clinical responses to Pandemrix, an adjuvant-containing inactivated vaccine against H1N1 influenza virus, then apply systems approaches to identify immunological markers that could be used to guide targeted vaccination campaigns for improving personal and population health[2].

Vaccines were born and evolved from trial and error. Success and failure were clear metrics defined by life or death, and most vaccine development has proceeded without much regard for the underlying immunological factors that produce immunity. This ignorance is entirely practical, given the complexity of the immune system and the immense number of factors required for predictive models that offer useful theoretical tools for improving vaccines. Today, however, improvements in medicine and public health have made it more challenging to understand vaccine efficacy from simple metrics alone. Comprehensive measures are now needed to decode the subtle connections between vaccine outcomes and their underlying immunological factors.

Advances in monitoring the human immune system have provided the means for obtaining comprehensive measurements from peripheral blood[3]. These advances have been paralleled by large gains in computing[4], which systems immunologists have leveraged to build computational models that have identified immunological signatures for effective responses to vaccination against seasonal influenza virus[5–8] and pandemic influenza virus[2,8]. The study by Sobolev *et al.* represents the first systems-immunology analysis exploring the influence of adjuvant-containing vaccine in a mostly antigen-naive population[2]. The cohort includes 178 subjects recruited with strict enrollment criteria designed to exclude people with previous vaccination against H1N1 or diagnosis of 2009 swine flu. Additionally, the combination of multiple high-dimensional biological measurements—serological (hemagglutination inhibition, micro-neutralization, cytokines and biomarkers), cytometric (multi-parameter flow cytometry), transcriptomic (microarray) and genetic (human leukocyte antigen haplotype)—and clinical adverse-events data obtained for the same subjects makes this study a valuable resource for immunologists, clinicians and vaccine developers (**Fig. 1**).

Although various formulations of vaccines against influenza virus exist, how an adjuvant-containing vaccine perturbs the immune system has not been investigated by a systematic approach. In concordance with other studies of non–adjuvant-containing vaccines against influenza virus, Sobolev *et al.* observe a robust innate immune response 1 day after vaccination and a robust plasma-cell signature—specifically transcriptional changes and increases in cell counts—7 days after vaccination[2]. Interestingly, they detect an age-related transcriptional difference, but this molecular signature does not correlate with the hemagglutination-inhibition antibody response. Although this finding must be confirmed with additional (preferably longitudinal) data, it suggests a potential signature for the identification of immunosenescence at an earlier age.

Sobolev *et al.* identify an early interferon and lymphoid response that can be seen 1 day after vaccination[2]. These signals have not been detected in other studies, but this might be explained by differences in vaccine formulation. Specifically, the adjuvant might mimic the response pattern found to an attenuated virus[6]. Furthermore, the high vaccine response rate (~80% of subjects show a change in hemagglutination-inhibition antibody titer of ≥4, before vaccination versus after vaccination) suggests that a strong interferon response shortly after vaccination helps the immune system develop antigen-specific plasma cells.

The most intriguing finding from this study is a molecular signature of adverse events and its potential connection to a pre-vaccination B cell phenotype ($CD24^+CD38^+CD19^+CD27^-$). A subset of transitional B cells is more abundant in the peripheral blood of subjects who report greater adverse events[2]. This discovery provides the first evidence of an immunological

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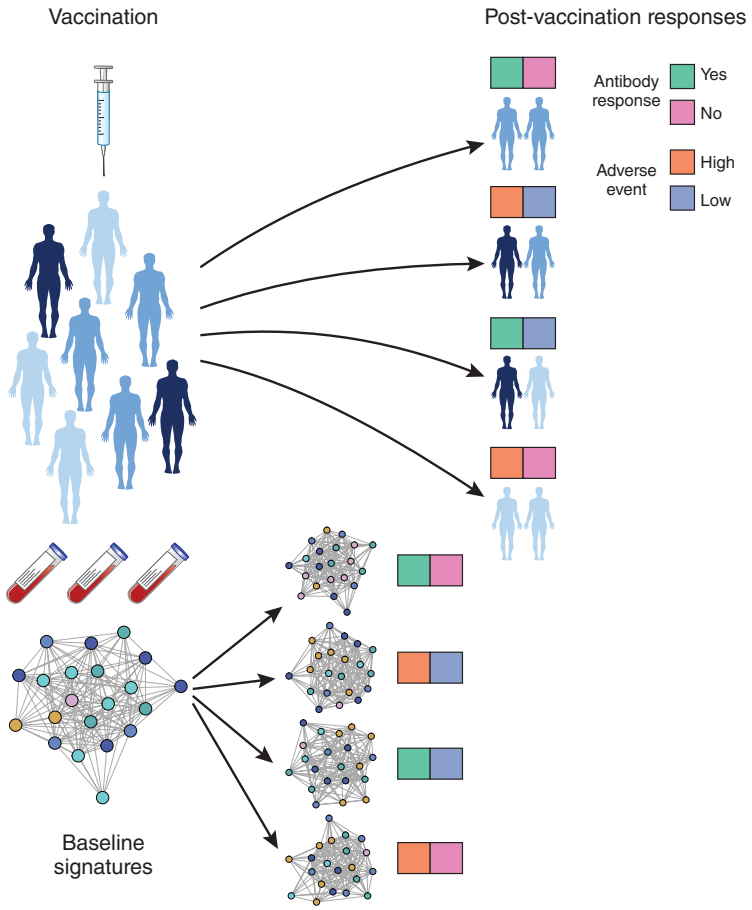

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Figure 1 Identifying immunological signatures that result in different responses to vaccination and adverse events. Multiplexed measurements obtained from peripheral blood samples collected at multiple time points from a healthy cohort of immunologically diverse subjects before and after vaccination with Pandemrix, an adjuvant-containing inactivated vaccine against H1N1 influenza virus. Integrative modelling identifies immunological signatures at baseline (before vaccination) that distinguish sub-groups of subjects with (Yes) or without (No) an antibody response to vaccination and who experience 'high' or 'low' adverse events following vaccination.

marker that might be used to identify people who are more likely to experience adverse events following vaccination. If confirmed, this phenotype could be used to match formulations with specific populations and achieve increased immunity in conjunction with minimal adverse events.

Natural immunological variation among people increases protection against pathogens at a population level, but this comes with the potential price of autoimmunity. Sobolev *et al.* show that subjects who experience 'medium' or 'high' adverse events are more likely to have elevated quantities of autoantibodies to thyroglobulin and thyroperoxidase before vaccination[2]. These biomarkers suggest sub-clinical dysregulation of the immune system, which might manifest as greater self-reactivity when triggered by perturbation of the immune system. Why these subjects experience more-severe adverse events presents an intriguing puzzle, and additional studies will be needed to elucidate whether elevated baseline quantities of autoantibodies signal pathophysiology following vaccination.

The most striking feature of vaccines is how well they work. Immunization schedules require only a few inoculations over a person's lifetime, and such immunization provides microorganism-specific protection rates that typically exceed 90–95% and last for many decades, if not for life. Given the immunological diversity in humans, elucidation of the full set of immunological factors that contribute to immunity has only just begin. Additional regulatory connections await discovery, and systems immunology approaches can help to identify the rules that govern immunity. These approaches should be applied to a broader array of formulations of vaccines against influenza virus, as well as those against other organisms[9].

The ability to collect vast streams of information and link together disparate data—biological, clinical, environmental and social—into predictive models to improve vaccination against influenza virus is unprecedented and will continue to grow[10]. Data from biological, environmental and social domains are relatively easy to compile, store and mine for insights that are both useful and unexpected[11,12]. However, data from the clinical domain are often missing, because of either privacy concerns or coordination challenges, and this information provides the greatest value, as Sobolev *et al.* show[2]. Although fully connected health records and universal monitoring has not yet been realized, immunological 'snapshots' could be collected at periodic intervals that follow normally scheduled exams, such as routine wellness visits. Over time, these 'snapshots' could be used to construct more accurate immunological baselines. Baseline values are the most important part of a response to a vaccine, yet little is understood about their stability and dynamic range among healthy people.

Sobolev *et al.* have identified novel baseline immunological markers[2] that highlight the importance of integrative and systematic modeling on large, diverse data sets. The study addresses some fundamental uncertainties about the immunological response to an adjuvant-containing vaccine against influenza virus and adds an important resource for identifying the immunological factors that result in successful immunization. Systems immunology aims to decode the factors that promote immunity to influenza virus. This resource moves the field one step closer to that goal, which will ultimately improve both personal health and population health.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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