Viewpoint

Use of serological surveys to generate key insights into the changing global landscape of infectious disease

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A central conundrum in the study of infectious disease dynamics is to define the landscape of population immunity. The proportion of individuals protected against a specific pathogen determines the timing and scale of outbreaks, and the pace of evolution for infections that can evade prevailing humoral immunity. Serological surveys provide the most direct measurement to define the immunity landscape for many infectious diseases, yet this methodology remains underexploited. To address this gap, we propose a World Serology Bank and associated major methodological developments in serological testing, study design, and quantitative analysis, which could drive a step change in our understanding and optimum control of infectious diseases.

Epidemic dynamics result from an interaction between the contagious spread of infection, the resulting depletion of population susceptibility, and its replenishment via births, immigration, or waning immunity. Understanding this interaction is key to assess the effect of vaccination, which artificially reduces the number of people susceptible to infection.

Researchers mainly observe infection dynamics and the effect of population (or herd) immunity in limiting spread via surveillance of clinically apparent cases of infection or deaths. This method has led to some powerful insights;[1] however, even in the simplest instances in which subclinical infection is uncommon, cases only provide information about the dynamics of infection. Susceptibility and immunity are hidden variables. For infections that people can be completely immunised against, such as measles, susceptible reconstruction can be used to estimate immune profiles,[2] but infection prevalence and vaccination coverage records are frequently inadequate to capture key social and geographical heterogeneities. Additionally, inference is weakened if the risk of infection is low.

Serological surveys (usually used to quantify the proportion of people positive for a specific antibody or, better yet, the titre or concentrations of an antibody) are potentially the most direct and informative technique available to infer the dynamics of a population's susceptibility and level of immunity. However, the use of current serological tests varies greatly depending on type of pathogens and there are major methodological gaps in some areas for some pathogens and tests. In terms of use of current serological methods, infections can be classified into four broad groups (appendix). The first group contains acute immunising, antigenically stable pathogens (eg, measles, rubella, and smallpox) for which serology provides a strong signal of lifetime protection and a clear marker of past infection (or vaccination).

The second group contains immunising, but antigenically variable pathogens (eg, influenza, invasive bacterial diseases, and dengue). Despite complexities (appendix), serology in some cases can provide powerful evidence, both for vaccine formulation and pandemic planning.[3,4] A serum bank would have been extremely useful in interpretation of the unusual profile of susceptibility associated with age in the 2009 influenza pandemic.[3] For these first two groups, if suitable serum banks existed, the deployment of current serological tests could have helped to clarify the association between serological profiles and protective immunity.

The third group includes infections for which infection-induced antibodies are not thought to be protective, such as tuberculosis in which the targets of the immune response vary with stage of infection; malaria, whereby infected erythrocytes generate several antibodies whose individual importance has not been fully elucidated (and might indicate exposure rather than protection[5]); and HIV. Although antibodies might not be representative of immunity against a pathogen, they do show current or previous infection.

Finally, the last broad grouping consists of infections that do not lead to reliably sustained, measurable antibody responses or for which presence of specific antibodies do not correlate with protection from future infection. These include many enteric infections and the human papillomavirus. In these cases, serological data can nonetheless be valuable to assess a population's coverage of vaccine programmes if vaccination leads to long-lasting antibody responses.

In the context of public health, for immunisation against group one infections, vaccination programmes aim to protect vaccinated individuals and indirectly protect unvaccinated individuals by maintaining high population immunity.[1] If a valid correlate of immunity is measurable in sera, serological surveys could be used to identify population subgroups in which immunity is low, or even to identify individuals in whom immunity has waned, and directly inform targeted vaccination strategies (appendix).

Household surveys are a major source of data for vaccination coverage in low-income countries.[6] The recent extension of efforts to measure biomarkers for infections such as HIV (eg, the Demographic Health Surveys) could provide infrastructure for sera collection for an expanded range of infections, thus leveraging an existing platform. For many infections, however, to

distinguish a vaccine-induced antibody response from that which follows natural infection is not possible. Additionally, after an initial successful vaccination, antibody levels might wane to become undetectable. Although these complications preclude simple interpretations of serological assays in the context of vaccination, they are an opportunity to develop new analytical techniques—eg, beyond positive versus negative to a quantitative assessment that might distinguish exposure from infection associated with transmission. Separation of natural and vaccinal immunity would be extremely useful where vaccination coverage is uncertain. However, by contrast with veterinary vaccines,[7] this difficult task has not been widely attempted for human infections, and is currently feasible for only a few infections, such as tetanus (infection does not lead to sustained antibody responses) and hepatitis B virus (vaccination only induces antibodies to the surface protein whereas infection also induces antibodies to the core protein). Increasing interest in the development of labelled vaccines is likely to substantially extend this range of infections, especially for newly developed vaccines.

The largest cost and logistical challenge involved in serological surveys is often in obtaining specimens. With these in hand, multiplexing testing to address a range of pathogen questions is a natural extension. Emergent data informs strategies for existing public health interventions, but could also contribute to help prioritise the launch of new vaccines. Successful templates for this approach were provided when prevalence of hepatitis surface antigen was used as an indicator of disease burden,[8] and age-specific prevalence of rubella antibody was used to estimate burden of congenital rubella syndrome.[9] Serological surveys in sentinel areas (focal areas for surveillance) could allow strategic deployment of vaccination or other interventions, maximising use of resources and timely intervention to benefit the entire population. For areas where immunity against a pathogen wanes, age profiles of serology can give insights into the rates of both waning and boosting of immunity from exposure to the infection (protective titres need to be known). Additional data availability would enable increased methodological research into both these inferential questions, and the connected question of translating age prevalence of infection into transmission intensity.

Beyond the first two groups (infections that people can be wholly or partly immunised against), the remaining main challenge is to develop new serological methods that clarify the role of non-immunising exposure, the complexities of cross-reactive antibodies, and the extent (or absence) of immune correlates of protection. If these questions can be addressed, serum banks for broad multipathogen targeting could be used to address various public health priorities, such as success of mass drug administration for neglected tropical diseases.[10] A combination of laboratory innovations (eg, automation, to circumvent laborious individual analyses) and analytical innovations are likely to be needed. Furthermore, with such developments serological surveys will have the potential to answer fundamental questions in infectious disease biology (appendix).

For all these reasons, we argue that a World Serology Bank would be a timely and powerful method for next generation surveillance of both established and emerging infections. Advances in the meteorology community provide an analogy: the National Oceanic and Atmospheric Administration has thousands of buoys continually reporting ocean environmental conditions.[11] It is extraordinary that no equivalent reporting mechanism is used for the world of animal and human infectious diseases. A World Serology Bank would be immediately useful to help optimise vaccination strategies, and the global end game of eradication for vaccine-preventable infections such as polio, measles, and rubella in which the mapping from individual serology to large-scale epidemic dynamics is especially clear. As spatiotemporal sampling, refinements in methodology, and multiplexing develop, this use of the World Serology Bank would only increase. Furthermore, we argue that the availability of a serum bank would be a key spur to help develop methods for infections that are serologically intractable.

An appropriate sampling scheme, powered for a range of infections, and with good laboratory standardisation will be essential. With this scheme in place, annual age stratified sampling of serology at key sentinel sites worldwide could provide a unique window into the global landscape of immunity. Both opportunistic analysis of existing samples and purpose built serum banks could contribute to this resource. Opportunistic samples might be particularly valuable with unusual patterns of infection—eg, showing the extent to which the immune landscape has constrained emergence of enteroviruses in Asia.[12] The potential for global spread of emerging infections underscores the importance of a global serological bank. In the recent outbreaks of Middle East respiratory syndrome coronavirus (MERS-CoV; in 2012) and Ebola virus (which began in 2013) it would have been invaluable to know if any evidence showed pre-existing immunity to these diseases in the populations where they emerged, clarifying the role of unseen infections or cross-immunity with other pathogen strains.

A system of distributed storage repositories worldwide that draws on existing models for logistics, ethics, and best practices in housing samples and data (appendix), would be a powerful addition to the global health landscape. Every country could contribute to and benefit from such a system. Expansion of the serum bank will need substantial methodological advances in serological techniques (appendix). Development of analytical and modelling techniques to interpret the resulting effects of population immunity[2,13] is also essential, and equally likely to be inspired by the availability of broad-scale data.

To conclude, systematic multiplex estimates of the spatiotemporal dynamics of individual and population immunity to various pathogens would be a powerful new system for global health informatics. A World Serology Bank could boost fundamental understanding of disease dynamics, correlates of protection,[14] effects of control programmes, risks or protective factors of emerging infections, and inform reactive policies in global health.

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