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Scientific Life

The Immunologists' Guide to Pandemic Preparedness

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Immunologists are central to fighting any pandemic. From pathogenesis to disease modeling, pharmaceuticals to vaccines, immunologists play a crucial role in translating basic science into effective response strategies. This article describes our view on how lessons from the coronavirus disease 2019 (COVID-19) pandemic can be developed into an immunologists' guide for preparedness for future pandemics.

Immunologists are central to the scientific fight against pandemics, despite having only a limited formal role to date. Pandemic preparedness is defined by the United Nations and the World Health Organization (WHO) as 'the ability, meaning knowledge, capacities and organizational systems, of governments, professional response organizations, communities and individuals to anticipate, detect and respond effectively to, and recover from, the impact of a likely, imminent or current health emergencies, hazards, events or conditions'^{i,ii}. Public health officials, epidemiologists, infectious disease physicians, virologists, bacteriologists, and vaccinologists all have defined roles in preparing for pandemics, but immunologists have largely been peripheral to the bigger enterprise.

The COVID-19 pandemic has helped show the value of immunologists. They have been integrated into quests for rapid diagnostics, vaccines, and therapeutics. They are asked for help with plasma collections and

monoclonal antibody production, assessments of cross-reactive T cells, or production of 'off-the-shelf' natural killer (NK) cells. Their assessments of immunity, durable or not, neutralizing or 'in name only', guide predictive modeling that influences public policy. Through diagnostic assays, therapeutics, and vaccines, immunologists are essential in understanding the pathogenesis of the disease, and counseling about time points for immunological interventions. However, the COVID-19 pandemic has boxed immunologists into silos, with vaccine immunologists dissociated from diagnostic immunologists, and B cell immunologists from T cell immunologists, prompting an article in *The Atlantic* by Ed Yong entitled, 'Immunology Is Where Intuition Goes to Die' [1]. Yet much can (and must) be learnt from other immunology specialists, as summed up in the byline of the article: 'Which is too bad because we really need to understand how the immune system reacts to the coronavirus'.

In this Scientific Life article, we discuss highlights in the rapid response to the current COVID-19 pandemic, and develop a road map, from our perspective, for immunologists to follow in preparation for the inevitable next pandemic: 'A Pandemic Preparedness Plan for Immunologists'.

How Have Immunologists Contributed to Fighting the COVID-19 Pandemic?

Coordination of Local Groups of Immunologists into Immunology Pandemic Task Forces

The speed of spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus around the world took many by surprise and, in transport hub cities such as New York City, the overwhelming number of patients focused attention on saving lives. In parallel, scientists in China and elsewhere made fundamental discoveries about the 'novel' human coronavirus, and its isolation and

sequencing hastened tests to identify the specific virus in diagnostic samples. Since there was similarity with SARS and Middle East respiratory syndrome (MERS) coronaviruses, coronavirologists and respiratory pathogen virologists started down a familiar path of virological discovery. Yet, there were differences from previous pathogens, namely, a lower case fatality rate and more cases of asymptomatic carriage, suggesting that immune responses differ in part from those directed against MERS or SARS coronaviruses.

In New York City, a rapid mobilization of immunologists, including students, fellows, staff, and faculty, at the Precision Immunology Institute at the Icahn School of Medicine (PrISM) came together to create 'The Sinai Immunology Review project' [2], which not only helped coalesce and catalog immunology research efforts at their medical school, including an immunology review [3], but also created a curation of preprint articles as an invaluable source to help sort through the explosion of non-peer-reviewed preprints [2]. At Oxford University, UK, a group of research students and early-career researchers created the OxImmuno Literature initiative, a team of ~100 researchers who read, reviewed, summarized, and blogged recent COVID-19 researchⁱⁱⁱ, and this has now expanded to include Cardiff University, UK, which had set up a similar initiative.

Access to Resources and Knowledge

The American Association of Immunologists (AAI), the British Society for Immunology, 'Immunopedia', and the International Union of Immunological Societies are a selection of immunology-focused societies, in addition to publishing companies, that set up online COVID-19 resources. A summary of current activities was reported recently: 'The global response to the COVID-19 pandemic: how have immunology societies contributed?' [4]. Major immunology specialty journals, such as *Immunity* and

Trends in Immunology within the Cell Press Coronavirus Resource Hub^{iv}, as well as others, such as *Nature Immunology* and *Science Immunology*, are collating relevant COVID-19 literature, making it freely available.

Participation of Immunologists in Research Efforts

AAI provides a list of AAI Members at the forefront of the coronavirus pandemic response, and highlights individuals involved in SARS-CoV-2 testing, vaccine, and immunopathogenesis research. At the La Jolla Institute for Immunology, an institute focused on immunology research, scientists have come together to fight COVID-19^v, and continue to provide regular updates on research progress through their 'COVID-19 Updates: Live from the Laboratory' series.

An Immunology Pandemic Preparedness Task Force: Practical Considerations

We propose that groups of immunologists coalesce both within national bodies and internationally to create a pandemic preparedness task force, which could be part of larger efforts, or independent in providing advice. We argue that the first order of business should be developing a plan for a scientific path forward: how to assess biological risk level and negotiate access to appropriate experimental space, and how to ensure the proper biobanking for samples needed for immunological studies. For example, many investigators have been impeded through slow institutional actions on institutional review boards (IRB) or institutional animal care and use committee (IACUC) approvals, and a 'pandemic' global IRB and IACUC plan should be in place to rapidly accelerate access to samples and procedures, adaptable to a new pandemic for rapid approval. Committees that normally approve these should have emergency powers to convene and approve such documents rapidly. Considering the novelty and seriousness of future pandemic

pathogens, appropriate containment workspace, including for animal studies [Biosafety Level 3 (BSL3)/Animal Biological Safety Level 3 (ABSL3)], space is essential, because most institutions have limited capacity at these biosafety levels. Plans should be in place for rapid temporary redeployment of such existing spaces for new pandemics. Research on diseases of major past importance should be paused for research on diseases of immediate present danger. Immunologists rely on carefully curated human samples for immunological studies and, unfortunately, during the COVID-19 pandemic, many institutional biobanks were not prepared for viable cryopreservation of peripheral blood mononuclear cells or samples from bronchoalveolar lavage fluid from patients with COVID-19. Widespread collection and access to these samples for investigators can be planned well in advance for rapid deployment when needed. This institutional planning, and the identification of staff with the skills and experience in immunological techniques, as well as securing emergency funding in place, are all actions that can be planned.

Securing the Immunologist's Role in a Pandemic Response

Immunological data are essential to understand the human–pathogen interface; the immunologists' seats at the pandemic response table should reflect their unique role as generators and custodians of such data. This type of input is necessary for

everything: from accurate mathematical modeling of disease spread, to determining markers of susceptibility to infection, to the selection of effective countermeasures against disease. Immunologists can uniquely guide: (i) the initial determination of serological responses and neutralizing antibodies against the pathogen, followed by isolation of B cells and the generation of monoclonal antibodies; (ii) the characterization of T cells, with epitope mapping and determination of any cross-reactive responses; (iii) analyses of T cell receptor (TCR) and B cell receptor (BCR) repertoires; (iv) studies on mucosal and innate immunity; and (v) the development of immunopathogenesis studies and animal models, among others. Integrating this knowledge into the local, national, and international epidemic preparedness structures is pivotal to any science-based response to pandemics.

Along these lines, a group of immunologists have come together to form a Coronavirus Immunotherapy Consortium (CoVIC), a global alliance modeled after the successful Ebola virus team and geared towards finding therapeutic antibodies to treat COVID-19. Other groups have proposed similar consortia: Pandemic Preparedness: Developing Vaccines and Therapeutic Antibodies For COVID-19 [5], and the plan for a Universal Vaccine for Pandemic Coronaviruses by scientific studies that dissect the Spike protein of SARS-CoV2 to seek broadly neutralizing antibodies

Box 1. Population Immunology: The Landscape or Terrain

The notion of an 'immunological landscape' is not new: the commonly used French medical term '*terrain*' captures more than just the direct translation (i.e., 'land'), extending its meaning to capture the dynamic relationship between the human organism and other life forms that surround and live within it. It has also been referred to as immunological 'dark matter'. Karl Friston speculated that Germany has more immunological 'dark matter', that is, people who might be impervious to COVID-19 infection, perhaps because they are geographically isolated or have some kind of natural resistance [7]. Emerging knowledge of how the human immune system may be intentionally 'reprogrammed' to increase resistance to pathogens, such as through Heterologous Vaccine Interventions (HVIs), opens the door to more active means of reducing pandemic impacts. One possibility might be to plan for intensified efforts to increase routine vaccination adherence at the first sign of the spread of a novel pathogen. While attempts to alter this immunological landscape may be tempting, pandemic responders need to appreciate the even greater importance of measuring its current and future condition through rapid serological surveys or T cell assays (e.g., a 'Quantiferon' type of assay).

Box 2. Lessons for the Next Pandemic: An Immunologist's View

Lessons would include:

- (i) The mobilization of immunologists to collect and evaluate the quality of new immunology research at national and international levels.
- (ii) The involvement of immunologists from day 1 of an epidemic/pandemic threat, gathering in research groups aiming to study the emerging threat.
- (iii) The expansion of 'traditional' immunosurveillance to a large and frequent universal population sampling; the aim would be to create a World and/or National Immunology Specimen Bank in which the 'immunological pulse' of a specific population could be established. Therefore, this could be used to stratify the population risks of acquiring the new pathogen or developing severe illness.
- (iv) The development of mathematical models that might quickly facilitate the study of the dynamics of immune responses against an emerging pathogen across molecular, genetic, cellular, and tissue scales.

that could work against newly emerging coronaviruses [6].

Since pandemics are part of our collective future, immunologists have a role in preparing populations through 'immunological surveillance'. While programs are well established for the identification of novel viruses, especially in south-east Asia, what is currently missing is coordinated measurements at the population-level immunological landscape or as termed in French, '*le terrain*' (Box 1). Serological surveillance for population-level antibody responses to specific corona-, paramyxo-, or nipah viruses can not only be used for known specific pathogens, but the threshold for test positivity could also be relaxed to provide an additional probe of virus-level cross-reactivity within a population. We posit that the pools of cross-reactive predicted T cell epitopes to common virus families that are more associated with pandemics, might be used to survey broad cross-reactive T cell immunity.

Baseline population-level measurements of innate immunity, including NK cell measurements, are also needed. Age, gender, race, demographics, and genetics, to name a few, are all necessary inputs for interpreting such new 'Big Data' sets. Yet, our knowledge of the 'immunological health or pulse' of a population is currently basic at best, and often, outright neglected (Box 2).

Thus, we encourage all immunologists to mobilize resources and efforts, and to increase and highlight their important contributions to fighting COVID-19 and/or future pandemics. Equally, we urge epidemiologists, disease modelers, health system managers, and public health policy-makers to recognize the crucial role of immunological data; it is necessary to craft meaningful ways for immunological research and knowledge to be incorporated into emergency response planning, and rapidly utilized in actual pandemic responses.

Acknowledgments

We thank our colleagues, friends, and families who have inspired and educated us over the past year. We also mourn those lost to COVID-19.

Resources

- ⁱwww.humanitarianresponse.info/en/coordination/preparedness/what-preparedness
- ⁱⁱ<https://extranet.who.int/sph/sites/default/files/document-library/document/Preparedness-9789241511827-eng.pdf>
- ⁱⁱⁱwww.medsci.ox.ac.uk/news/oximmuno-literature-blog-covid-19-research-papers-explained-simply
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<https://doi.org/10.1016/j.it.2020.12.003>

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