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Enterovirus D68: a test case for the use of immunological surveillance to develop tools to mitigate the pandemic potential of emerging pathogens

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In the autumn of 2014, the USA faced an unexpected spike in cases of previously healthy children stricken with polio-like paralysis following a febrile respiratory illness. Since that time, research efforts have shed light on the causes, mechanisms, and outcomes of this disease, now termed acute flaccid myelitis.[1] However, subsequent seasonal outbreaks have continued, in North America and Europe in 2016 and 2018, and have been increasingly recognised around the globe. To date, there remain no known effective treatments or prevention strategies for acute flaccid myelitis, which has left over 650 children in the USA profoundly affected, most with permanent paralysis. Following the absence of a predicted spike in cases in 2020, most likely due to non-pharmaceutical interventions in response to the COVID-19 pandemic, the next acute flaccid myelitis outbreak is looming, but timing remains unknown.

Epidemiological, clinical, and laboratory data indicate that non-polio enteroviruses, most notably enterovirus D68, are the predominant drivers behind the recent increase in acute flaccid myelitis cases.[2] Enterovirus D68 is an emerging RNA virus spread via respiratory transmission, causing outbreaks of severe respiratory symptoms including wheezing and respiratory distress. Laboratory models suggest that enterovirus D68 can infect neurons and spread via retrograde axonal transport in vitro and can lead to spinal cord motor neuron death resulting in acute flaccid myelitis-like paralysis in mice. Monoclonal antibodies and vaccine candidates are in early preclinical stages of development, but there are currently no approved therapies or vaccines against enterovirus D68.

The COVID-19 pandemic has underscored the urgency required to meet the threat of unexpected spikes of illnesses due to emerging pathogens. Comprehensive immunological surveillance that rapidly maps reactivity to viral infections of known and unknown causes, and which represent potential epidemic and pandemic threats, is currently inadequate. The implementation and deployment of such global reconnaissance for infectious diseases would enable rapid development of diagnostic and therapeutic agents and vaccines to pre-empt and thus mitigate widespread disease. As non-pharmaceutical interventions for the COVID-19 pandemic are lifted, respiratory viruses, including enterovirus D68, are likely to return with consequentially larger susceptible populations. The challenge presented by enterovirus D68, and the likelihood of an impending resurgence, makes this an ideal test case for the ability of immunological surveillance to rapidly develop tools to mitigate the pandemic potential of an emerging pathogen.

Since 2014, outbreaks of enterovirus D68 cases in the USA have geographically and temporally coincided with seasonal biennial spikes in acute flaccid myelitis cases.[3] Understanding the epidemiological dynamics of enterovirus D68 has remained a key question in predicting its future outbreaks and identifying its causal link with acute flaccid myelitis.

Biennial epidemic patterns have historically been found in acute immunising infections, hinting at the strength and duration of immunity against natural enterovirus D68 infections. Classical studies of pre-vaccination measles outbreaks in the UK lend insight into core mechanisms driving biennial patterns: large outbreaks deplete the susceptible pool and limit the size of future outbreaks until the susceptible pool is replenished via birth cohorts. Epidemiological analyses of biennial outbreaks of enterovirus D68 and other enteroviruses support this mechanism.[3,4]

Because of the ongoing COVID-19 pandemic, non-pharmaceutical interventions such as mask wearing and social distancing most likely prevented the predicted enterovirus D68 outbreak in 2020, but increased the susceptible pool of individuals, creating an immunity gap (appendix pp 1–2). This gap could, in turn, cause a large outbreak after the interventions are lifted (appendix pp 1–2). Although delayed outbreaks are expected to be larger due to additional increases in the susceptible pool, even a modest reduction in transmission rates—either due to partial lifting of COVID-19 interventions (appendix pp 1–2)

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or seasonality—can reduce the size of the outbreak. For example, a 60% reduction in transmission rate in 2020 results in a delayed, but smaller, outbreak due to decreased transmission of enterovirus D68 during winter. Although the exact timing of the next enterovirus D68 outbreak is difficult to predict, large outbreaks of enterovirus D68, and therefore acute flaccid myelitis, are likely to be imminent. An analogy can be made to the 1950s in the USA when the baby boom increased the susceptible pool and led to a sudden, drastic increase in poliovirus poliomyelitis cases.[5]

The need to further understand seroprevalence of enterovirus D68 in preparation of the next potential outbreak and the absence of current countermeasures for acute flaccid myelitis, creates an opportunity to use enterovirus D68 as a test case to pilot the development of an immunological surveillance programme to help alleviate future outbreaks of enterovirus D68, with implications for other serious childhood respiratory diseases and emerging human pathogens with pandemic potential. Although some passive, retrospective surveillance exists for enterovirus D68 and acute flaccid myelitis, there is a critical need for real-time immunology-based surveillance systems to provide specialised biological specimens, such as prospectively collected peripheral blood mononuclear cells, serum, and plasma, from children likely to have primary infection with contemporary circulating enterovirus D68 strains and other respiratory diseases. These types of specimens are a key component to rapid development of vaccine candidates, such as the highly successful SARS-CoV-2 vaccines. Enterovirus D68 presents a timely opportunity to pilot an immunological surveillance programme because of the high probability of an impending resurgence of this pathogen of public health significance in need of rapid development of novel therapies and vaccine candidates.

The COVID-19 pandemic has demonstrated a critical need to establish a pre-emptive stockpile of tangible immunobiological countermeasures to accelerate the response to potential pandemic threats. To address this need we have established a pandemic response repository through microbial and immunological surveillance and epidemiology (PREMISE) initiative (appendix pp 1–2). While rapid detection and surveillance of novel and emerging pathogens are well-recognised core components of pandemic preparedness, deep analysis of host immune responses at a population-wide scale is a parallel, but currently insufficient, fundamental component of a swift, effective response to infectious threats.[6] PREMISE aims to conduct immune analysis of targeted and broad human cohorts to detect reactivity against potentially pandemic viruses, and to identify immunogens suitable for vaccine discovery and monoclonal antibodies for prevention and therapy using a pathogen-agnostic approach. Deliverables will include sequence information of immunogenic regions and monoclonal antibodies specific for viruses of concern, and resources for early detection and diagnostic assays. Additionally, seroepidemiology data will shed light on the duration of maternal antibody protection, age at primary infection, and dynamics of spread of recently emerging strains to guide pandemic response. PREMISE is not a global serosurveillance network or an early warning system, although its goal is to use information from serosurveillance networks for immunological and virological screening and product design. PREMISE is also not a prototype pathogen approach to vaccine design, which is a virological approach, but aims to use an immunological approach to work synergistically with prototype pathogen approaches to identify immunologically relevant proteins leading to the discovery of immunobiological products. The strengths of PREMISE will be its ability to map the landscape of immunological activity to known and unknown pathogens and to use these findings to discover immunobiologicals to anticipate and accelerate the global response to pandemic threats. Using enterovirus D68 as a test case for PREMISE will provide insight into enterovirus D68 seroepidemiology and establish an immunological biorepository to expedite the ability to respond to future enterovirus D68 acute flaccid myelitis outbreaks, as well as establish best practices for future pandemic pathogen immune surveillance.

Preparedness for emerging pathogens, such as enterovirus D68, relies on both pathogen surveillance and immunological surveillance to guide rapid development of diagnostic, therapeutic, and preventative tools to combat the next pandemic. By using PREMISE to combat future outbreaks of enterovirus D68 acute flaccid myelitis, we aim to rapidly develop countermeasures for this devastating disease and from there expand the programme to better

prepare for future emerging pathogens with pandemic potential.

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