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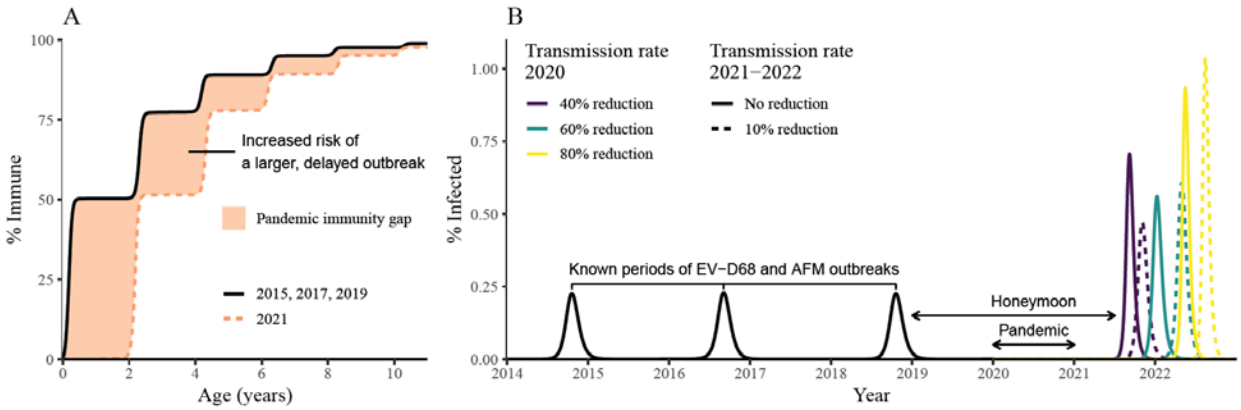
Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Nguyen-Tran H, Park SW, Messacar K, et al. Enterovirus D68: a test case for the use of immunological surveillance to develop tools to mitigate the pandemic potential of emerging pathogens. *Lancet Microbe* 2022; published online Jan 7. https://doi.org/10.1016/S2666-5247(21)00312-8.

SUPPLEMENTAL FIGURE 1: Impact of Immunity Gap on Enterovirus D68 Dynamics, Implications for Future Pandemics, and Preparedness through Immunologic Surveillance



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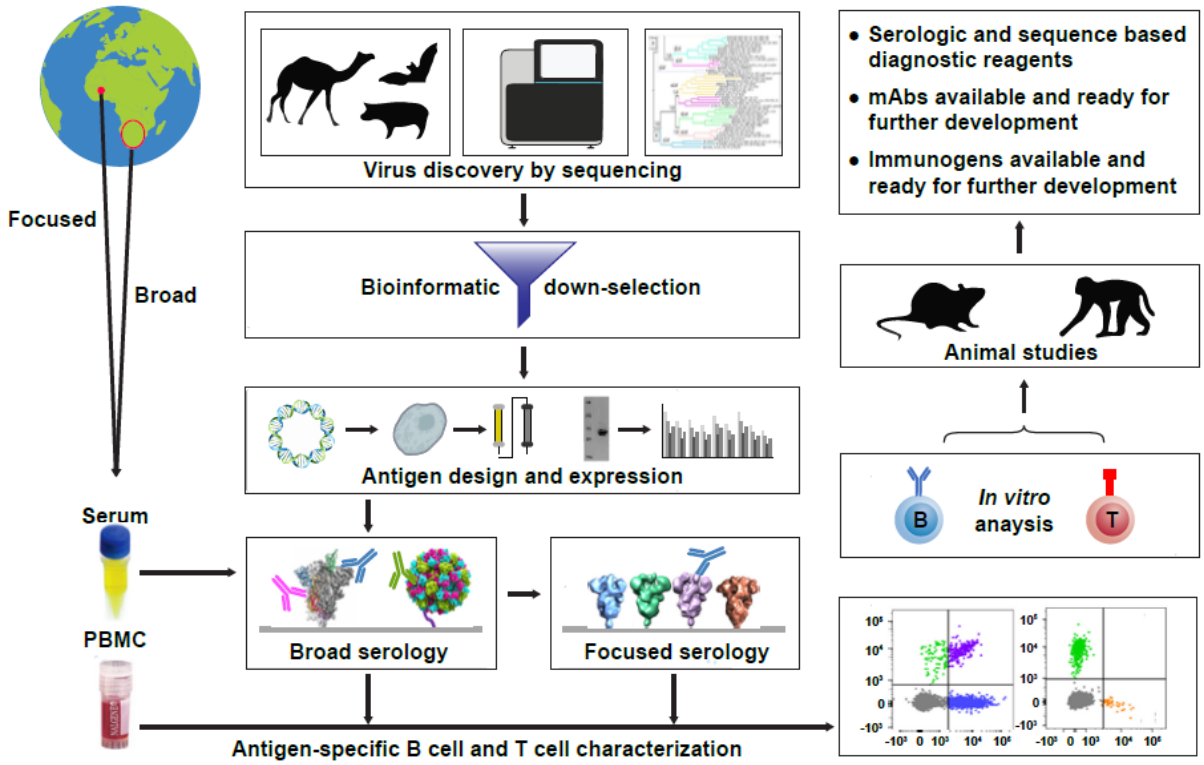

Legend (A) Immunity gap predicted by the SIR model between population-level immunity at the beginning of typical odd years (2015, 2017, 2019), which followed major biennial outbreaks, and population-level immunity at the beginning of 2021, assuming 40% reduction in transmission rates in 2020 due to nonpharmaceutical efforts to reduce the spread of SARS-CoV-2. (B) SIR model predictions of future EV-D68 outbreaks following a honeymoon period, or a period of low transmission during which susceptibles can build up undetectably, resulting in an eventual large outbreak. We assume 40%-80% reduction in transmission rates during 2020, followed by a complete (and no reduction in transmission rate; solid lines) or partial (and 10% reduction in transmission rate; dashed lines) lifting of interventions in 2021-2022. Reductions in transmission rates are modeled relative to their corresponding pre-pandemic values (see Supplementary text). (C) The PREMISE workflow begins with focused and broad cohorts providing samples of serum and peripheral blood mononuclear cells (PBMCs) and virus discovery using various databases to select sequences to provide antigens for design and expression. Serum samples will then be analyzed using these antigens via broad and focused serology and, if a signal is detected, PBMCs will be analyzed to look at antigen-specific B and T cell characterization. Finally, *In vitro* analysis will be conducted followed by animal studies yielding PREMISE deliverables.

SUPPLEMENTARY METHODS

We make qualitative predictions about EV-D68 outbreaks using the Susceptible-Infected-Recovered (SIR) model, which assumes that infections provide serotype-specific, life-long immunity—previous studies have shown that the dynamics of many enterovirus serotypes, including EV-D68, are consistent with those predicted by the SIR model[3,4]. Assuming homogeneous mixing, the dynamics of proportions of susceptible (*S*), infected (*I*), and recovered (*R*) individuals can be expressed as:

$$\frac{dS}{dt} = \mu - \beta(t)SI - \mu S$$

$$\frac{dI}{dt} = \beta(t)SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

where μ represents the birth and death rates, $\beta(t)$ represents the transmission rate, and γ represents the recovery rate. To account for seasonality, we assume that the transmission rate follows a sinusoidal function:

$$\beta(t) = \mathcal{R}_0\gamma\left(1 + b_0\cos\left(\frac{2\pi(t-\phi)}{52}\right)\right).$$

where $\mathcal{R}_0$ represents the basic reproduction number, b_0 represents the seasonal amplitude, and ϕ determines the timing of peak transmission.

In order to simulate biennial epidemics between summer and fall, we use parameters that are broadly consistent with earlier estimates[3,4]: $\mathcal{R}_0$ = 30, $1/\gamma$ = 1 week, b_0 = 0.1, ϕ = 30, and $1/\mu$ = 80×52 weeks. We note that changes in birth rate is equivalent changes in the basic reproduction number. The classical biennial measles epidemics during the pre-vaccination era required a lower $\mathcal{R}_0$ = 17 but had a higher birth rate $1/\mu$ = 50 × 52 weeks. Given that current birth rates are much lower, a higher $\mathcal{R}_0$ is required to generate stable biennial epidemics.

The initial conditions are assumed to be *S*(0) = 0.05 and *I*(0) = 0.001. The model is then run for 55 years to remove any transient effects and to allow the system to reach stable biennial cycles.

The beginning of year 55 is taken to be the beginning of 2014. In the beginning of 2020 (thus, year 61), the transmission rate is reduced to simulate the impact of nonpharmaceutical interventions. Then, we increase transmission rate in the beginning of 2021 (thus, year 62) to account for the relaxation of intervention measures. The introduction and lifting of interventions are modeled by adjusting the transmission rate as follows:

$$\beta(t) = \big(1 - \theta(t)\big)\mathcal{R}_0\gamma\left(1 + b_0\cos\left(\frac{2\pi(t-\phi)}{52}\right)\right).$$

Here, $\vartheta(t)$ determines the degree of reduction in transmission rates:

$$\theta(t) = \begin{cases} 0 & t < 61 \times 52 \\ \theta_1 & 61 \times 52 \le t < 62 \times 52 \\ \theta_2 & 62 \times 52 \le t \end{cases}$$

where t has a unit of weeks, θ_1 is allowed to vary between 0.4–0.8, and θ_2 is allowed to vary between 0–0.1.

Given the force of infection predicted by the SIR model, $\lambda(t) = \beta(t)I$, seroprevalence at age *a* at time *t* is given by:

$$p_t(a) = 1 - \exp\left(-\int_0^a \lambda(t-s)\mathrm{d}\,s\right),$$

which corresponds to the probability that an individual born at time *t*−*a* has been infected by time *t* (thus age *a*). We compute the age-dependent seroprevalence at the beginning of year 2019 and at the beginning of year 2021. Then, the immunity gap corresponds to the differences in seroprevalence between those two time points.