CLADE X MODEL SUMMARY

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The Clade X model simulates an outbreak of a moderately transmissible pathogen in a fully susceptible population. The model is intended to be a realistic representation of how a novel infectious disease could become a pandemic in the absence of adequate control measures.

MODEL DESCRIPTION

We used an ordinary differential equation approach to simulate the Clade X pandemic. A graphic depiction of the model structure and a table of the key parameters are available in the Appendix. The model contains 8 compartments representing different stages of infection. Key features of the model include 2 compartments for individuals infectious in the community: those with severe illness (I_S) who go on to be hospitalized (H) at a rate κ_2, and those with mild illness (I_M) who remain in the community for the duration of the infection, γ days. The model assumes that individuals with severe illness in the community are the most infectious due to increased viral load and more severe symptoms. Those with mild illness and those in the hospital have reduced probability of transmission, by a factor of ϵ, to account for lower viral load, less mild symptoms, and reduced contact with others. Hospitalized patients remain in the hospital for α_2 days. At the end of this time, a fraction of them (δ) succumb to the disease and die (D). The remainder survive and enter a long convalescence period (C; ρ days in length) during which they are no longer infectious but are not well enough to participate in daily responsibilities like work. Those with mild illness also face the same period of convalescence before fully recovering (R).

MODEL EQUATIONS

$$\frac{dS}{dt} = -\frac{\beta S(I_S+\epsilon_M I_M+\epsilon_H H)}{N} \quad (1)$$

$$\frac{dE}{dt} = \frac{\beta S(I_S+\epsilon_M I_M+\epsilon_H H)}{N} - (1-\theta)\kappa_1 E - \theta\kappa_2 E \quad (2)$$

$$\frac{dI_M}{dt} = (1-\theta)\kappa_1 E - \gamma I_M \quad (3)$$

$$\frac{dI_S}{dt} = \theta\kappa_2 E - \alpha_1 I_s \quad (4)$$

$$\frac{dH}{dt} = \alpha_1 I_S - (1-\delta)\alpha_2 H - \delta\alpha_2 H \quad (5)$$

$$\frac{dC}{dt} = \gamma I_M + (1-\delta)\alpha_2 H - \rho C \quad (6)$$

$$\frac{dR}{dt} = \rho C \quad (7)$$

$$\frac{dD}{dt} = \delta\alpha_2 H \quad (8)$$

INITIAL ATTACKS

The model assumes that the first cases of Clade X in the world are the result of deliberate attacks in the cities of Caracas, Venezuela, and Frankfurt, Germany. The number of people infected by the attack in each of these cities is 50 and 60, respectively. Because victims of a deliberate biological release may be exposed to a larger dose of infectious pathogens than those infected naturally, the proportion of index cases hospitalized is around 80%. In contrast, the proportion of cases hospitalized among naturally acquired infections is 50%. The case fatality risk (CFR) among hospitalized patients for most of the affected cities is 20%. However, the CFR was inflated to 50% for Caracas to reflect the degradation of the healthcare and public health systems.

GLOBAL SPREAD

Following the 2 initial attacks, 300 of the largest cities in the world were stochastically seeded with infectious cases over time to represent disease spread through international travel. The rate at which new cities were added to the model grows exponentially, much like the growth of the epidemic itself. The number of imported cases ranged from 1 to 7 for each city. In order to capture greater geographic fidelity, a separate model pipeline was created for the United States, using the same model structure described above. The towns of Bethesda, Maryland, and Berkshire, Massachusetts, were seeded in accordance with the exercise storyline. In addition, 300 of the largest cities and towns

in the United States were seeded randomly. As with the global model, the rate at which new cities were added to the model grows exponentially.

The model was run for each individual city in turn. To simulate the stochastic nature of outbreaks, parameters for each city were randomly selected from realistic distributions. The force of infection, β, was chosen from a normal distribution calibrated to produce an overall basic reproduction number of 1.8 (the reproduction number of individual cities ranged from 1.0 to 2.6). The infectiousness of hospitalized cases was reduced by between 20% and 60% to represent uneven capacity for effective infection control. Similarly, the CFR of hospitalized patients was chosen from a uniform distribution of between 15% and 30%, reflecting expected variation in the ability of healthcare systems to provide high-quality care when faced with large numbers of critically ill patients.

The case counts reported in the exercise represent infections in hospitalized patients exclusively, under the assumption that mild illnesses in the community are less likely to be captured by surveillance systems. The exercise also reports only on the 300 global and 300 US cities represented in the model. Not accounting for smaller countries and cities, the numbers reported in the scenario are conservative. However, like all models of this type, a core assumption is that the trajectory of the outbreak remains continuous. In real outbreaks, the trajectory is constantly changing in response to a number of factors, like collective behavior change, which tend to slow outbreak growth.

VACCINE MODELING

The exercise ends with illustrative examples of how the trajectory of the outbreak would have changed had a vaccine been available at various time points in the scenario. The vaccine was assumed to confer full immunity 30 days after administration. In order to model these scenarios, an additional compartment for the vaccine-immune was added to the United States model. Scenarios in which the vaccine was introduced at 6, 9, 12, and 18 months were modeled and compared.

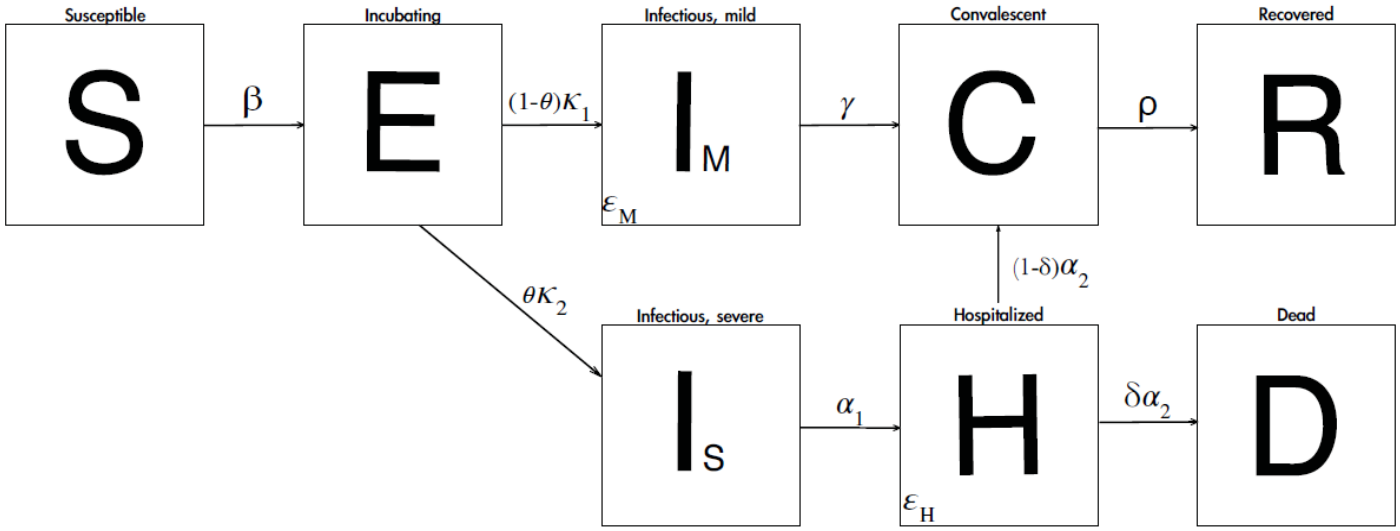
Upon the introduction of the vaccine, the equivalent of 0.8% of the susceptible population was moved to the vaccine-immune compartment each model-day. This rate was chosen to approximate a realistic vaccine production schedule, in which production and distribution ramps up until there is enough product for the entire susceptible population. For the scenario in which the vaccine is introduced at 12 months, there are 29 million doses produced and distributed in the United States during the first month.

Because new cities are added to the modeled timeline as the outbreak spreads, some cities did not become seeded until after the introduction of the vaccine. In those instances, the number of susceptible individuals made immune through vaccination prior to the introduction of Clade X was

estimated by multiplying the number of days between vaccine availability and Clade X introduction by 0.8%. The model was then instantiated with those adjusted initial conditions.

For the vaccine epilogue, the final case estimates reported in the scenario include both hospitalized and mild cases. The case counts are also scaled to account for the number of Americans living outside of the 300 largest cities. In contrast to the scenario case reporting, which focuses on hospitalized cases, the epilogue case counts represent improved surveillance and disease burden estimates that generally only become possible retrospectively, or after a public health crisis has stabilized.

Appendix: Key Model Parameters



β	transmission rate	variable	ε	reduced infectiousness	variable
κ_1	incubation period, mild	5 days	θ	fraction severe	50%
κ_2	incubation period, severe	5 days	α_1	days to hospitalization	3 days
γ	infectious period in community	7 days	δ	case fatality risk in hospitalized	variable - 20% on average
ρ	post-infectious recovery rate	90 days	α_2	infectious period in hospitalized	10 days