Estimated impact of mitigation measures: Overview of mathematical modelling consultation

Ira Longini
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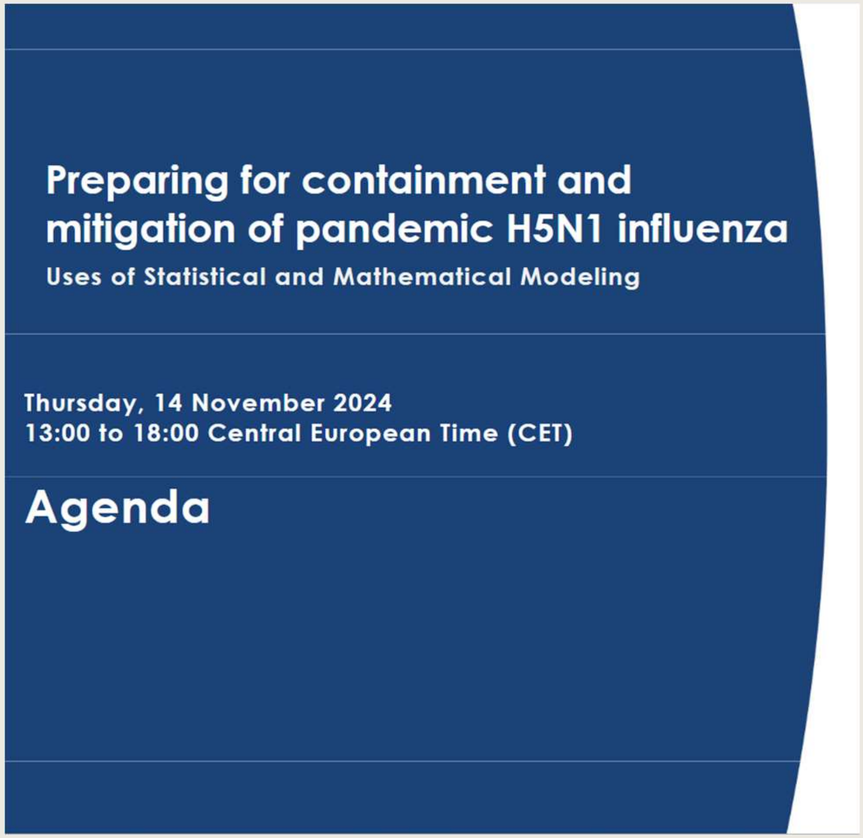
World Health Organization

R&DBlueprint

UF UNIVERSITY of FLORIDA



Preparing for containment and mitigation of pandemic H5N1 influenza

Uses of Statistical and Mathematical Modeling

Thursday, 14 November 2024
13:00 to 18:00 Central European Time (CET)

Agenda

WHO expert group on the mathematical modeling and quantitative epidemiology on the diseases of greatest epidemic and pandemic threat

Ira Longini, U Florida (Chair)
Stefano Merler, BKF (Bruno Kessler Foundation)
Valentina Marziano, BKF
Piero Poletti, BKF
Giorgio Guzzetta, BKF
Alex Vespignani, Epistorm, NE Univ.
Jessica Davis, Epistorm, NE University
John Edmunds, LSHTM
Adam Kucjarski, LSHTM
Sebastian Funk, LSHTM
Nick Davies, LSHTM
Neil Ferguson, Imperial
Nigel Gay, WHO
Matt Hitchings, UF
Alhassane Toure, WHO
Ben Cowling, U Hong Kong
Claudio Stuchiner, Oswaldo Cruz Foudation
Wilfred Ndifon, African Institute for Math Sciences
Elizabeth Halloran, FHCC, U Wash

https://www.who.int/news-room/events/detail/2024/11/14/default-calendar/preparing-for-containment-and-mitigation-of-pandemic-h5n1-influenza--uses-of-statistical-and-mathematical-modeling

OBJECTIVES

- Outline the current pandemic threat and potential containment or mitigation of influenza A (H5N1) or some other variant
- Understand the analytical and statistical tools available and how to apply them to containment efforts
- Understand the current mathematical modeling tools available and how to apply them to containment and mitigation efforts
- Describe what new analytic and mathematical models need to be developed and integrated into the response
- Devise an approach to coordinate the analytical and modeling efforts both within and outside of WHO with a cohesive collaborative plan

OUTCOMES

- Development of an emergency response with analytical and mathematical methods for pandemic influenza A(H5N1)
- Enhanced collaboration and partnerships
- Key steps and timelines: Provided an outline of essential steps and timelines to address the identified research gaps and opportunities, ensuring a structured approach to advancing the research agenda

Three Pillars of Pandemic Control Modeled

Antivirals

- Given stockpiling, will be available for prophylaxis and treatment.
  Stockpiles oseltamivir, inhaled zanamivir, iv peramivir, baloxavir

Vaccines

- Late arrival-may require two doses.
- Distribution to some countries may be an issue.

Nonpharmaceutical Interventions

- Limited data on effect of closing schools, social distancing, masks, *etc.*
- May be all that is available in many countries.

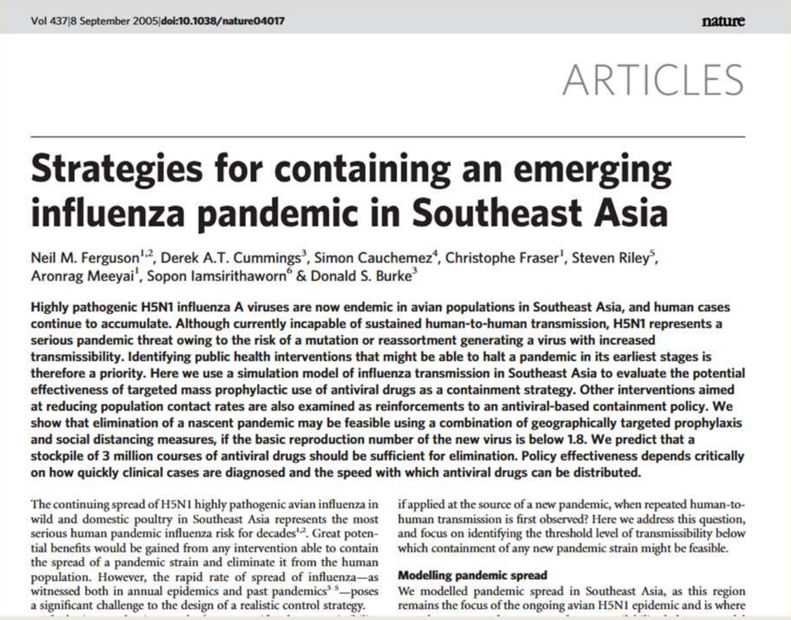
World Health Organization

Source: A Monto

R&DBlueprint
Powering research
to prevent epidemics

Modeling Pandemic Influenza at the Source

"It is optimal to stop or at least slow down a potential pandemic influenza strain at the source if possible."



Vol 437|8 September 2005|**doi:10.1038/nature04017** **nature**

ARTICLES

Strategies for containing an emerging influenza pandemic in Southeast Asia

Neil M. Ferguson[1,2], Derek A.T. Cummings[3], Simon Cauchemez[4], Christophe Fraser[1], Steven Riley[5], Aronrag Meeyai[1], Sopon Iamsirithaworn[6] & Donald S. Burke[3]

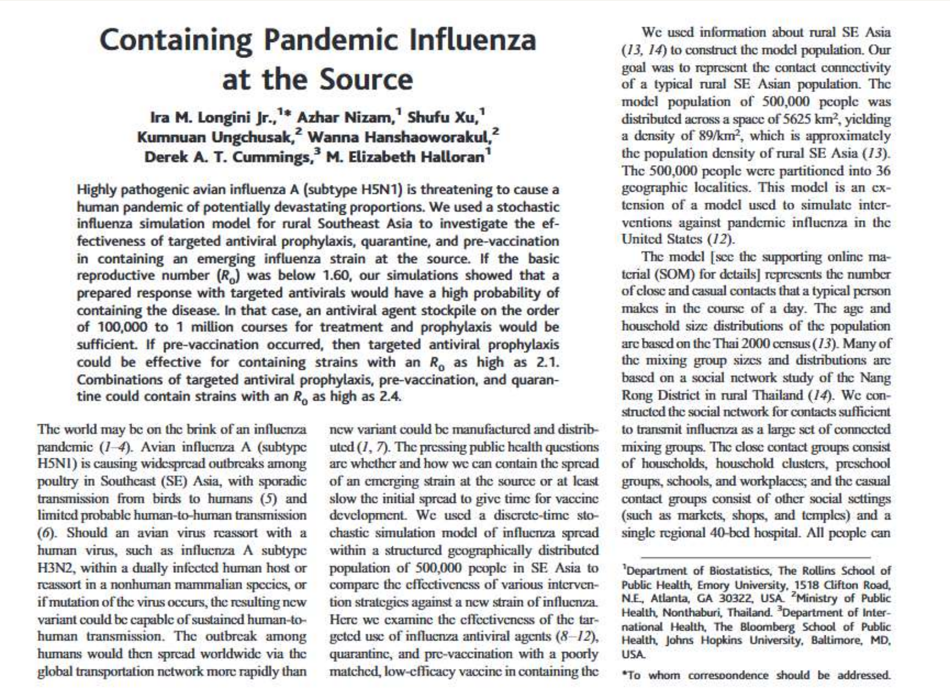
Highly pathogenic H5N1 influenza A viruses are now endemic in avian populations in Southeast Asia, and human cases continue to accumulate. Although currently incapable of sustained human-to-human transmission, H5N1 represents a serious pandemic threat owing to the risk of a mutation or reassortment generating a virus with increased transmissibility. Identifying public health interventions that might be able to halt a pandemic in its earliest stages is therefore a priority. Here we use a simulation model of influenza transmission in Southeast Asia to evaluate the potential effectiveness of targeted mass prophylactic use of antiviral drugs as a containment strategy. Other interventions aimed at reducing population contact rates are also examined as reinforcements to an antiviral-based containment policy. We show that elimination of a nascent pandemic may be feasible using a combination of geographically targeted prophylaxis and social distancing measures, if the basic reproduction number of the new virus is below 1.8. We predict that a stockpile of 3 million courses of antiviral drugs should be sufficient for elimination. Policy effectiveness depends critically on how quickly clinical cases are diagnosed and the speed with which antiviral drugs can be distributed.

The continuing spread of H5N1 highly pathogenic avian influenza in wild and domestic poultry in Southeast Asia represents the most serious human pandemic influenza risk for decades[1,2]. Great potential benefits would be gained from any intervention able to contain the spread of a pandemic strain and eliminate it from the human population. However, the rapid rate of spread of influenza—as witnessed both in annual epidemics and past pandemics[3–5]—poses a significant challenge to the design of a realistic control strategy.

if applied at the source of a new pandemic, when repeated human-to-human transmission is first observed? Here we address this question, and focus on identifying the threshold level of transmissibility below which containment of any new pandemic strain might be feasible.

Modelling pandemic spread

We modelled pandemic spread in Southeast Asia, as this region remains the focus of the ongoing avian H5N1 epidemic and is where



Containing Pandemic Influenza at the Source

Ira M. Longini Jr.,[1*] Azhar Nizam,[1] Shufu Xu,[1] Kumnuan Ungchusak,[2] Wanna Hanshaoworakul,[2] Derek A. T. Cummings,[3] M. Elizabeth Halloran[1]

Highly pathogenic avian influenza A (subtype H5N1) is threatening to cause a human pandemic of potentially devastating proportions. We used a stochastic influenza simulation model for rural Southeast Asia to investigate the effectiveness of targeted antiviral prophylaxis, quarantine, and pre-vaccination in containing an emerging influenza strain at the source. If the basic reproductive number (R_0) was below 1.60, our simulations showed that a prepared response with targeted antivirals would have a high probability of containing the disease. In that case, an antiviral agent stockpile on the order of 100,000 to 1 million courses for treatment and prophylaxis would be sufficient. If pre-vaccination occurred, then targeted antiviral prophylaxis could be effective for containing strains with an R_0 as high as 2.1. Combinations of targeted antiviral prophylaxis, pre-vaccination, and quarantine could contain strains with an R_0 as high as 2.4.

The world may be on the brink of an influenza pandemic (*1–4*). Avian influenza A (subtype H5N1) is causing widespread outbreaks among poultry in Southeast (SE) Asia, with sporadic transmission from birds to humans (*5*) and limited probable human-to-human transmission (*6*). Should an avian virus reassort with a human virus, such as influenza A subtype H3N2, within a dually infected human host or reassort in a nonhuman mammalian species, or if mutation of the virus occurs, the resulting new variant could be capable of sustained human-to-human transmission. The outbreak among humans would then spread worldwide via the global transportation network more rapidly than new variant could be manufactured and distributed (*1, 7*). The pressing public health questions are whether and how we can contain the spread of an emerging strain at the source or at least slow the initial spread to give time for vaccine development. We used a discrete-time stochastic simulation model of influenza spread within a structured geographically distributed population of 500,000 people in SE Asia to compare the effectiveness of various intervention strategies against a new strain of influenza. Here we examine the effectiveness of the targeted use of influenza antiviral agents (*8–12*), quarantine, and pre-vaccination with a poorly matched, low-efficacy vaccine in containing the

We used information about rural SE Asia (*13, 14*) to construct the model population. Our goal was to represent the contact connectivity of a typical rural SE Asian population. The model population of 500,000 people was distributed across a space of 5625 km², yielding a density of 89/km², which is approximately the population density of rural SE Asia (*13*). The 500,000 people were partitioned into 36 geographic localities. This model is an extension of a model used to simulate interventions against pandemic influenza in the United States (*12*).

The model [see the supporting online material (SOM) for details] represents the number of close and casual contacts that a typical person makes in the course of a day. The age and household size distributions of the population are based on the Thai 2000 census (*13*). Many of the mixing group sizes and distributions are based on a social network study of the Nang Rong District in rural Thailand (*14*). We constructed the social network for contacts sufficient to transmit influenza as a large set of connected mixing groups. The close contact groups consist of households, household clusters, preschool groups, schools, and workplaces; and the casual contact groups consist of other social settings (such as markets, shops, and temples) and a single regional 40-bed hospital. All people can

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*To whom correspondence should be addressed.

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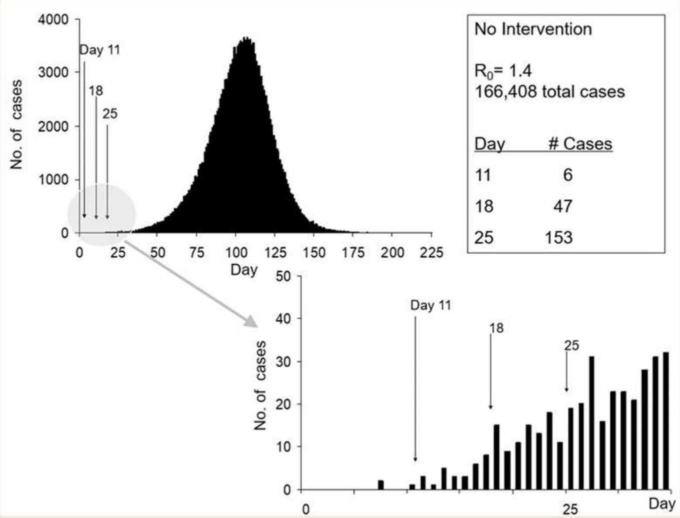
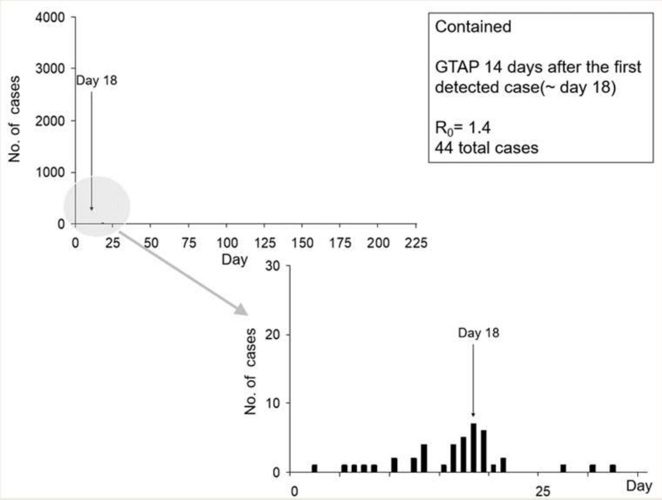
Mathematical modeling of targeted use of antivirals and vaccines

The outbreak is containable with TAP if transmissibility is reasonably low ($R_0 \leq 1.4$) and intervention occurs with 21 days of first detected case





Localized quarantine and other social distancing measures would be important for containment for viruses with higher transmissibility ($R_0 \geq 1.7$)

Prevaccination of the population with a low efficacy vaccine makes a big difference, even at the 50% coverage level

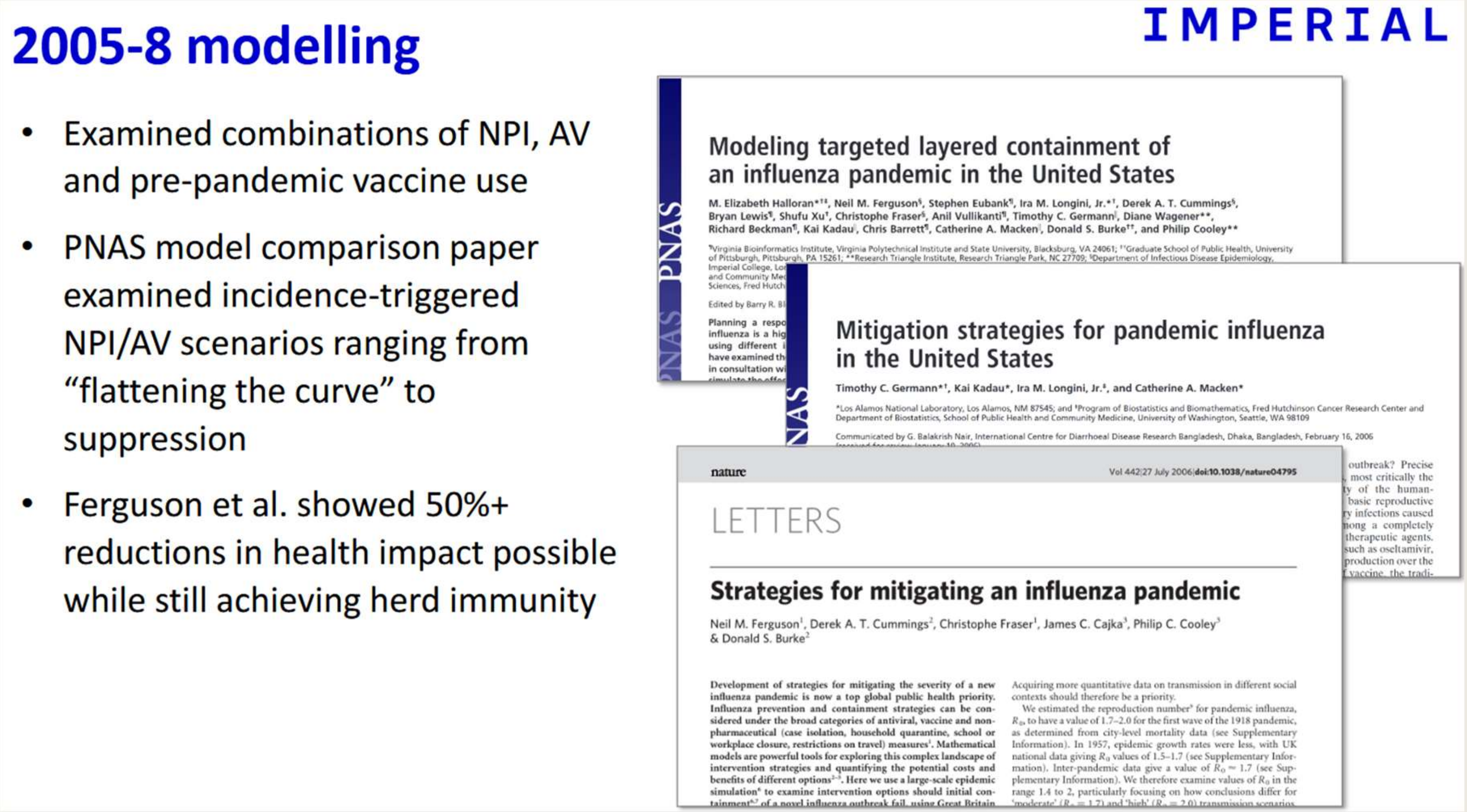
Work that needs to be done

The development and deployment of vaccine for potential pandemic strains for at-risk populations should move forward as quickly as possible.

Surveillance and detection of early pandemic influenza transmission is extremely important in all potentially at-risk regions of the world.

More modeling needs to done in a variety of at-risk populations and under different scenarios.

Country level modelling of transmission and mitigation measures



2005-8 modelling

IMPERIAL

- Examined combinations of NPI, AV and pre-pandemic vaccine use
- PNAS model comparison paper examined incidence-triggered NPI/AV scenarios ranging from "flattening the curve" to suppression
- Ferguson et al. showed 50%+ reductions in health impact possible while still achieving herd immunity

PNAS

Modeling targeted layered containment of an influenza pandemic in the United States

M. Elizabeth Halloran[*,†,‡], Neil M. Ferguson[§], Stephen Eubank[¶], Ira M. Longini, Jr.[*,†], Derek A. T. Cummings[§], Bryan Lewis[¶], Shufu Xu[†], Christophe Fraser[§], Anil Vullikanti[¶], Timothy C. Germann[‖], Diane Wagener[**], Richard Beckman[¶], Kai Kadau[‖], Chris Barrett[¶], Catherine A. Macken[‖], Donald S. Burke[††], and Philip Cooley[**]

PNAS

Mitigation strategies for pandemic influenza in the United States

Timothy C. Germann[*,†], Kai Kadau[*], Ira M. Longini, Jr.[‡], and Catherine A. Macken[*]

[*]Los Alamos National Laboratory, Los Alamos, NM 87545; and [‡]Program of Biostatistics and Biomathematics, Fred Hutchinson Cancer Research Center and Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98109

Communicated by G. Balakrish Nair, International Centre for Diarrhoeal Disease Research Bangladesh, Dhaka, Bangladesh, February 16, 2006

nature Vol 442|27 July 2006|doi:10.1038/nature04795

LETTERS

Strategies for mitigating an influenza pandemic

Neil M. Ferguson[1], Derek A. T. Cummings[2], Christophe Fraser[1], James C. Cajka[3], Philip C. Cooley[3] & Donald S. Burke[2]

Development of strategies for mitigating the severity of a new influenza pandemic is now a top global public health priority. Influenza prevention and containment strategies can be considered under the broad categories of antiviral, vaccine and non-pharmaceutical (case isolation, household quarantine, school or workplace closure, restrictions on travel) measures[1]. Mathematical models are powerful tools for exploring this complex landscape of intervention strategies and quantifying the potential costs and benefits of different options[2-5]. Here we use a large-scale epidemic simulation[6] to examine intervention options should initial con-

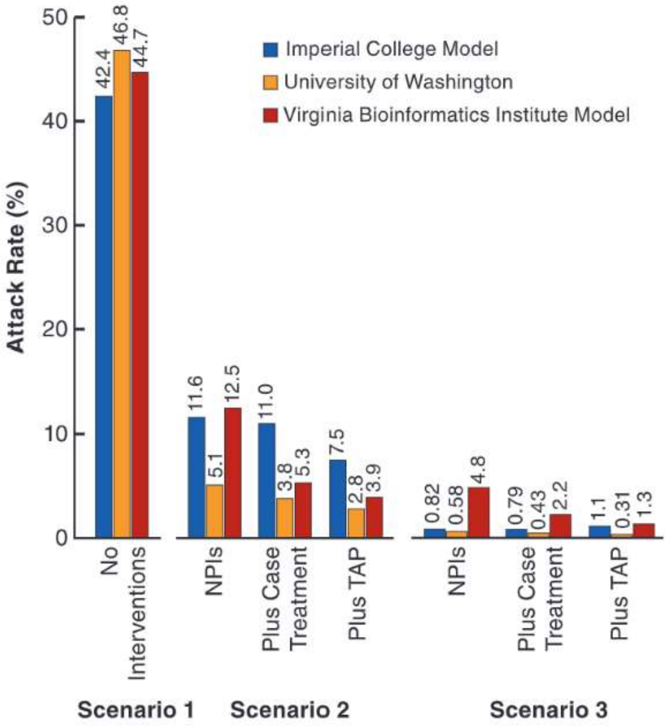
Acquiring more quantitative data on transmission in different social contexts should therefore be a priority.

We estimated the reproduction number[8] for pandemic influenza, R_0, to have a value of 1.7–2.0 for the first wave of the 1918 pandemic, as determined from city-level mortality data (see Supplementary Information). In 1957, epidemic growth rates were less, with UK national data giving R_0 values of 1.5–1.7 (see Supplementary Information). Inter-pandemic data give a value of $R_0 \approx 1.7$ (see Supplementary Information). We therefore examine values of R_0 in the range 1.4 to 2, particularly focusing on how conclusions differ for

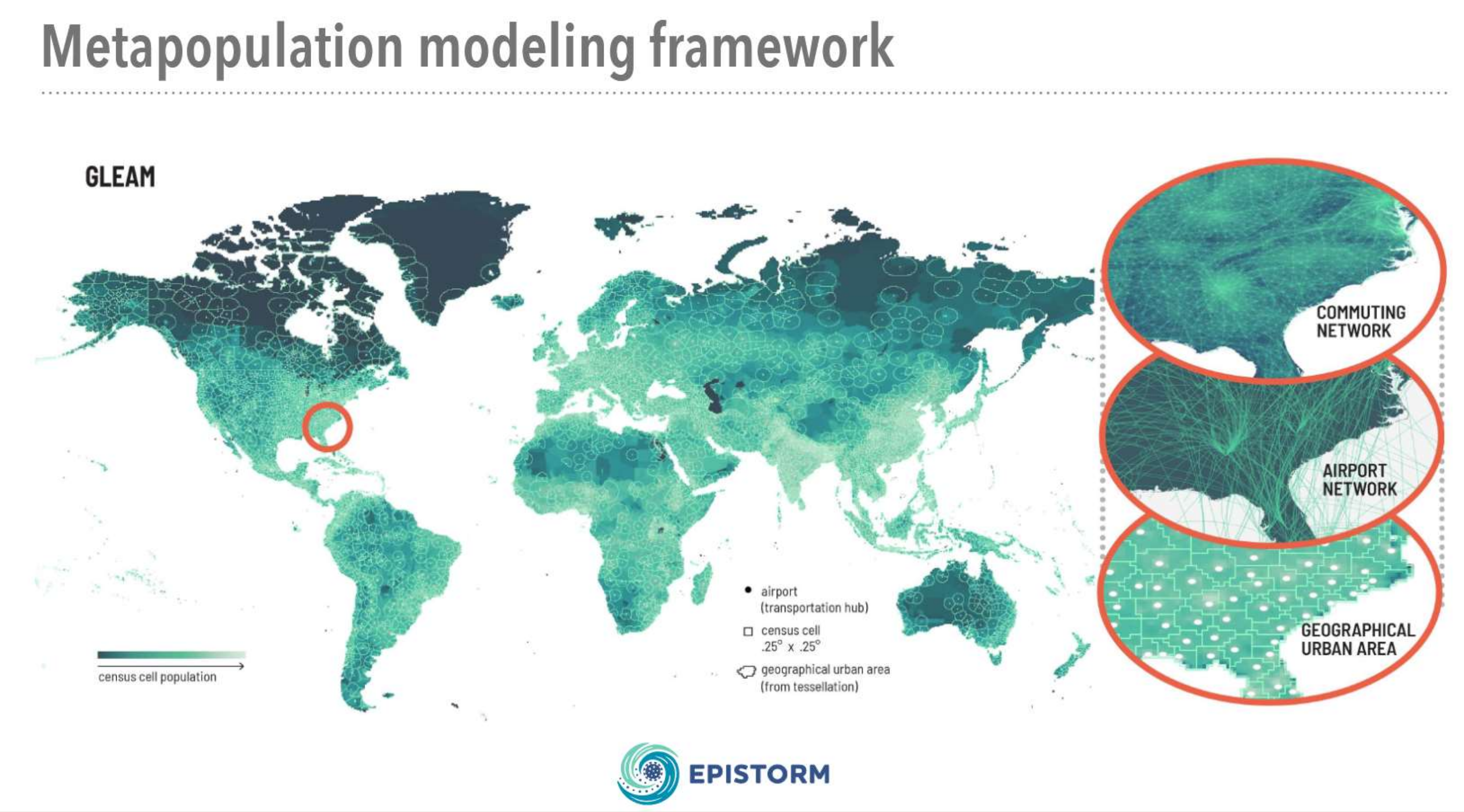
Source: N Ferguson

2005-8 modelling: limitations

- Optimistic assumptions about symptomatic case ascertainment (60%+)
- AV and vaccine scenarios assumed stockpiles to be substantial fraction of population size
- Human influenza-like epidemiological parameters assumed (R_0, T_g)
- Not modelled:
  - Viral evolution
  - Adaptive policies (other than incidence triggers)
  - Border restrictions (some work done separately)
  - Contact tracing (only household/school/workplace)
  - Healthcare demand/mortality
  - Economic impacts (separate analyses)

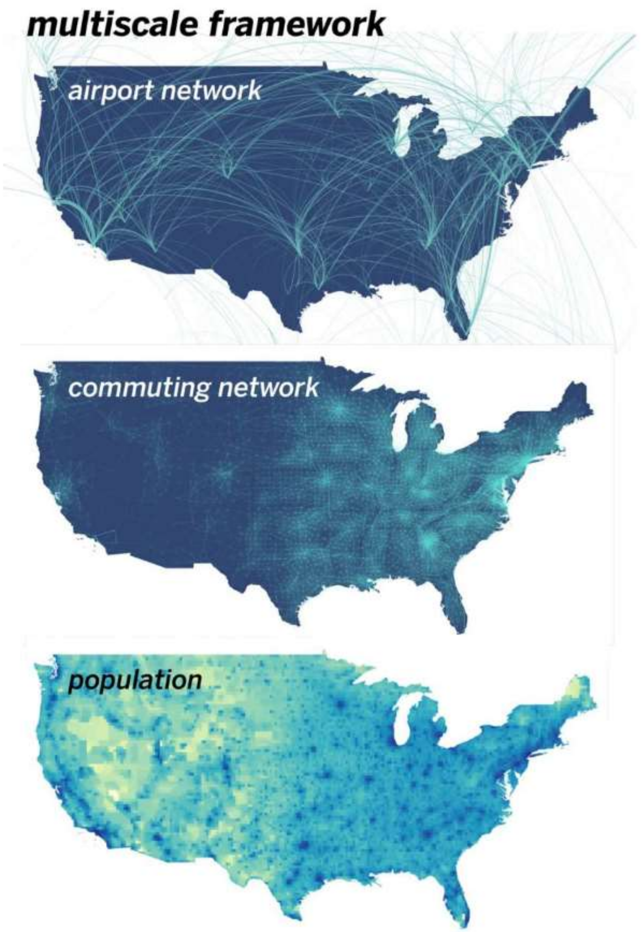


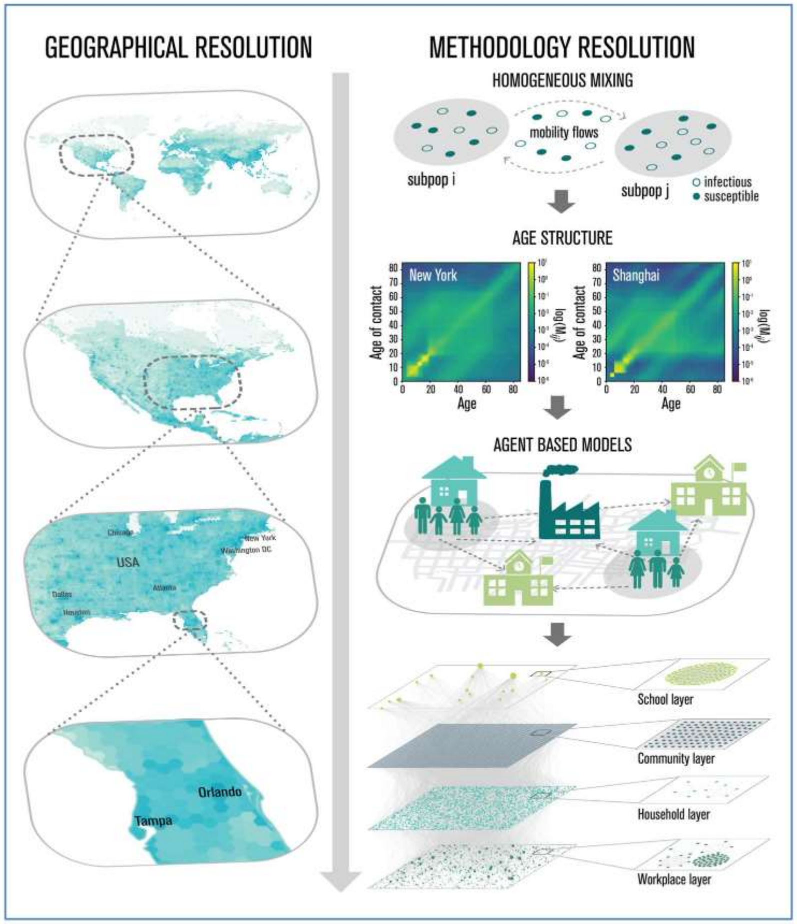
Global modelling of transmission and mitigation measures



Metapopulation modeling framework

Source: A Vespignani


multiscale framework
airport network
commuting network
population

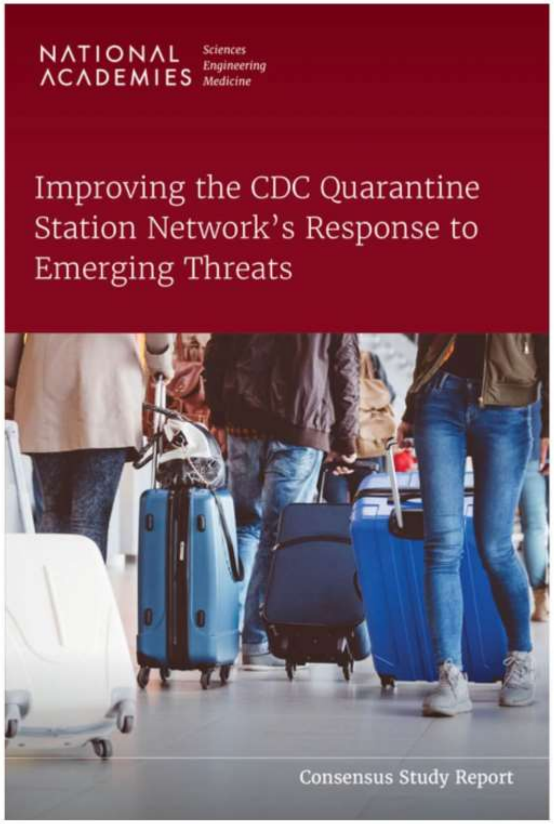

GEOGRAPHICAL RESOLUTION
Chicago
New York
Washington DC
USA
Atlanta
Dallas
Houston
Orlando
Tampa
METHODOLOGY RESOLUTION
HOMOGENEOUS MIXING
mobility flows
subpop i
subpop j
○ infectious
● susceptible
AGE STRUCTURE
New York
Shanghai
Age of contact
Age
log(M)
AGENT BASED MODELS
School layer
Community layer
Household layer
Workplace layer

MOBS LAB

World Health Organization

R&D Blueprint
Powering research
to prevent epidemics

- Containment and monitoring for H5N1 should happen now when we have a smoking gun (poultry/cattle farming).
- More rapid modeling with specific information on the outbreak (seasonality, starting dates, intervention capacities)- SMH Insighnet effort.
- Developing a realistic playbook considering a large catalog of possible scenarios



NATIONAL ACADEMIES *Sciences Engineering Medicine*

Improving the CDC Quarantine Station Network's Response to Emerging Threats

Consensus Study Report

MOBS LAB

Next steps

- Follow up meetings to address main areas of specific needs
  - Looking into methods & models, including AI methods
- Set up a consortium of modellers with the aim to deliver analysis quickly and in a coordinated way
  - Brainstorming on such a mechanism: roles, responsibilities, etc.
- Dive into data availability and associated conditions
  - Linking with ongoing WHO activities e.g., the update of guidance of surveillance during an influenza pandemic, “Unity Study” network

Next Steps

- Follow-up meeting(s) on how to utilize early sequencing and phylogenetic data in the formulation of early transmission of mathematical models.
  - How to leverage virus genetics data in the continued modeling of transmission and control

Thank You!