

Modeling the Impact of Vaccine Uptake

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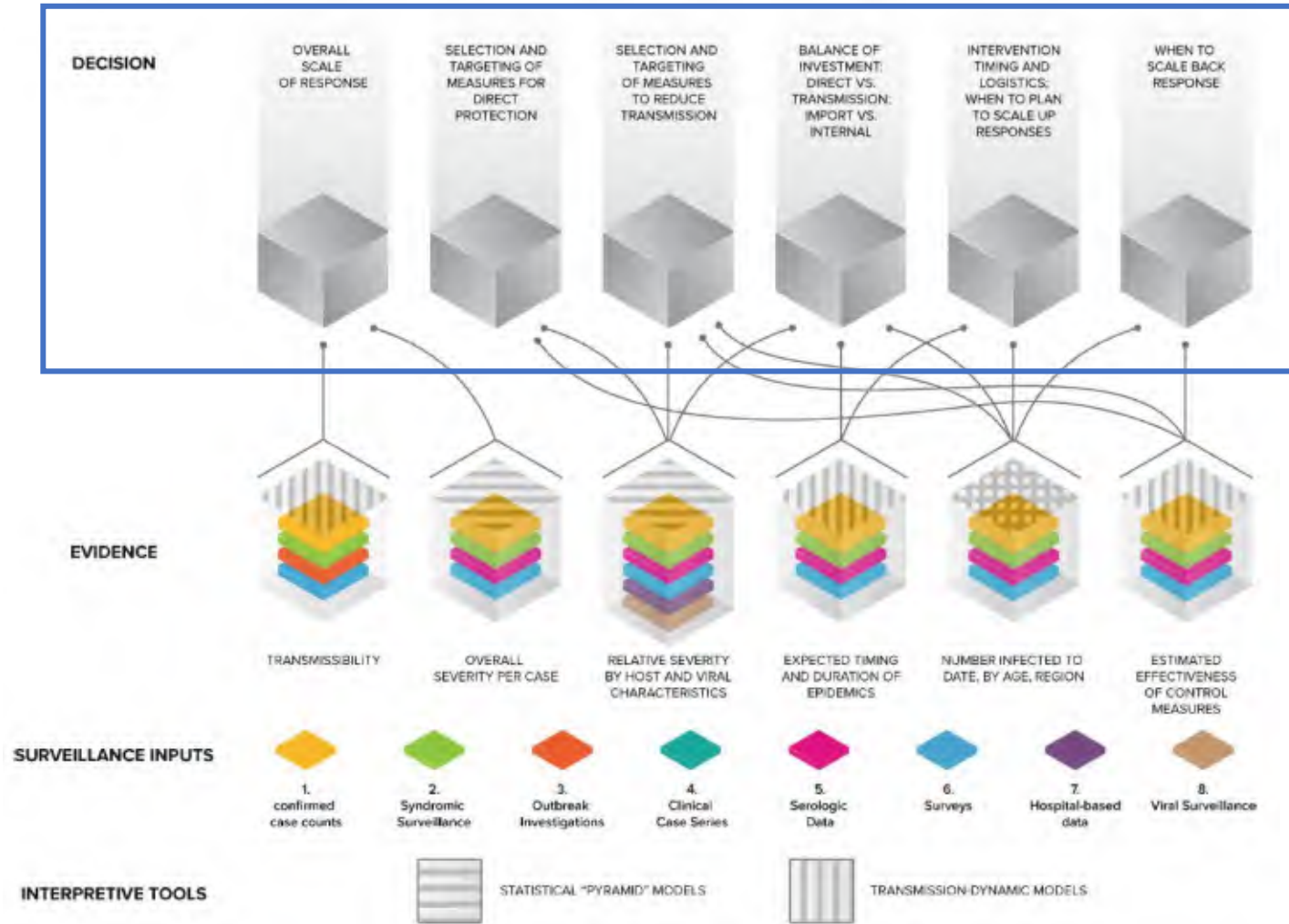
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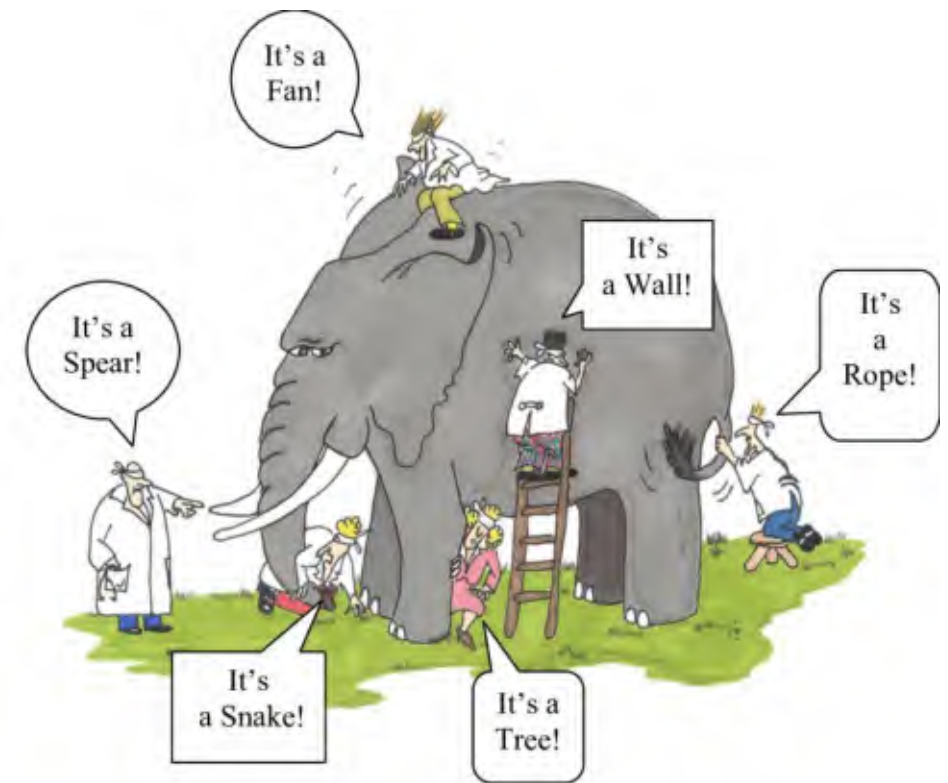
Learning Objectives

1. To discuss the basic concepts and current trends in infectious disease epidemiology
2. To discuss herd immunity and indirect effect of vaccination.
3. To discuss different effects of vaccines and how they are estimated.

The context



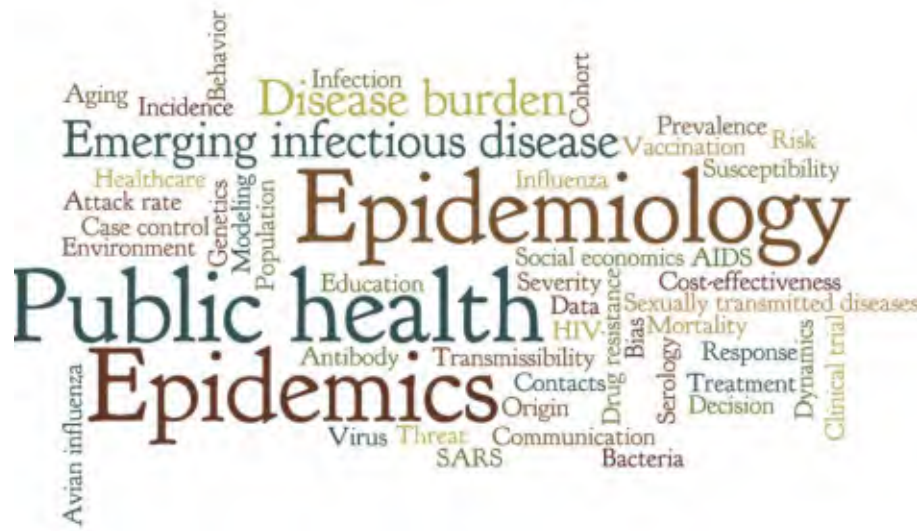
The Blind Men and the Elephant



Epidemiology is the basic science of public health

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems

- Methodologies for extracting insights from real-world observations and data



Where and **when** does the disease of interest appear?

What is the burden of the disease in the population?

Do people **who** have the disease have any common characteristics that are not present among people who do not have the disease (i.e. **why**)?

Infectious vs non-infectious diseases

Infectious diseases are:

- Caused by pathogens including viruses, bacteria, parasites
- Almost always communicable, i.e. transmitted from person to person

Influenza virus



Malaria parasite

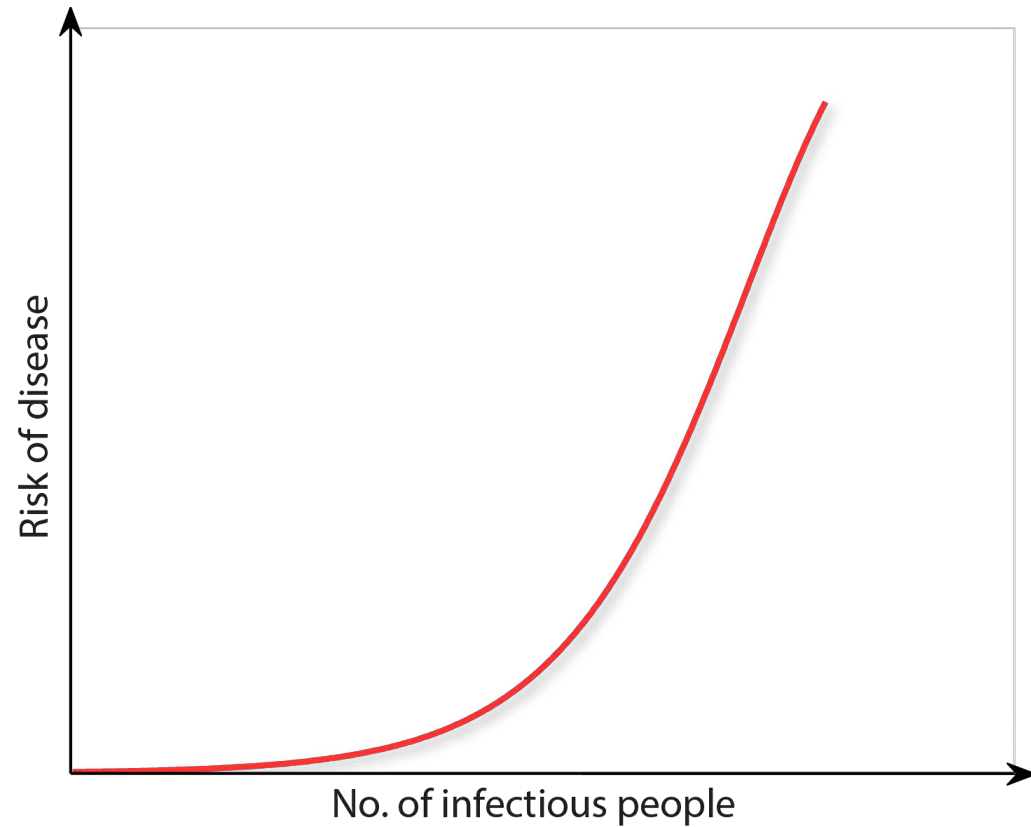


Route of transmission

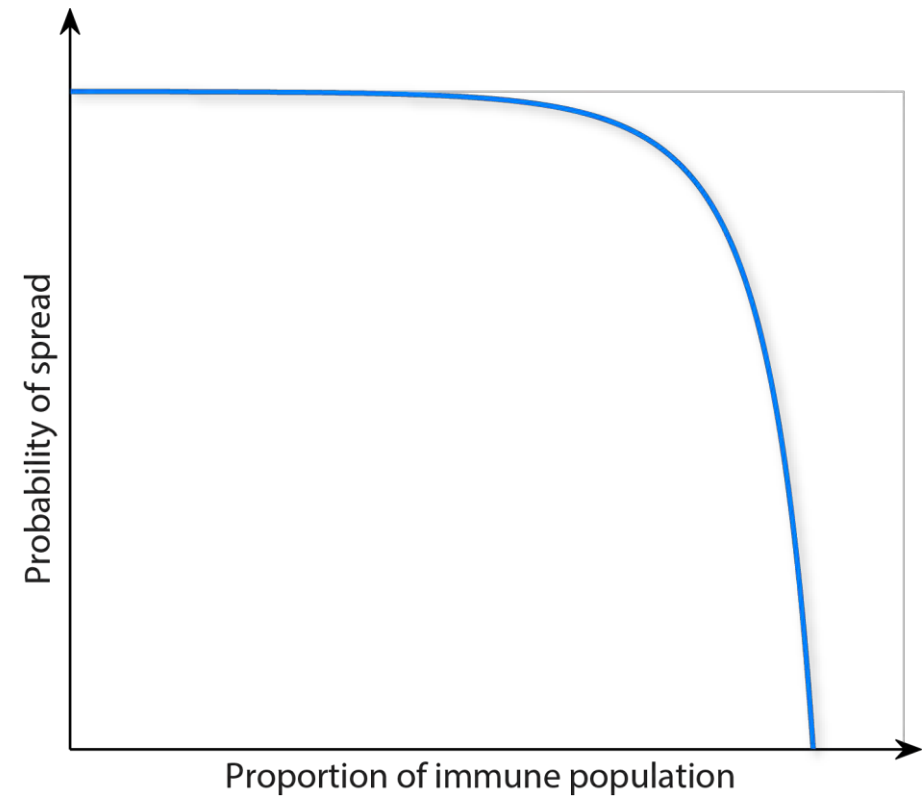
Direct	Indirect
Skin-skin (Herpes type 1)	Airborne (TB)
Mucuous-mucuous (STI)	Food-borne (Salmonella)
Across placenta (Rubella)	Water-borne (Hepatitis A)
Through breast milk (HIV)	Vector-borne (Malaria)
Sneeze-cough (Influenza)	

Basic facts about infectious diseases

The risk of getting a communicable disease increases with the number of people who have the disease in the population



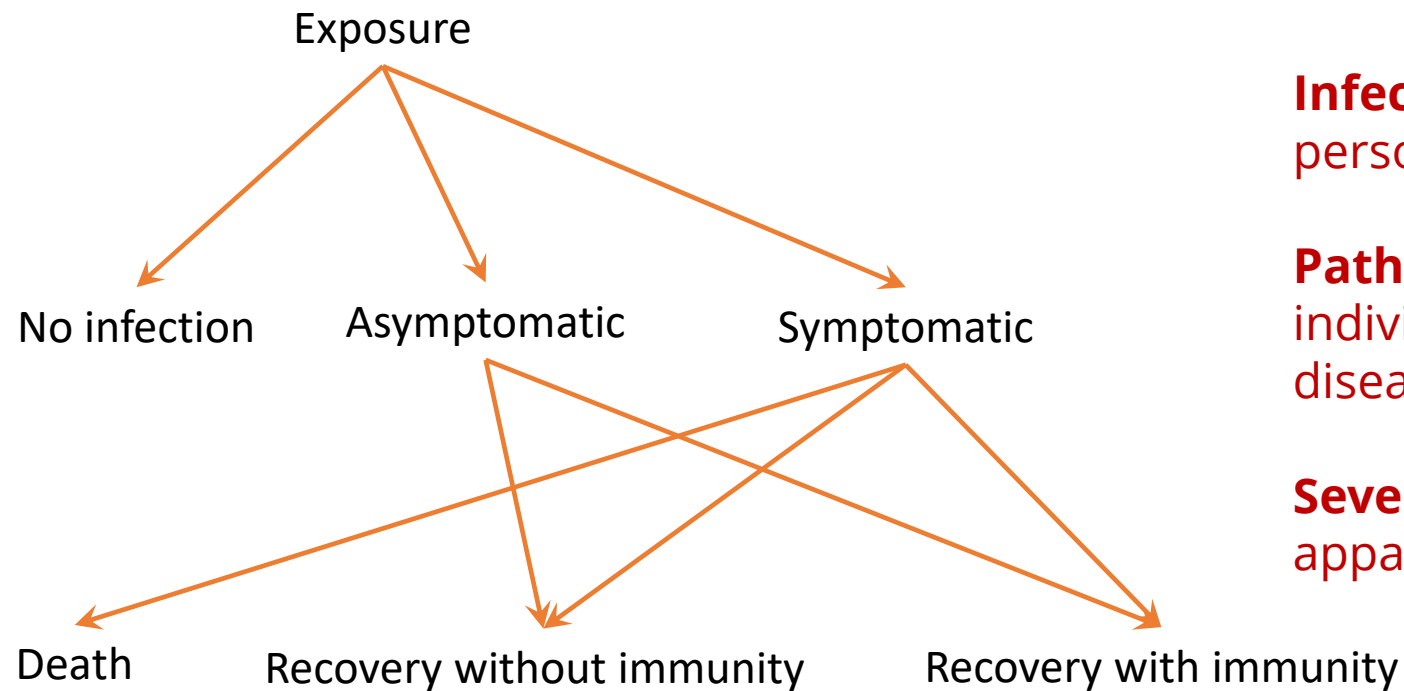
Sustained transmission of communicable diseases relies on replenishment of susceptibles (via newborns, waning of immunity, etc)



Natural history of infectious diseases

For some infectious diseases (e.g. measles), a recovered person gains long-lasting immunity against re-infection by the same pathogen

An individual is *susceptible* if he is neither infected nor immune (i.e. can potentially be infected)



Infectivity: the proportion of exposed persons who become infected.

Pathogenicity: the proportion of infected individuals who develop clinically apparent disease.

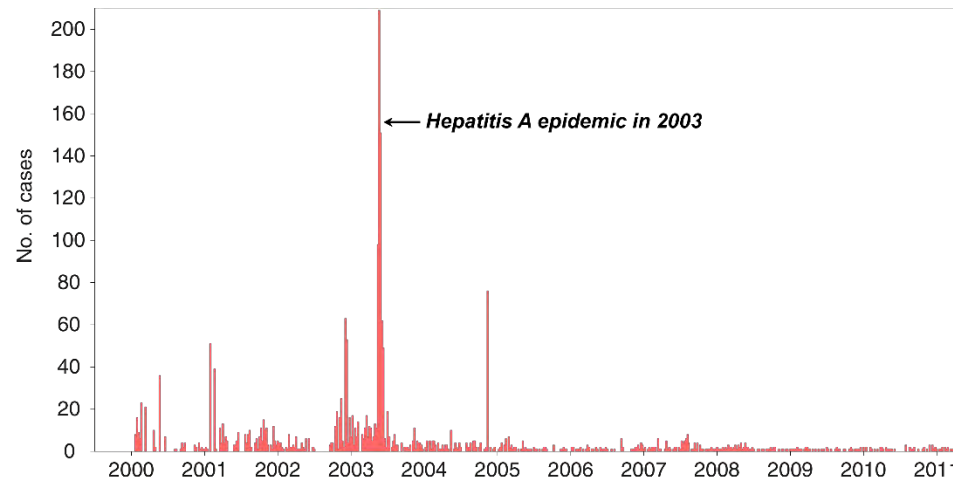
Severity: the proportion of clinically apparent cases that are severe or fatal.

Epidemic

Epidemic: the occurrence of diseases above what is normally expected in a population

For some diseases, cases occur throughout the year at some background rate. An epidemic corresponds to an abrupt and significant increase of cases

*Weekly number of hepatitis A cases
Pennsylvania, 2000-2011*



Why do epidemics occur?

- A recent increase in amount or virulence of the agent
- The recent introduction of the agent into a setting where it has not been before
- An enhanced mode of transmission so that more susceptible persons are exposed
- A change in the susceptibility of the host response to the agent

Epidemic

An extreme example: A single case of smallpox would constitute an epidemic in the current world

The smallpox vaccine, created by Edward Jenner in 1796, was the first successful vaccine to be developed.



<https://www.who.int/health-topics/smallpox>



In 1967, WHO launched an intensified plan to eradicate smallpox.

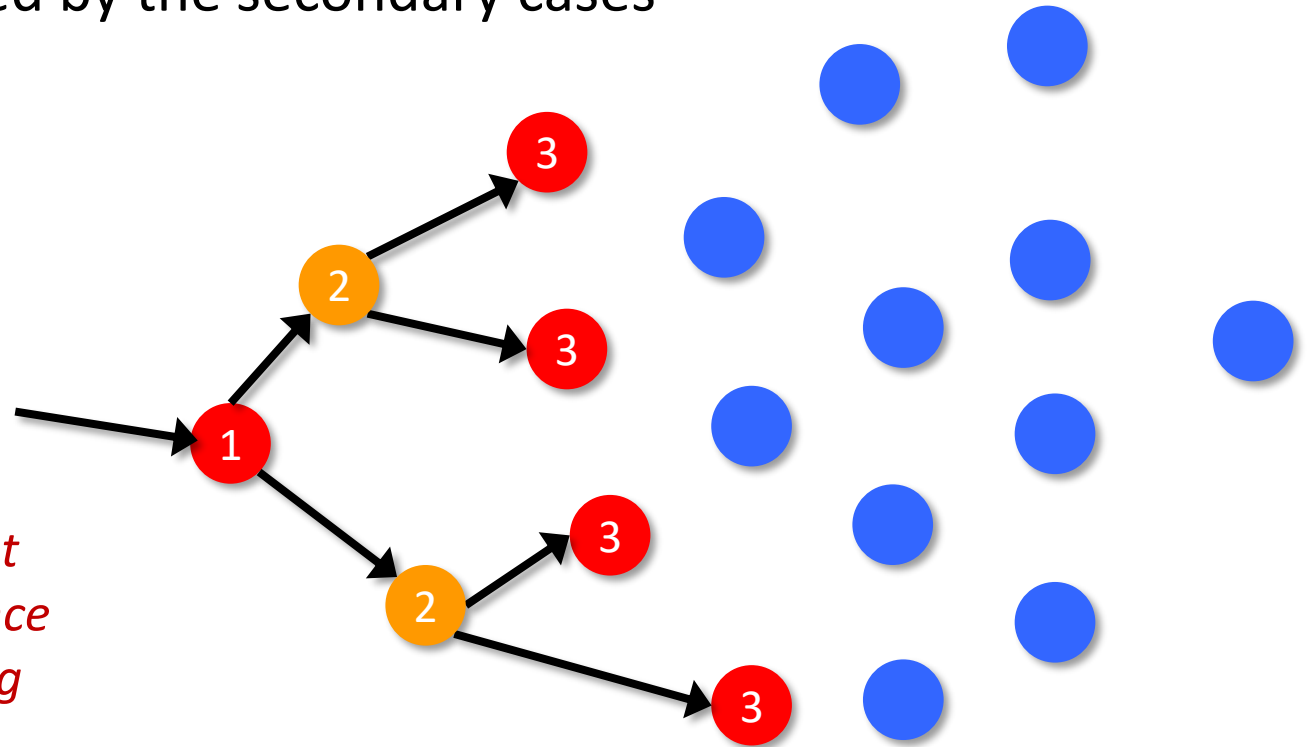
In 1980, WHO declared smallpox eradicated.

Chain of disease transmission

Primary cases – first infections in the population

Secondary cases – infections caused by the primary cases

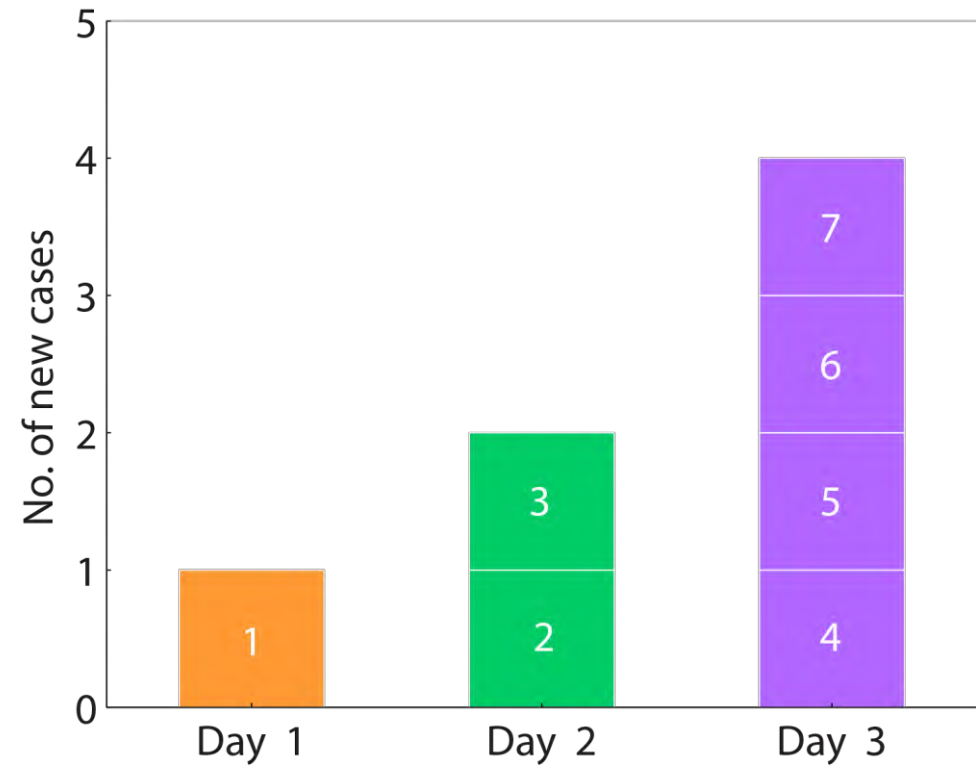
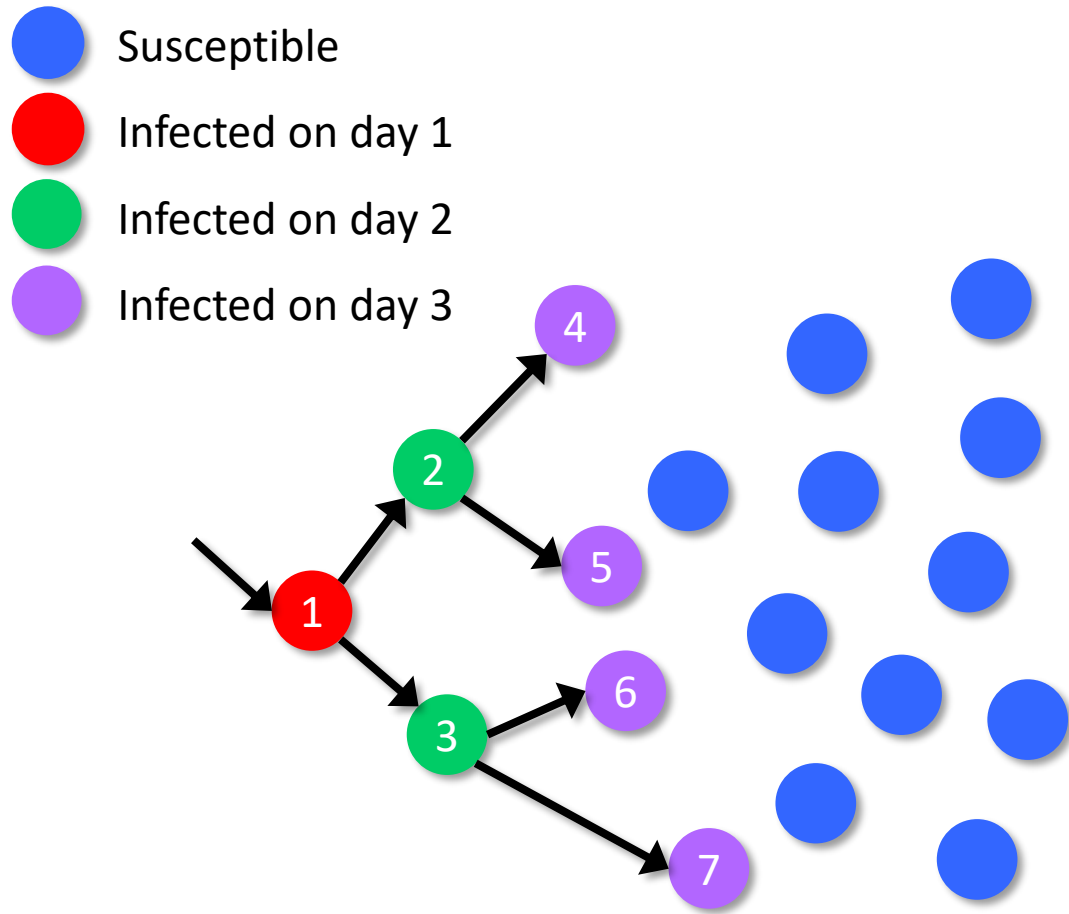
Tertiary cases – infections caused by the secondary cases



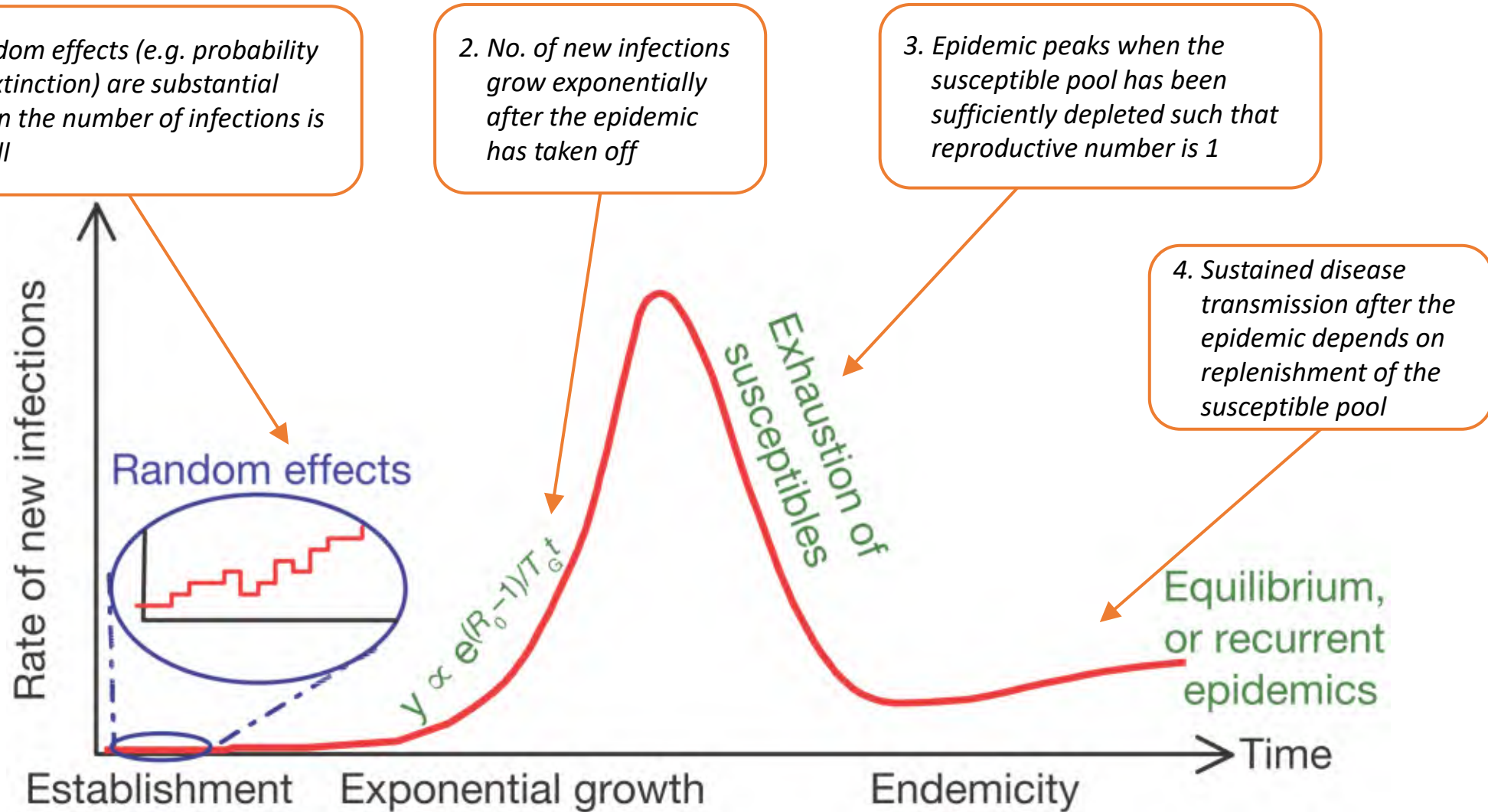
Subclinical infections are typically not registered by public health surveillance unless there is intense contact tracing and laboratory testing

Epidemic curve

The “epicurve” is a graph that shows the number of cases over time (usually by the date of illness onset).



Anatomy of an (unmitigated) epidemic



Case definition

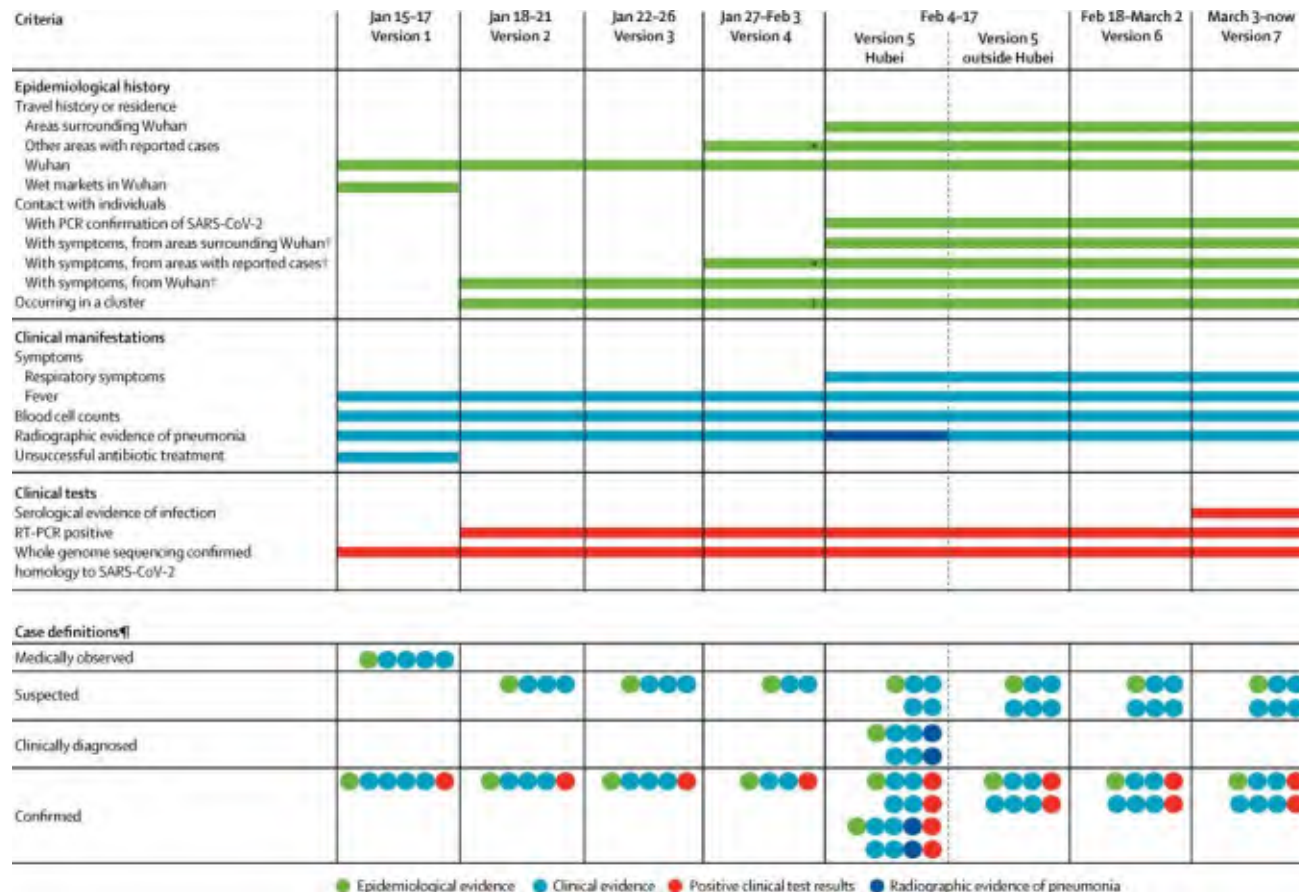
- Epidemiologic study of a disease starts with the case definition of the disease.
- A consensus on case definition is essential for comparing disease patterns across time and health jurisdictions.
- The case definition of a disease could be based on laboratory results, clinical symptoms as well as epidemiologic links.
- Case definitions might be revised to improve disease surveillance and control as more is learned about the disease.

Defining cases is notoriously challenging during outbreaks when symptoms are non-specific and mimic other diseases.

- If the case definition is too specific (i.e. too narrow), many infections will be missed.
- If the case definition is too broad (i.e. too sensitive), public health operations (i.e. contact tracing and quarantine) and healthcare system (hospital beds) might be overloaded.

Effect of changing case definitions for COVID-19 on the epidemic curve and transmission parameters in mainland China: a modelling study

Tim K Tsang, Peng Wu, Yun Lin, Eric H Y Lau, Gabriel M Leung, Benjamin J Cowling



“From Jan 15 to March 3, 2020, seven versions of the case definition for COVID-19 were issued by the National Health Commission in China. We estimated that when the case definitions were changed, the proportion of infections being detected as cases increased by 7·1 times (95% credible interval [CrI] 4·8–10·9) from version 1 to 2, 2·8 times (1·9–4·2) from version 2 to 4, and 4·2 times (2·6–7·3) from version 4 to 5.

The case definition was initially narrow and was gradually broadened to allow detection of more cases as knowledge increased, particularly milder cases and those without epidemiological links to Wuhan, China, or other known cases. These changes should be taken into account when making inferences on epidemic growth rates and doubling times, and therefore on the reproductive number, to avoid bias.”

SOUNDING BOARD

FROM THE NATIONAL ACADEMY OF MEDICINE

Long Covid Defined

E. Wesley Ely, M.D., M.P.H., Lisa M. Brown, M.P.H., and Harvey V. Fineberg, M.D., Ph.D.,
for the National Academies of Sciences, Engineering, and Medicine Committee on Examining
the Working Definition for Long Covid^{*}

Box 1. 2024 NASEM Long Covid Definition[‡]

Long Covid is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

Long Covid manifests in multiple ways. A complete enumeration of possible signs, symptoms, and diagnosable conditions of long Covid would have hundreds of entries. Any organ system can be involved, and patients can present with the following:

- **Single or multiple symptoms, such as** shortness of breath, cough, persistent fatigue, postexertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
- **Single or multiple diagnosable conditions, such as** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome and other forms of dysautonomia, myalgic encephalomyelitis–chronic fatigue syndrome, mast-cell activation syndrome, fibromyalgia, connective-tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjögren's syndrome.

Important Features of Long Covid

- It can follow asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may have been recognized or unrecognized.
- It can be continuous from the time of acute SARS-CoV-2 infection or have a delayed onset for weeks or months after what had appeared to be full recovery from acute infection.
- It can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, sexual orientation, race, ethnic group, or geographic location.
- It can exacerbate preexisting health conditions or present as new conditions.
- It can range from mild to severe and can resolve over a period of months or can persist for months or years.
- It can be diagnosed on clinical grounds; no biomarker that is currently available conclusively determines the presence of this condition.
- It can impair patients' ability to work, attend school, take care of family, and care for themselves, resulting in profound emotional and physical effects on the patients, their families, and caregivers.

^{*} This definition has been slightly edited from the original report¹ with no intended change in meaning.

Table 1. Components of Long Covid Definitions.[‡]

Elements of Disease Definition	U.S. CDC, 2020 ¹¹	U.K. NICE, 2020 ¹²	U.S. OASH, 2022 ¹³	WHO Adults, 2022 ¹⁴	WHO Children, 2022 ¹⁵	U.S. RECOVER, 2023 ¹⁶	NASEM, 2024 ¹
Classification							
Uses the term "long Covid"	Yes	No	Yes	No	No	No	Yes
Describes long Covid as a disease state	No	No	No	No	No	No	Yes
Places long Covid among infection-associated chronic conditions	No	No	No	No	No	No	Yes
Attribution to infection							
Allows inclusion of asymptomatic, mild, or severe acute SARS-CoV-2	Yes	No	No	No	No	Yes	Yes
Requires proof of confirmed or probable infection or requirement of SARS-CoV-2 test	No	No	No	Yes	Yes	No	No
Timing							
States symptoms or conditions present for at least 3 mo	No	Yes	No	No	No	Yes	Yes
Indicates continuous or delayed onset of symptoms or conditions	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinical features							
Indicates long Covid is a single or multiple organ disease state	No	Yes	Yes	No	No	Yes	Yes
Includes new clinical features or exacerbation of preexisting features	No	No	No	Yes	Yes	No	Yes
Mentions severity of symptoms	No	No	Yes	No	No	Yes	Yes
Describes continuous, relapsing–remitting, or progressive nature of symptoms	No	Yes	Yes	Yes	Yes	Yes	Yes
Includes language on recovery timeline (can resolve or persist for months to years)	No	No	No	No	No	Yes	Yes
Patient-oriented features							
Includes equity language	No	Yes	No	No	No	No	Yes
Highlights effect on daily functioning	No	No	No	Yes	Yes	Yes	Yes
Incorporates alternative diagnoses	No	No	No	No	Yes	No	Yes
Indicates that diagnosis is a clinical judgment due to absence of proven biomarkers	No	No	Yes	No	No	No	Yes
Includes risk factors	No	No	Yes	No	No	No	No [†]

[‡] CDC denotes Centers for Disease Control and Prevention, NASEM National Academies of Sciences, Engineering, and Medicine, NICE National Institute for Health and Care Excellence, OASH Office of the Assistant Secretary for Health, RECOVER Researching Covid to Enhance Recovery (National Institutes of Health), and WHO World Health Organization.

[†] Risk factors are described in the NASEM report that contains the definition but are not specifically included in the definition.

Incidence and prevalence

$$\text{Incidence} = \frac{\text{No. of cases occurred during a defined time period}}{\text{Population size}}$$

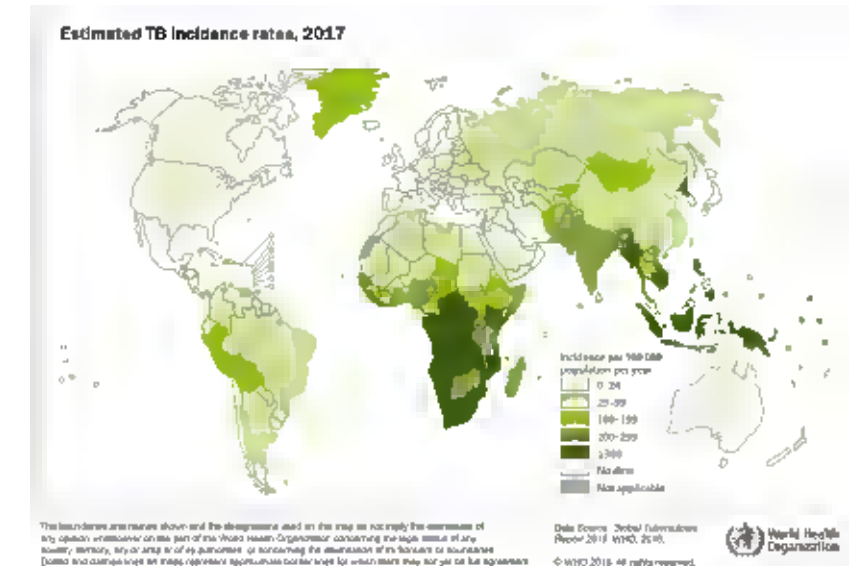
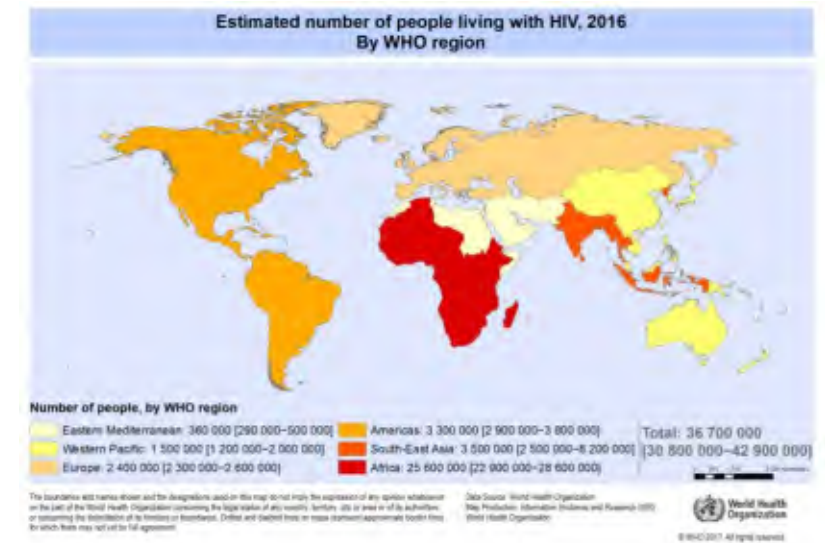
112 new cases of AIDS in Hong Kong in 2020

Population size of Hong Kong in 2020 is 7.5 million

$$\text{AIDS incidence in Hong Kong in 2012} = \frac{112}{7.5 \times 10^6} = 1.5 \text{ per } 100,000$$

Prevalence

$$= \frac{\text{Total no. of cases at a specific time}}{\text{Population size}}$$



Infectious diseases: past vs present

Past

“One can think of the middle of the 20th Century as the end of one of the most important societal changes in history – the conquest and elimination of infectious diseases as a significant factor in society.”

*Macfarlane Burnet, 1962
Nobel Laureate*

“The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.”

*William H Stewart
Surgeon General of the USA, 1967*

Present

“If history is our guide, we can assume that the battle between the intellect and will of the human species and the extraordinary adaptability of microbes will be never-ending.”

*Tony Fauci
Director, US NIAID*

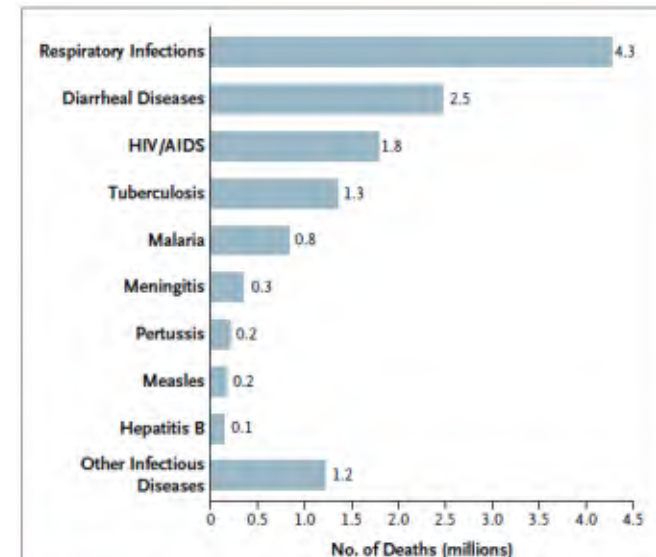


Figure 1. Leading Causes of Global Deaths from Infectious Diseases. Of an estimated 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are believed to be caused by infectious diseases. Cause-specific mortality estimates are provided by the World Health Organization.^{43,44} The data do not include deaths from secondary infectious causes, such as rheumatic fever and rheumatic heart disease, liver cancer and cirrhosis, or other chronic diseases.

*Fauci et al
NEJM 2012*



Ten threats to global health in 2019

1. **Global influenza pandemic**
2. **Ebola and other high-threat pathogens**
3. **Non-communicable diseases**
4. **Vaccine hesitancy**
5. **Antimicrobial resistance**
6. **Air pollution and climate change**
7. **Fragile and vulnerable settings**
8. **Weak primary health care**
9. **Dengue**
10. **HIV**

Vaccine-preventable diseases

 World Health Organization

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Immunization, Vaccines and Biologicals

The Immunization, Vaccines and Biologicals department is responsible for targeting vaccine-preventable diseases, guiding immunization research and establishing immunization policy.

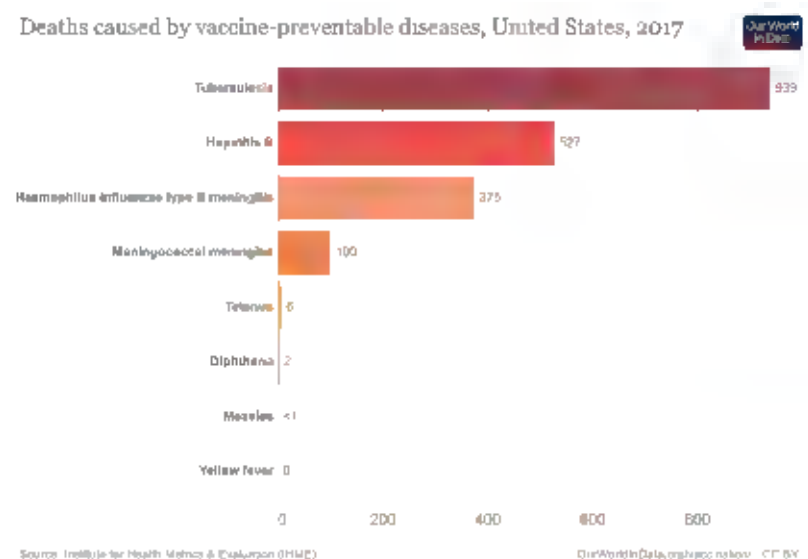
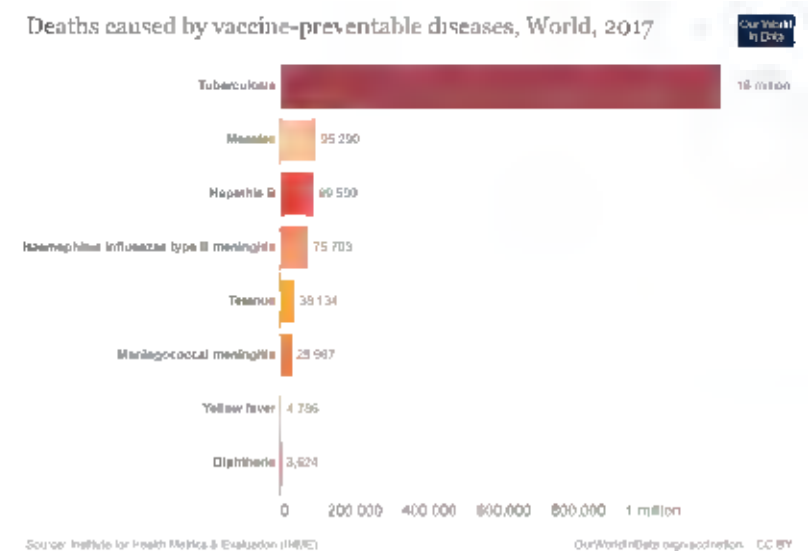
Available vaccines

- Cholera
- COVID-19 (corona virus)
- Dengue
- Diphtheria
- Hepatitis
- Haemophilus influenzae* type b (Hib)
- Human papillomavirus (HPV)
- Influenza
- Japanese encephalitis
- Malaria
- Measles
- Meningococcal meningitis
- Mumps
- Pertussis
- Pneumococcal disease
- Poliomyelitis
- Rabies
- Rotavirus
- Rubella
- Tetanus
- Tick-borne encephalitis
- Tuberculosis
- Typhoid
- Varicella
- Yellow Fever

Pipeline vaccines

- Enterotoxigenic *Escherichia coli*
- Group B *Streptococcus* (GBS)
- Herpes Simplex Virus
- HIV-1
- Malaria
- Neisseria gonorrhoeae*
- Nontyphoidal *Salmonella* Disease
- Norovirus
- Paratyphoid fever
- Respiratory Syncytial Virus (RSV)
- Schistosomiasis Disease
- Shigella
- Group A *Streptococcus* (GAS)
- Tuberculosis
- Improved Influenza Vaccines

<https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases>



Expanded Program on Immunization

 World Health Organization

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50th anniversary of the Expanded Programme on Immunization (EPI)



50th anniversary of the Expanded Programme on Immunization (EPI)

1 January – 31 December 2024

WHO's Expanded Programme on Immunization: averting more than four million deaths every year

From an international health authority >



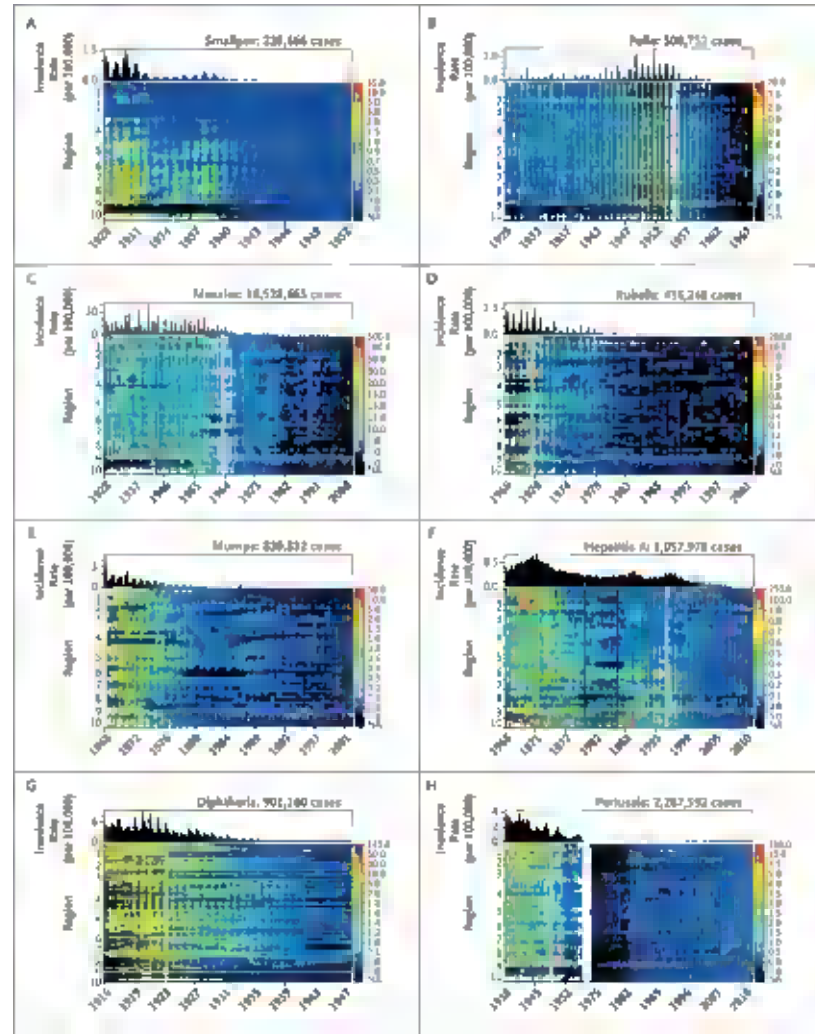
Vaccines now give us hope of eliminating cervical cancer.

Watch on  YouTube

Watch later Share

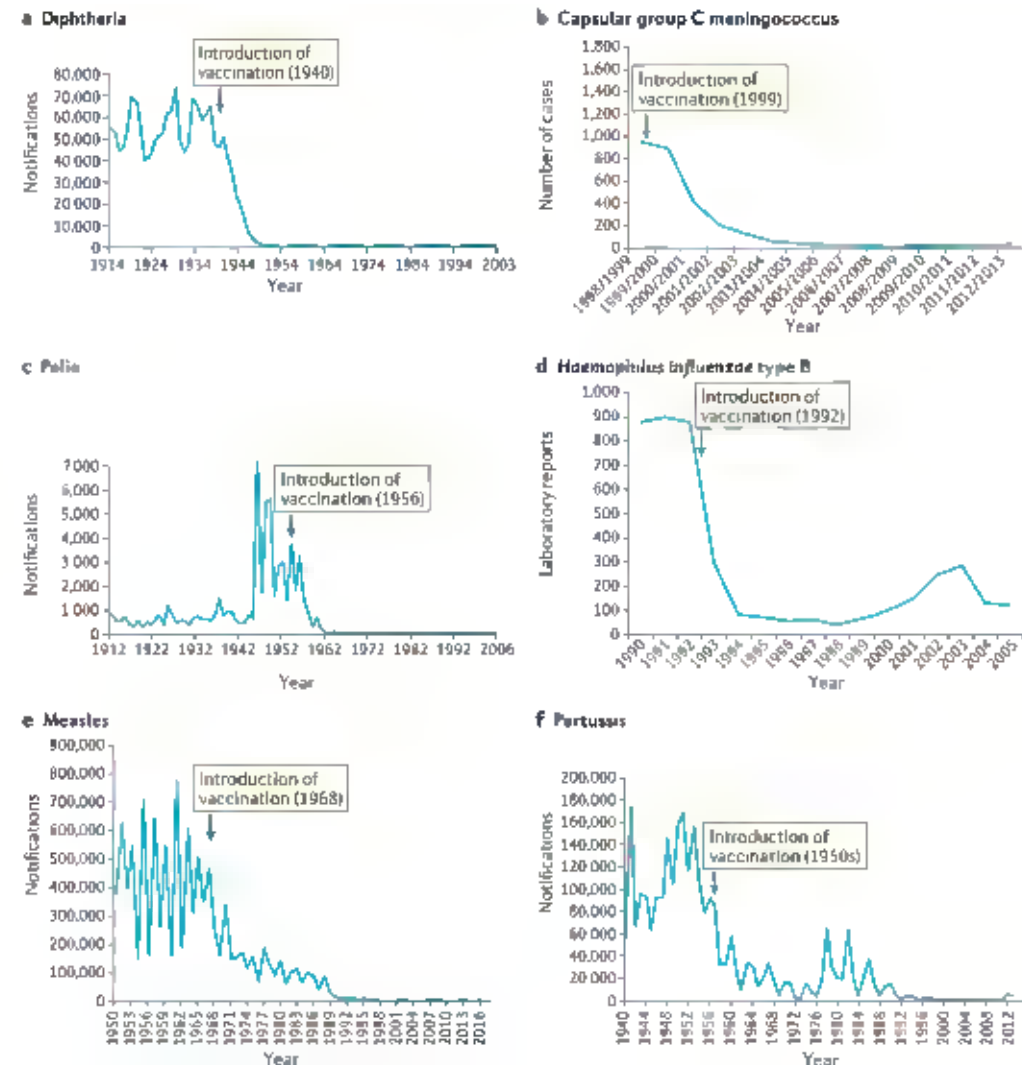
The WHO estimates that 2–3 million lives are saved each year by current immunization programs. Mortality of children under 5 decreased from 93 to 39 deaths per 1,000 live births between 1990 and 2018.

USA



van Panhuis et al *NEJM* 2013

UK



Pollard and Bijker *Nat Rev Immunol* 2021



ENSURE HEALTHY LIVES AND PROMOTE WELL-BEING FOR ALL AT ALL AGES

Target 3.2: By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births

Target 3.3: By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

Target 3.8: Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

Target 3.b: Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, ...

Target 3.d: Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks



Estimating the health impact of vaccination against ten pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study



Xiang Li*, Christinah Mukandavire*, Zulma M Circunaba, Susy Echeverria-Londano, Kaja Abbast, Hannah E Clapham†, Mark Jit†, Hope I Johnson†, Tamas Papadopoulos†, Emilia Vynnycky†, Marc Brisson, Emily D Carter, Andrew Clark, Margaret J de Villiers, Kirsten Ewertson, Matthew J Ferrari, Ivane Garmkheidze, Katy A M Gaythorpe, Nicholas C Grassly, Timothy B Hallett, Wes Hinsley, Michael L Jackson, Kévin Jean, Andromachu Karachakou, Petra Klepac, Justin Lessler, Xi Li, Sean M Moore, Shevanthi Nayagam, Duy Manh Nguyen, Homie Razavi, Devin Razavi-Shearer, Stephen Resch, Collin Sanderson, Steven Sweet, Stephen Sy, Yvonne Torn, Hira Tamir, Quan Minh Tran, Caroline L Trotter, Shawn Truelove, Kevin van Zandvoort, Stéphane Verguet, Neff Walker, Amy Winter, Kim Woodruff, Neil M Ferguson, Tim Garske, for the Vaccine Impact Modelling Consortium

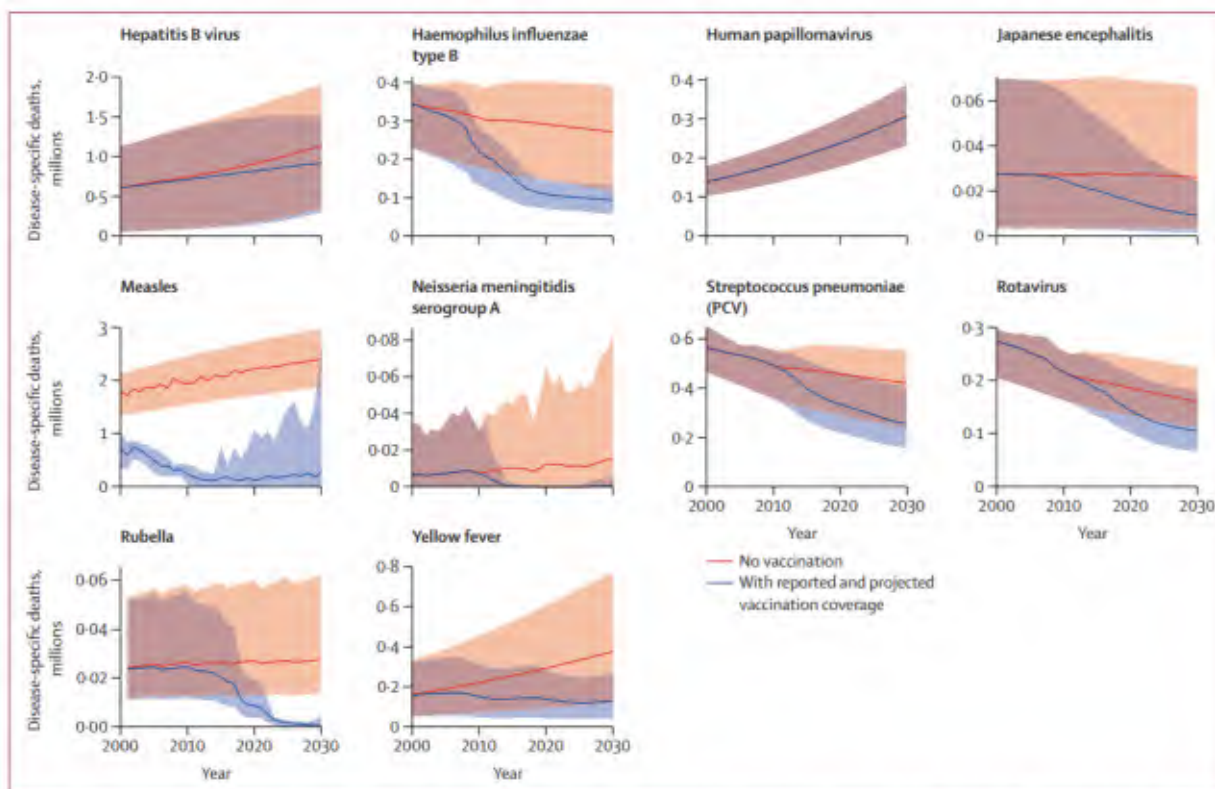


Figure 2: Estimates of disease-specific deaths by calendar year, from 2000 to 2030, across 98 countries, for reported and projected vaccine coverage and counterfactual (no vaccination) coverage. Lines show estimates of deaths for the two scenarios, for all ages. The corresponding shaded areas show the 95% credible intervals (2.5% and 97.5% quantiles). The grey shaded parts show the area where the 95% credible intervals for the two scenarios overlap. PCV=pneumococcal conjugate vaccine.

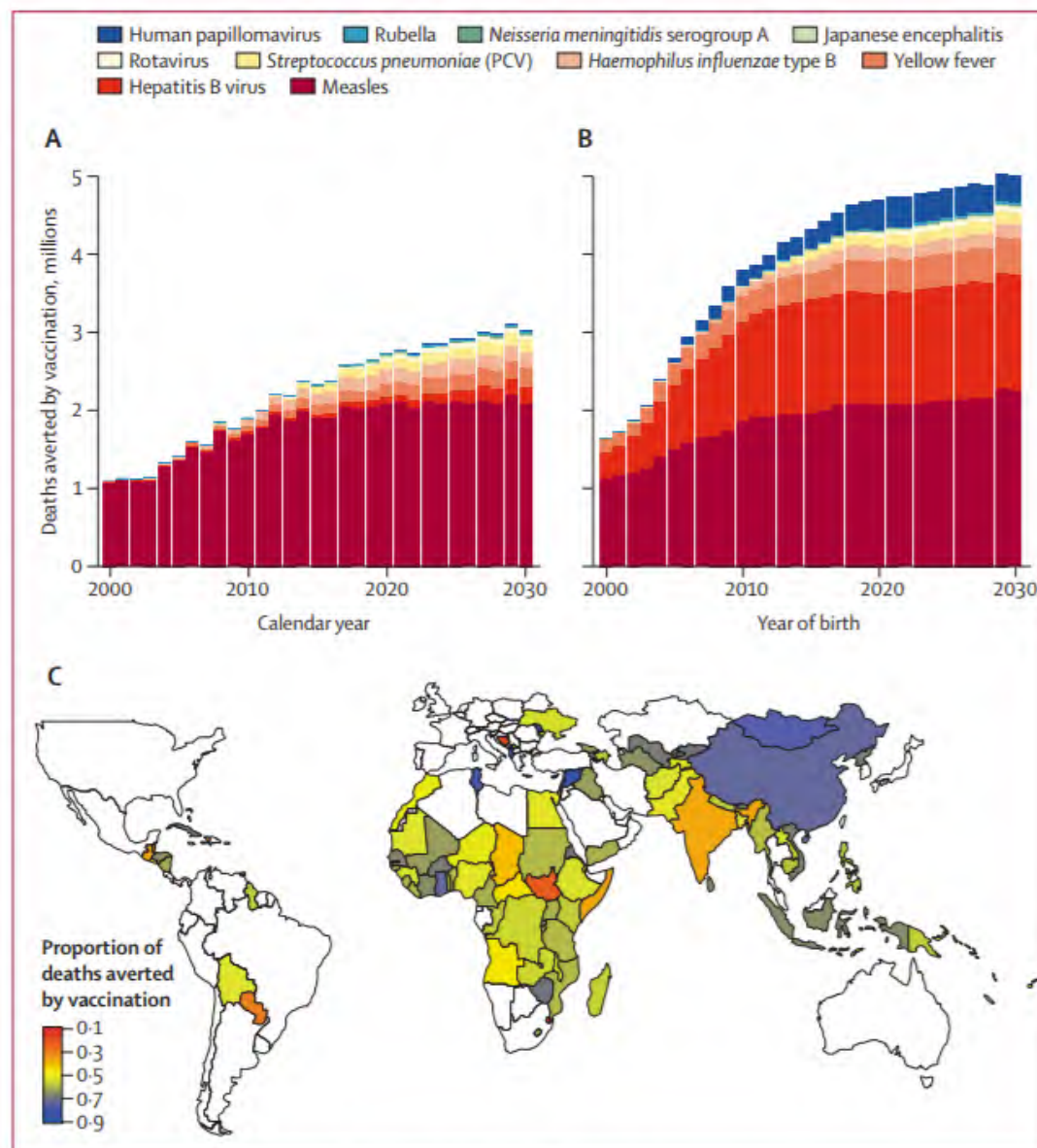


Figure 3: Estimates of deaths averted by vaccination in 98 countries

(A) Estimates of death averted by calendar year (summing across all ages) and pathogen. (B) Estimates of deaths averted by year of birth (summing across lifetime) and pathogen. (C) Proportion of lifetime deaths due to the ten pathogens considered in the no-vaccination counterfactual scenario that are predicted to be averted by vaccination, by country, across 2000–19 birth cohorts. PCV=pneumococcal conjugate vaccine.

Emerging and re-emerging infectious diseases



1983



1997



2003



2009



2013



2014



2020

Emerging infectious diseases (EID)

- Infectious diseases that have newly appeared in the human population.

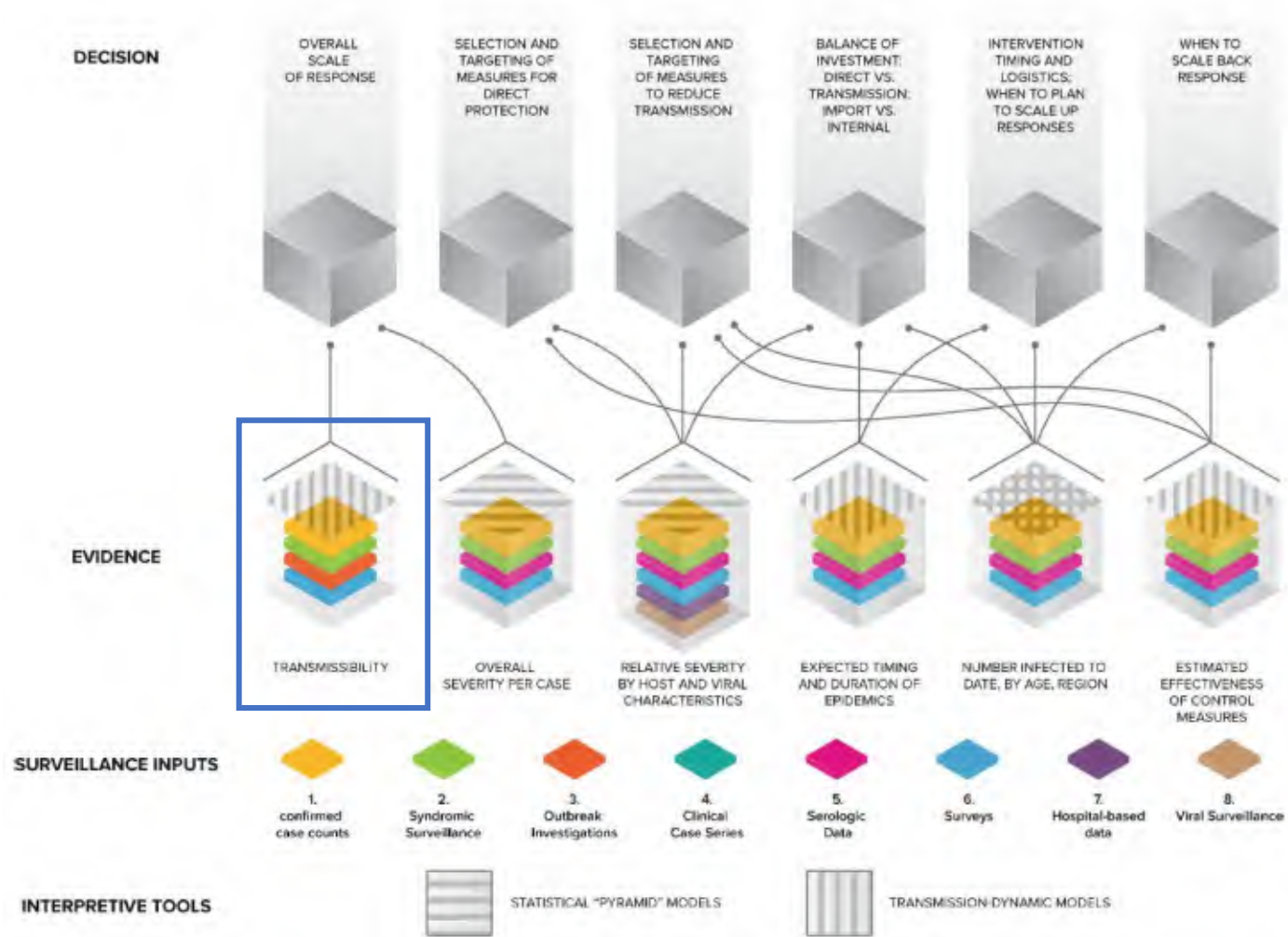
Re-emerging infectious diseases

- Infectious disease that are rapidly increasing in incidence or geographic distribution .

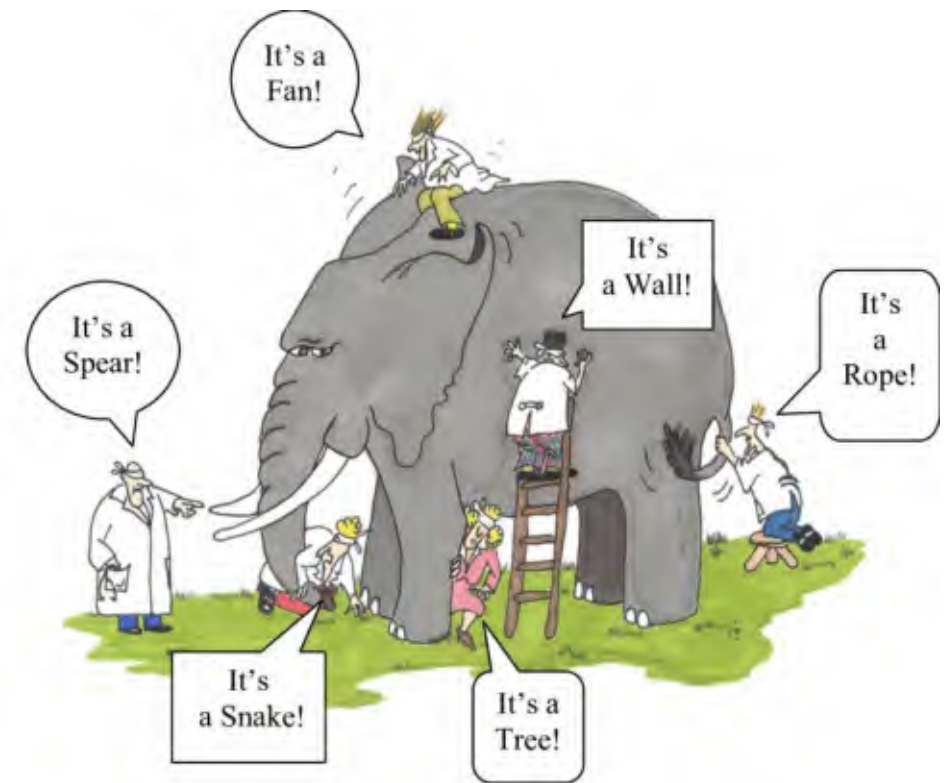
Zoonosis

- An infectious disease that can be transmitted from non-human animals (wild, domestic) to humans.

The context



The Blind Men and the Elephant



Determinants of transmissibility

Biological characteristics of the pathogen

- Tropism, structures, genomics
- Variants (e.g. COVID-19), strains (e.g. flu), serotypes (pneumococcus), types (HPV)

Susceptibility and immunity in the population

- Age, comorbidities, past infections, genetics, etc

Patterns of contact conducive to transmission

- Route of transmission, e.g. respiratory vs sexually-transmitted infections

Public health and social measures (PHSMs)

- Lockdowns, business curfews, bans of large gatherings, hand hygiene, face masks, etc

Environmental factors

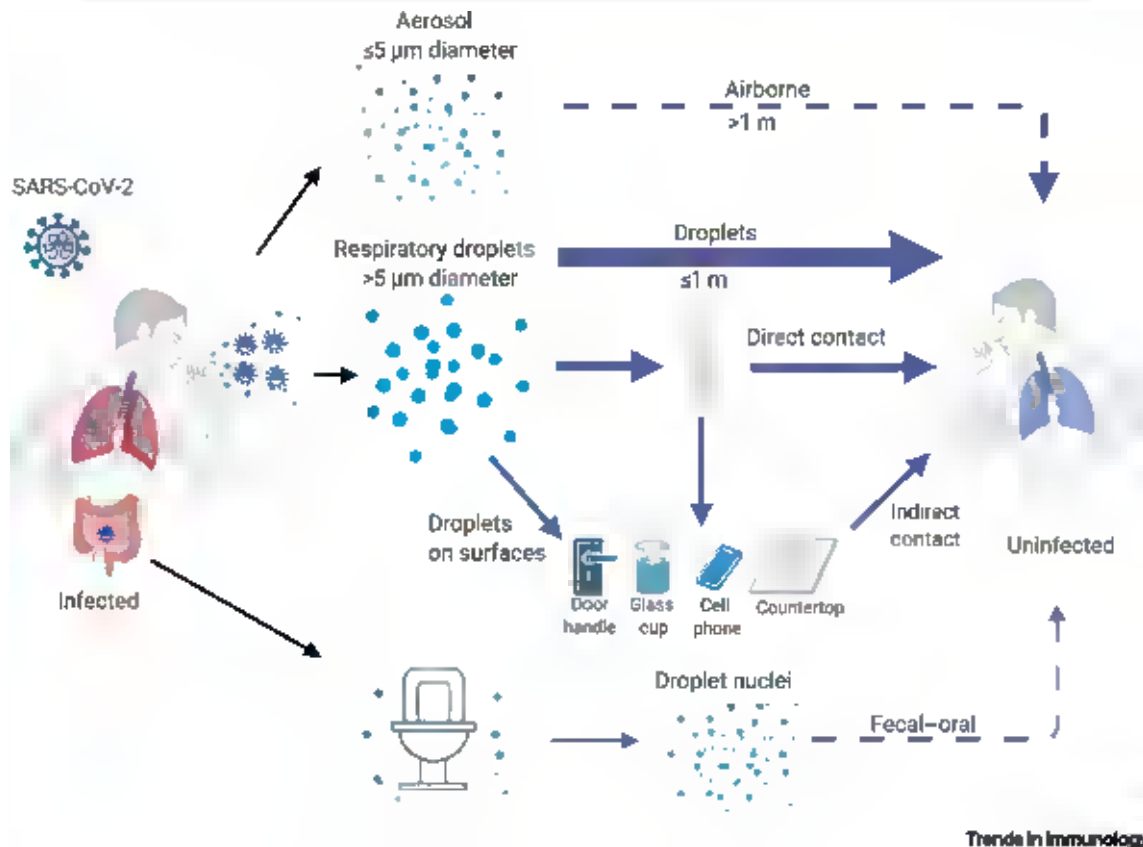
- Temperature, humidity, indoor ventilation, sunlight, etc

Stochastic effects (especially when prevalence is low)

- Importation, super-spreading events, etc

Review

Mechanisms of SARS-CoV-2 Transmission and Pathogenesis

Andrew G. Harrison,^{1,2} Tao Lin,^{1,2} and Penghua Wang^{1,*}Harrison et al *Trends in Immunol* 2020

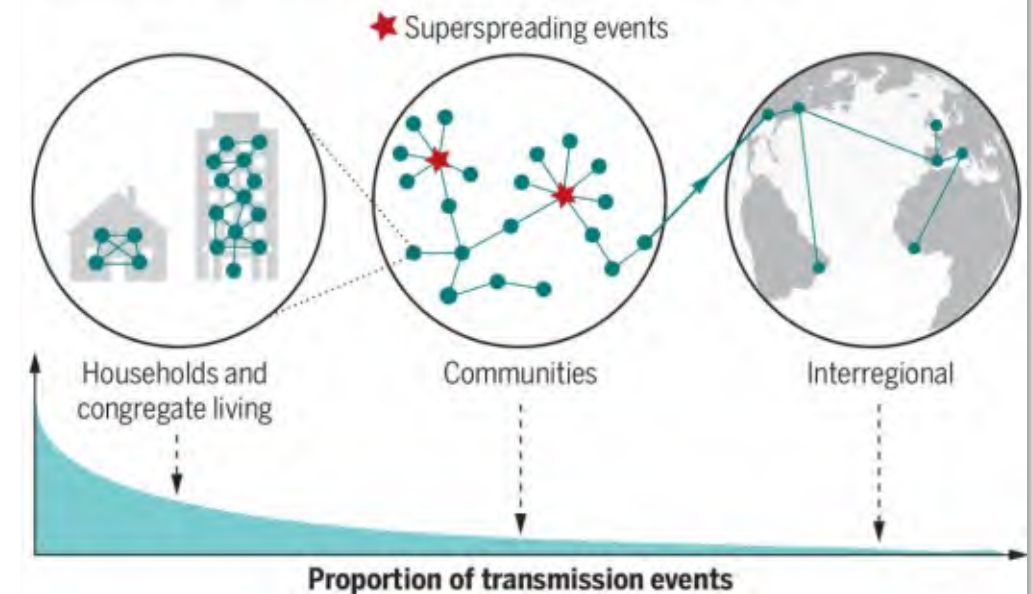
VIEWPOINT: COVID-19

The engines of SARS-CoV-2 spread

Fighting SARS-CoV-2 requires a clear framework for understanding epidemic spread

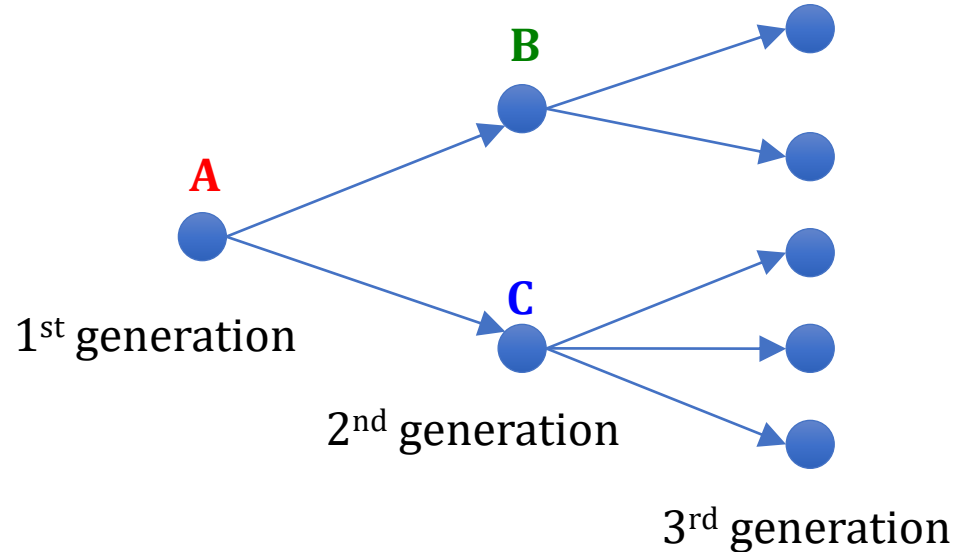
SARS-CoV-2 spread across spatial scales

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mostly transmitted within households and household-like settings. A decreasing proportion of transmission events take place at increasing spatial scales, but these events become more critical for sustaining the pandemic.

Lee et al *Science* 2020

How to measure transmissibility?

R_0 is the average number of secondary cases generated by an index case in a fully susceptible population:



$$R_0 = \frac{2 + 2 + 3}{3} = 2.3$$

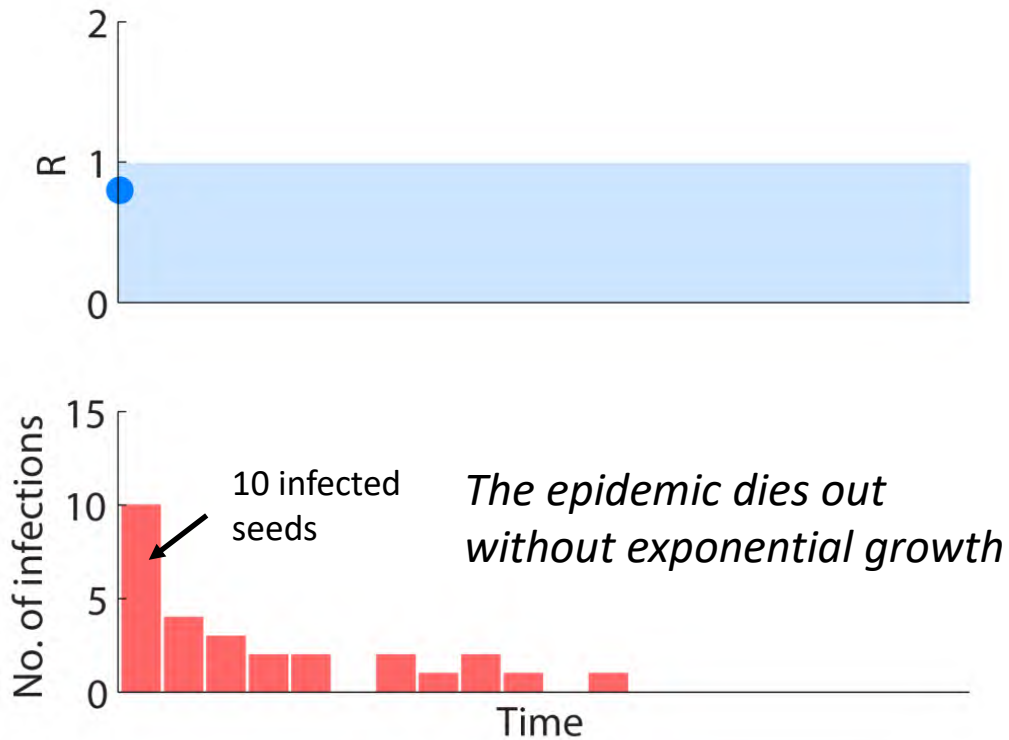
Reproductive number, R : Same as R_0 except that the population needs not be completely susceptible

- Some time after the epidemic has started, in which case we usually denote the reproductive number by R_t .
- If the population has been partially immunized.

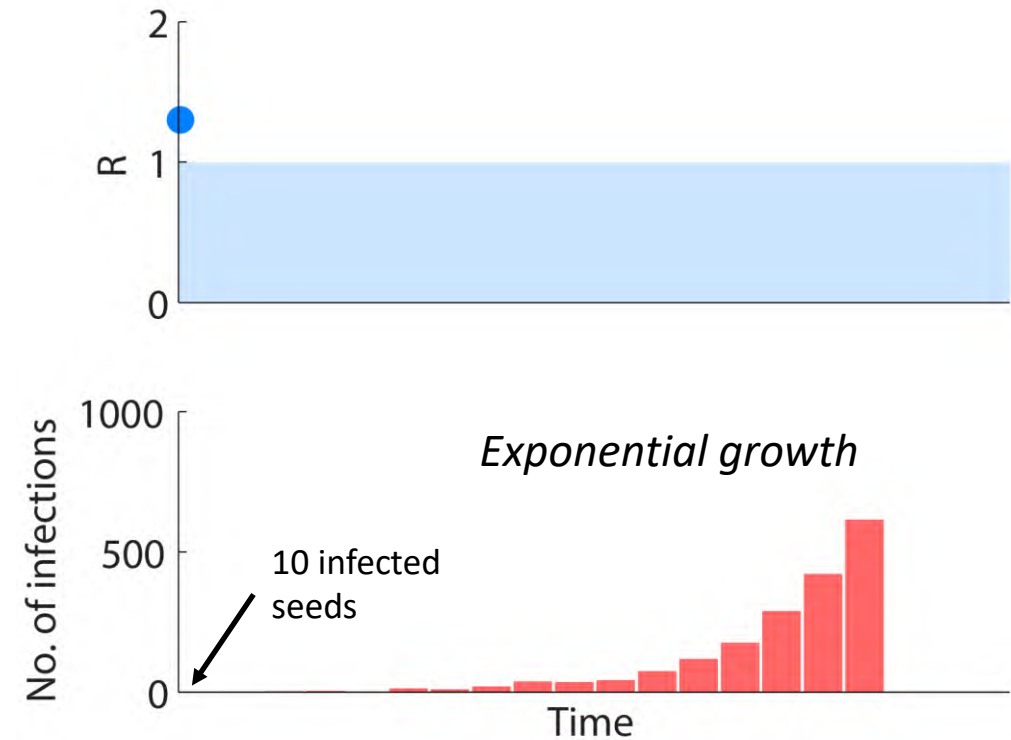
Why is R so important?

R indicates the potential of exponential epidemic growth

$R < 1$: The epidemic will die out without exponential growth



$R > 1$: The pathogen can lead to an exponentially growing epidemic



Estimating R_t from Epidemic Curves



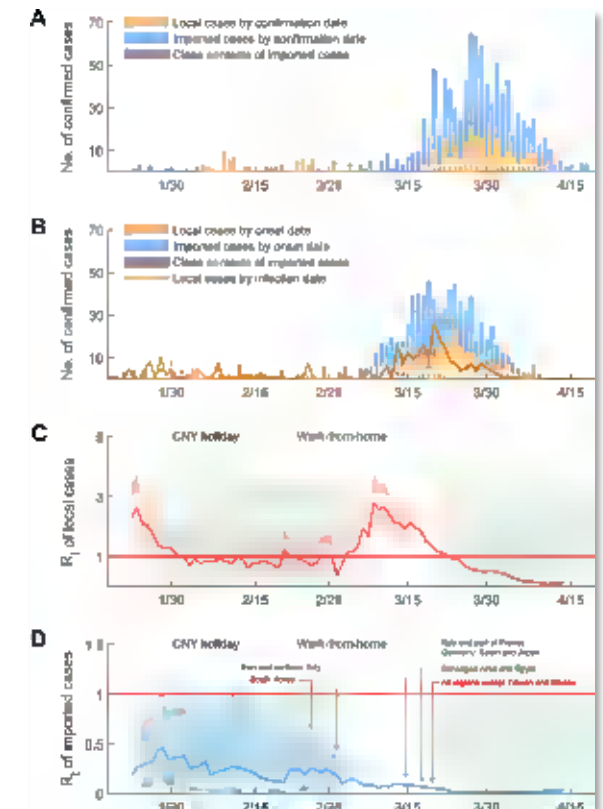
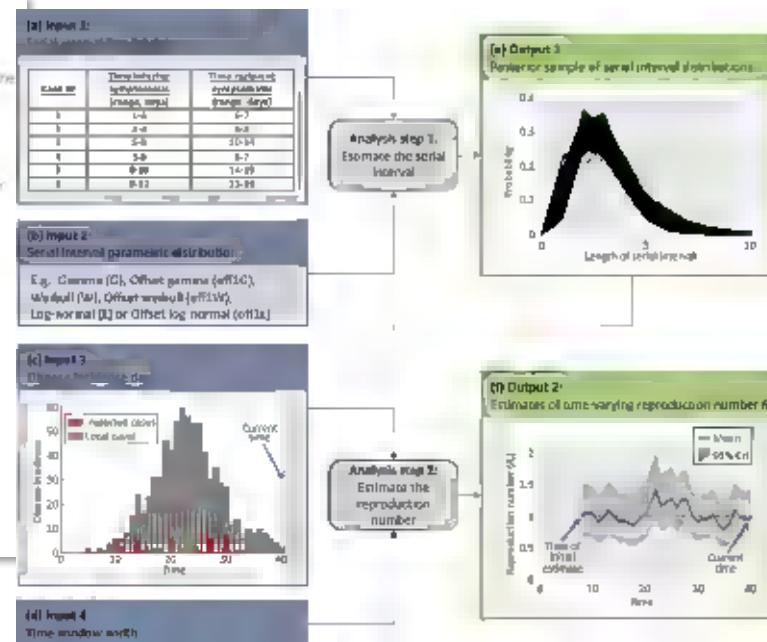
EpiEstim App

This web application generates an estimate of infectious disease transmissibility throughout an outbreak. The time-dependent reproduction number (R_t) is inferred from disease incidence time series and patient data or estimates of the serial interval. For more information about how to use this application, please see the [wiki](#). For the most part, we assume that users will want to upload their own data, however there are also some [example datasets](#) built in, to illustrate how the application might be used.

For more information on uploading your own data and on the required format of the data, please [click here](#).

The authors request users to cite the original publication when referring to this tool, any results generated from it, or the R software application in which this tool is based (EpiEstim 2).

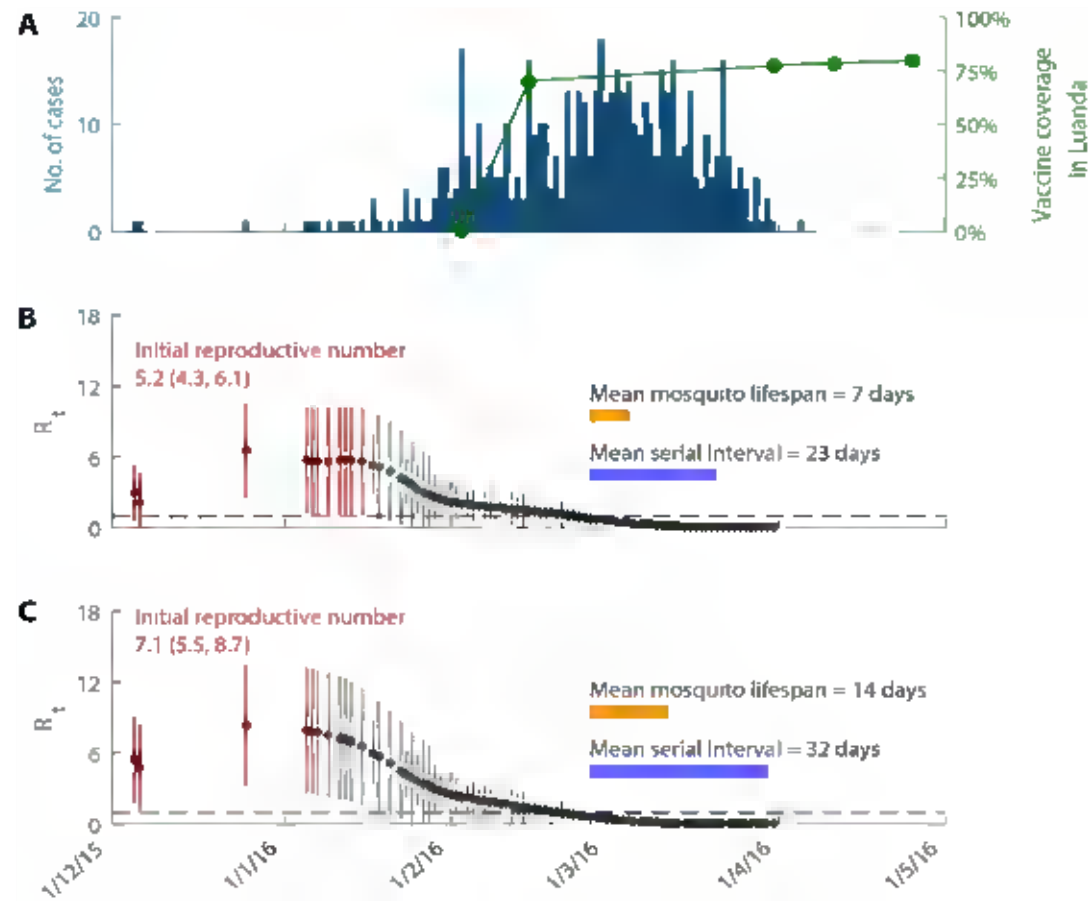
Thompson RN, Stockwin JE, van Gaalen RD, Polonsky JA, et al. Improved inference of time-varying reproduction numbers during infectious disease outbreaks. *Epidemics* (2019).





Fractional dosing of yellow fever vaccine to extend supply: a modelling study

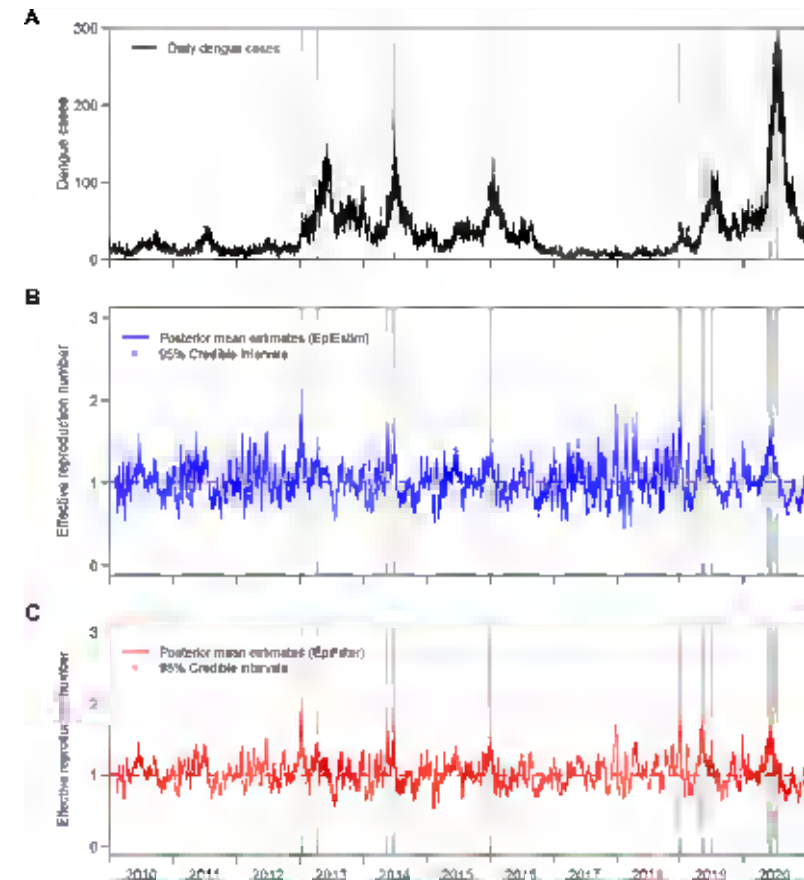
Joseph T Wu, Corey M Peak, Gabriel M Leung, Marc Lipsitch



Wu et al *Lancet Infect Dis* 2016

Fine-scale estimation of effective reproduction numbers for dengue surveillance

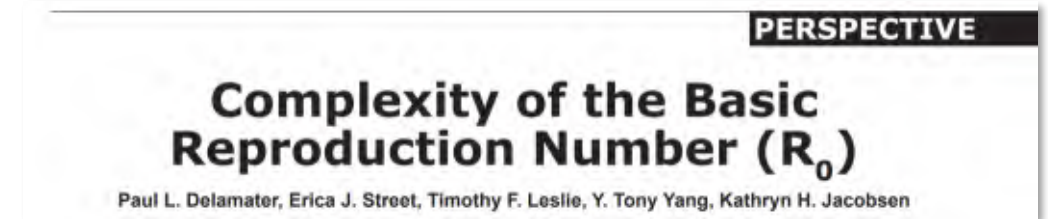
Janet Ong, Stacy Soh, Soon Hoe Ho, Annabel Seah, Borame Sue Dickens, Ken Wei Tan, Joel Ruihan Koo, Alex R. Cook, Daniel R. Richards, Leon Yan-Feng Gao, Lee Ching Ng, Jue Tao Lim



Ong et al *PLOS Comp Bio* 2021

Interpretation of R_0 Estimates

Disease	R_0	Mean serial interval (day)
Measles	12-18	12-16
Chickenpox (varicella)	10-12	18-23
Mumps	10-12	16-26
Rubella	6-7	18-26
Pertussis	~5	28-33
COVID-19 (Delta variant)	~5	~3
Smallpox	3.5-6.0	10-14
COVID-19 (Alpha variant)	4-5	~3
COVID-19 (ancestral strain)	2-4	~5
SARS	2-4	~7
Diphtheria	1.7-4.3	6-10
Common cold	2-3	~3
Ebola (2014 outbreak)	1.4-1.8	~14
Influenza (2009 pandemic strain)	1.3-2.0	~3
Influenza (seasonal strains)	1.2-1.4	~2
MERS	0.3-0.8	~5



- R_0 is affected by numerous biological, sociobehavioral, and environmental factors that govern pathogen transmission .
- R_0 is not a biological constant for a pathogen.
- R_0 is rarely measured directly, and modeled R_0 values are dependent on model structures and assumptions.
- Some R_0 values reported in the scientific literature are likely obsolete.
- R_0 must be estimated, reported, and applied with great caution because this basic metric is far from simple.

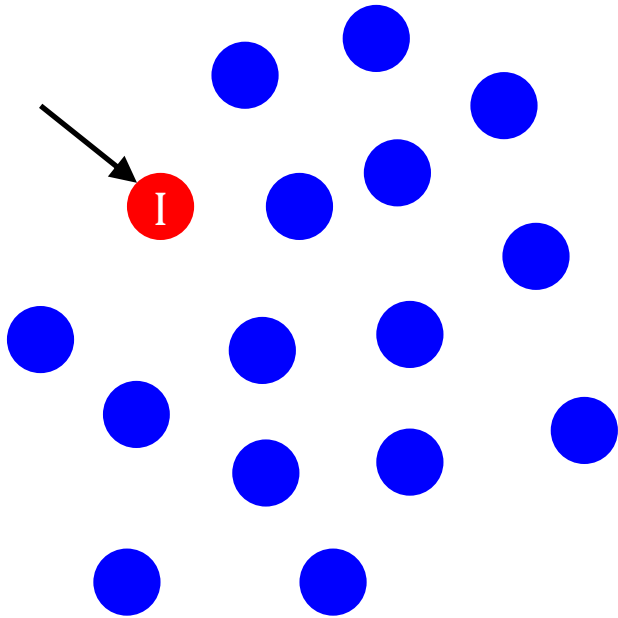
What is herd immunity?

Immunizing an individual indirectly reduces the risk of infection of his contacts, his contacts' contacts, and so on, i.e. the whole population

● Susceptible

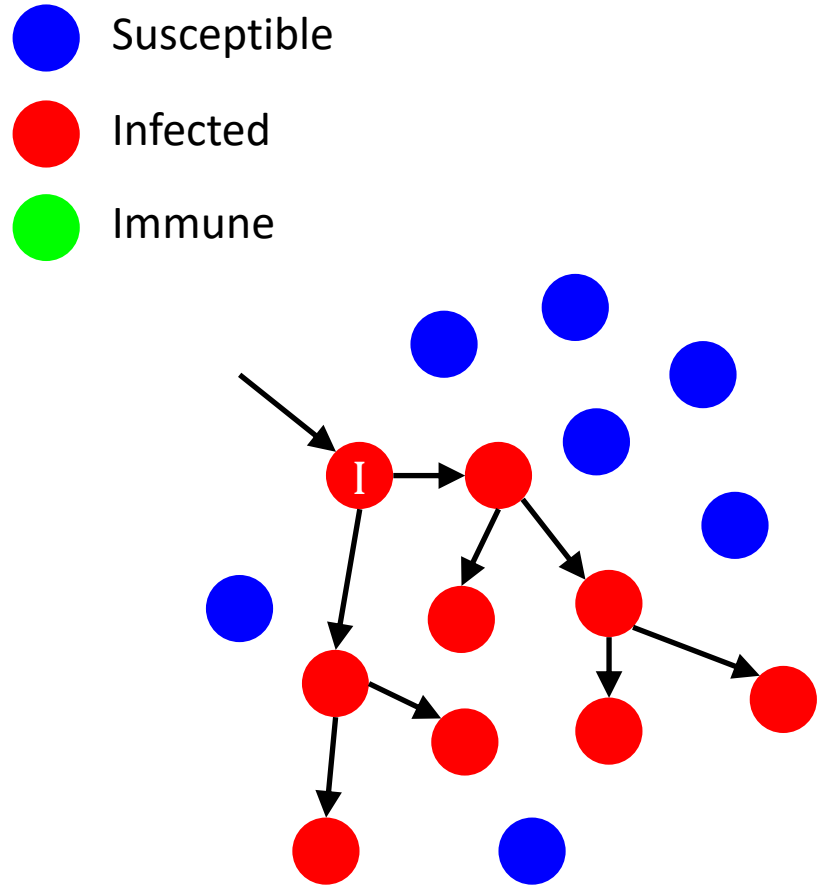
● Infected

● Immune



What is herd immunity?

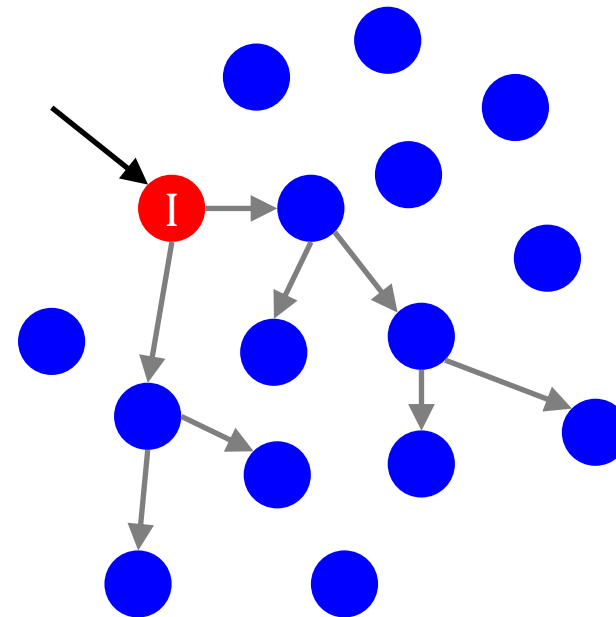
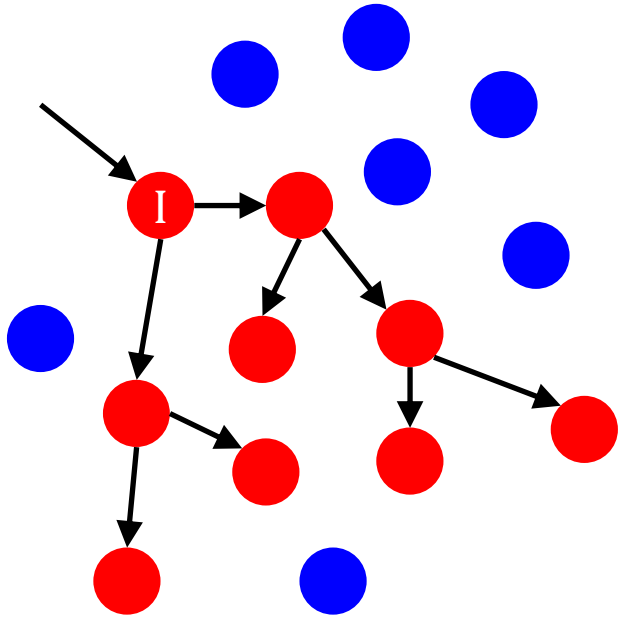
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What is herd immunity?

Immunizing an individual indirectly reduces the risk of infection of his contacts, his contacts' contacts, and so on, i.e. the whole population

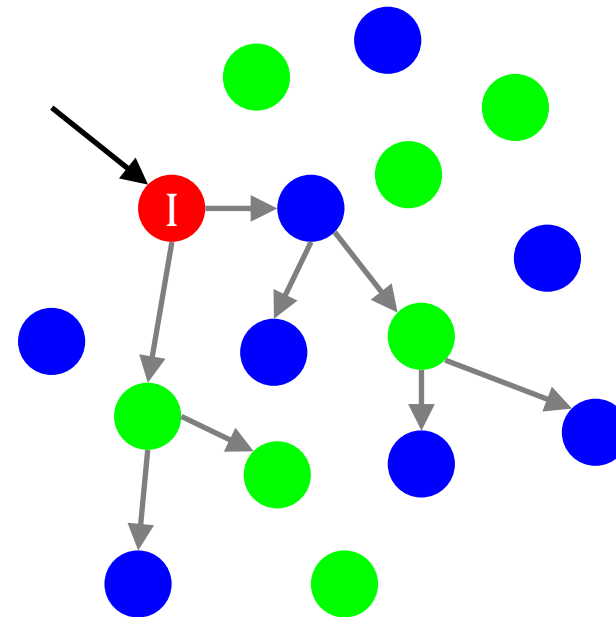
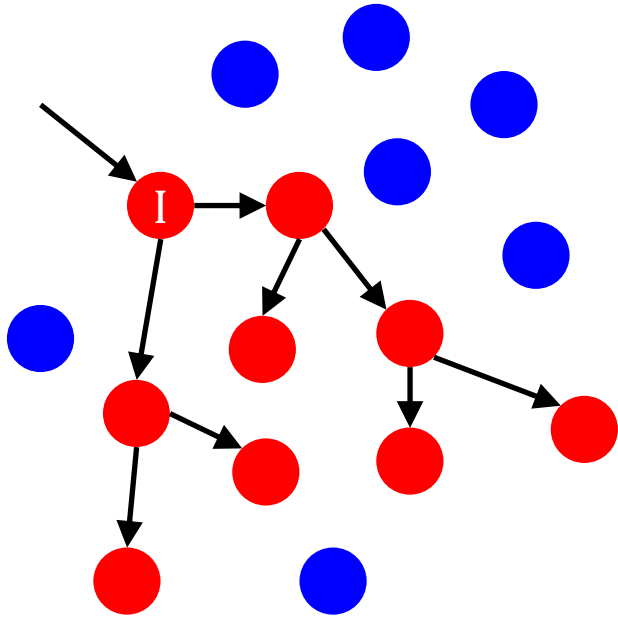
- Susceptible
- Infected
- Immune



What is herd immunity?

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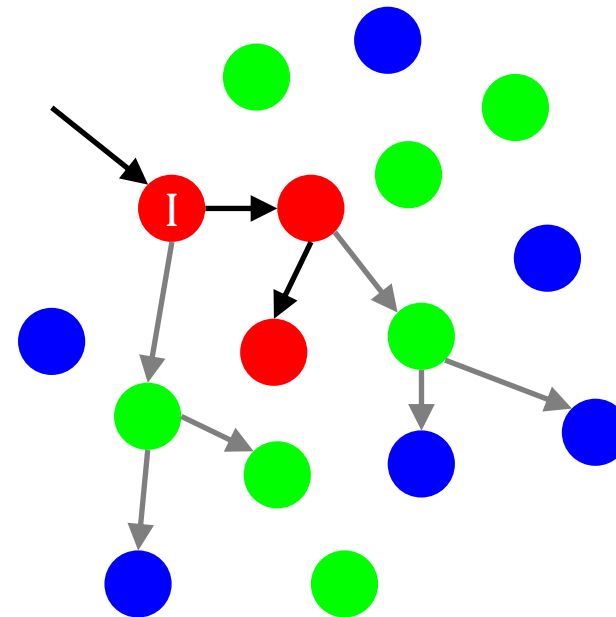
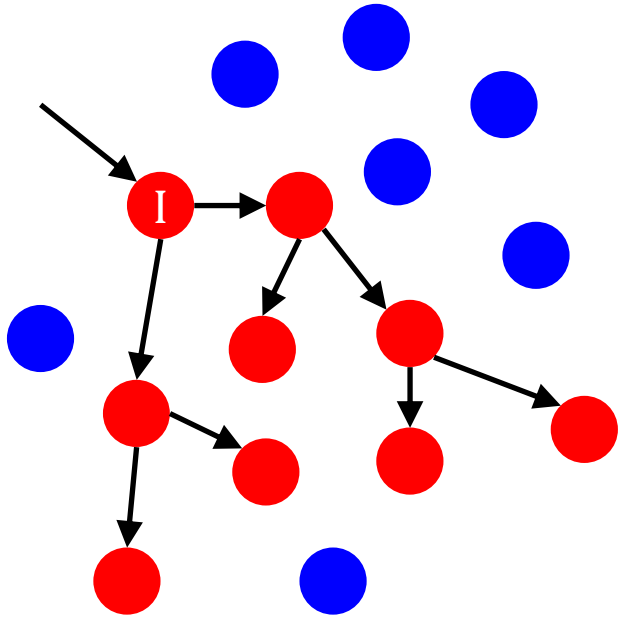
- Susceptible
- Infected
- Immune



What is herd immunity?

Immunizing an individual indirectly reduces the risk of infection of his contacts, his contacts' contacts, and so on, i.e. the whole population

-  Susceptible
-  Infected
-  Immune



What is herd immunity?

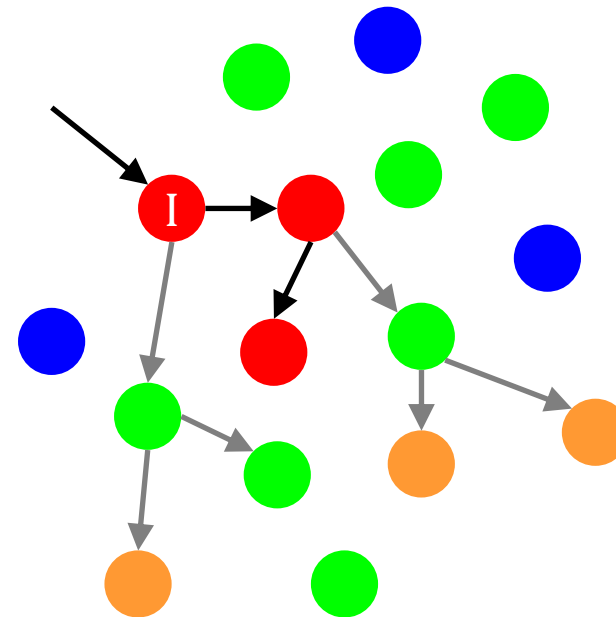
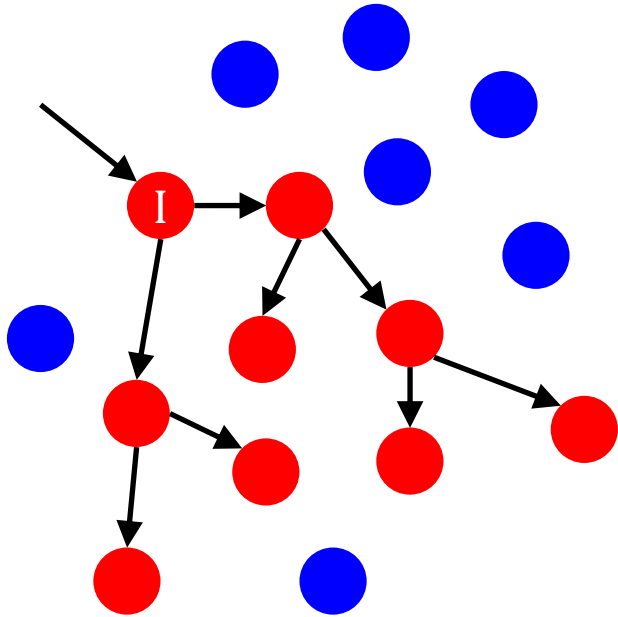
Immunizing an individual indirectly reduces the risk of infection of his contacts, his contacts' contacts, and so on, i.e. the whole population

● Susceptible

● Infected

● Immune

● Indirectly protected by herd immunity



Real-world evidence of herd immunity – COVID-19 vaccines

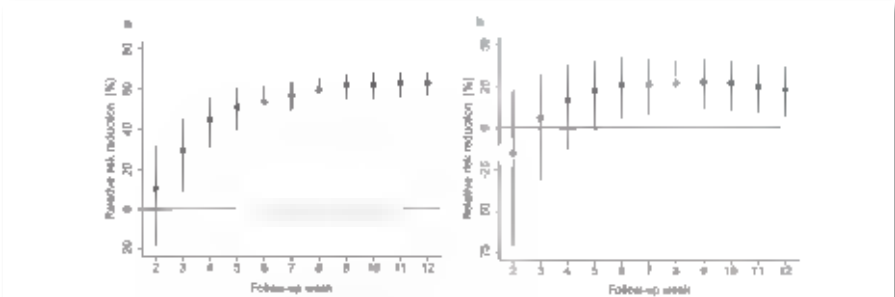
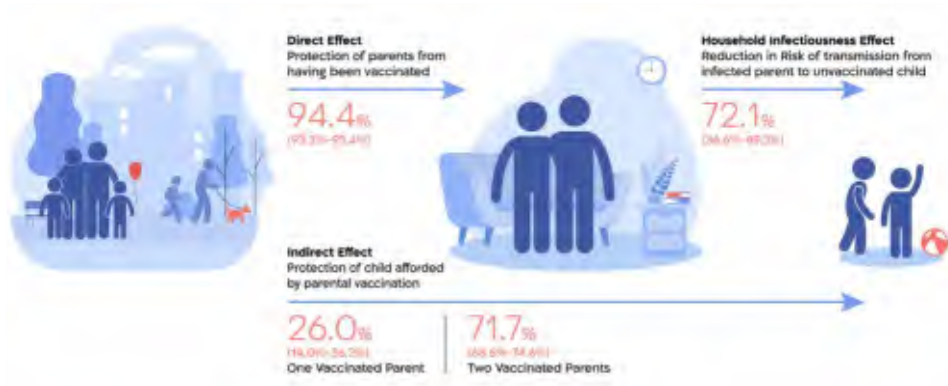
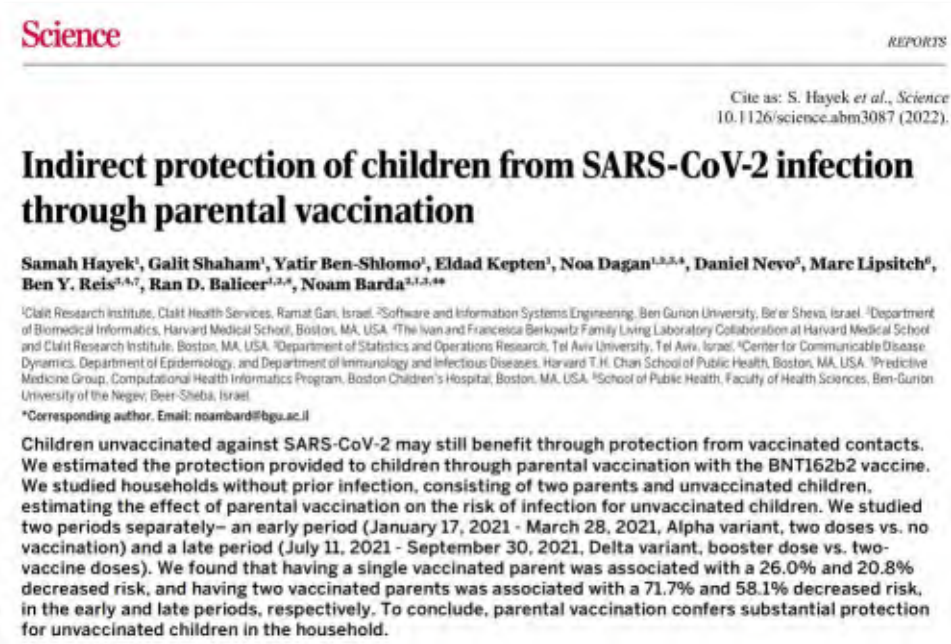


Fig. 1 Vaccine effectiveness in vaccinated healthcare workers and their unvaccinated partners living in the same household. This figure plots vaccine

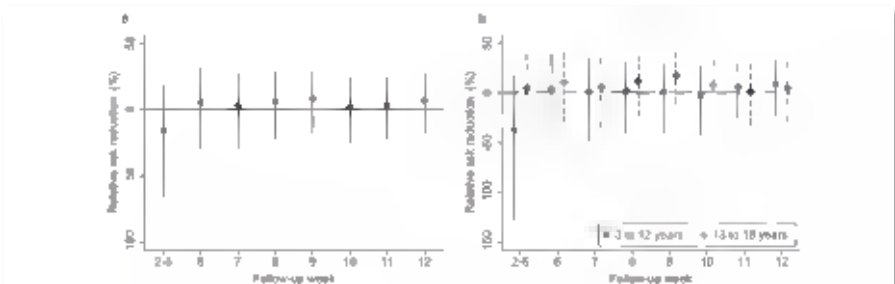
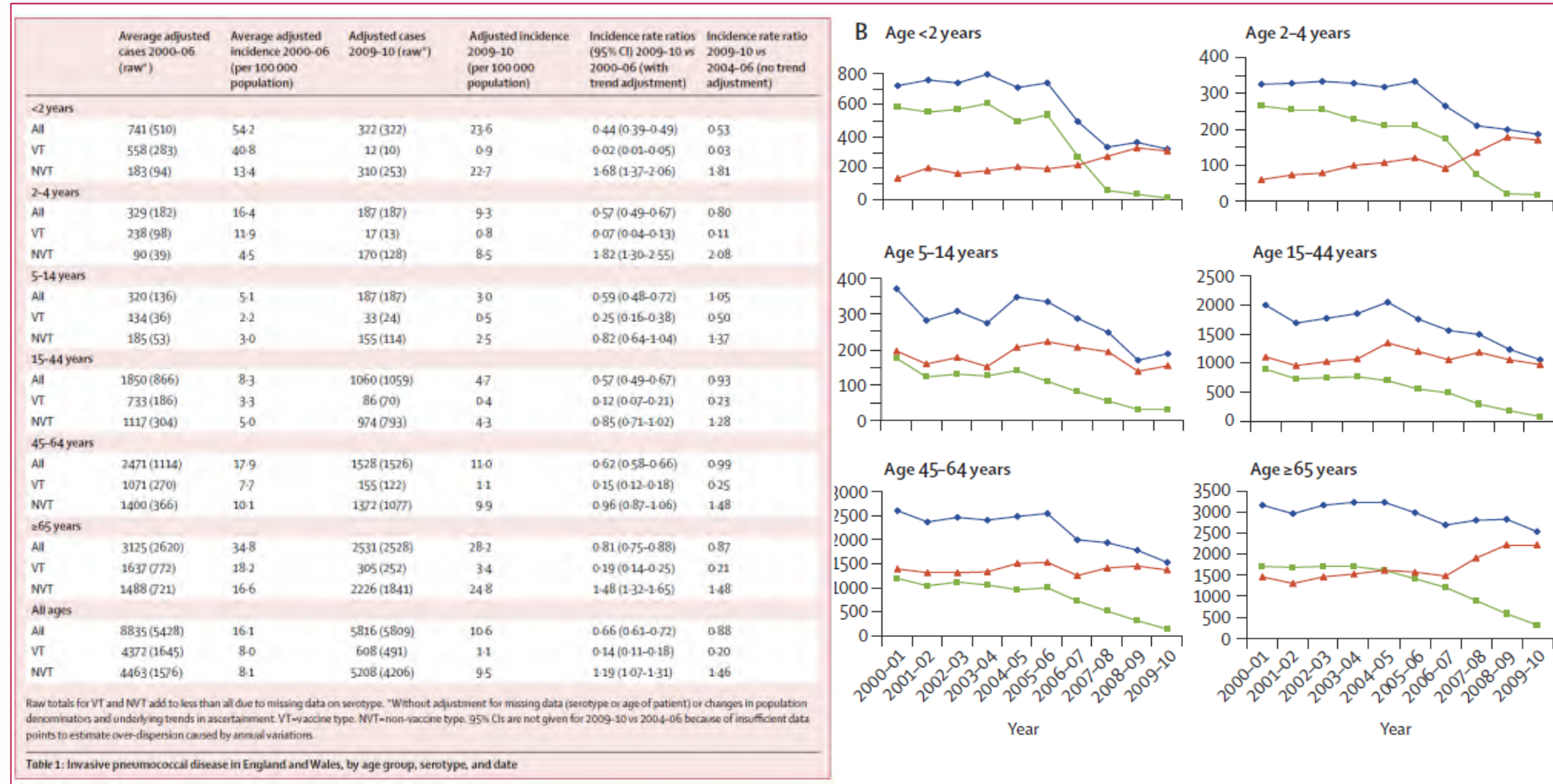


Fig. 2 Vaccine effectiveness in unvaccinated children and adolescents. This figure plots vaccine effectiveness estimates by week after the first dose of

Real-world evidence of herd immunity – PCV

In September, 2006, the seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the UK with a vaccination schedule of 2, 4, and 13 months, and catch-up vaccination for children aged up to 2 years



Real-world evidence of herd immunity – HPV vaccine

- From Jul 2007 to Dec 2009, Australia provided free quadrivalent HPV vaccination to all women aged 12-26 y
- Significant decline in diagnoses of genital warts among **young females** AND **young heterosexual males**

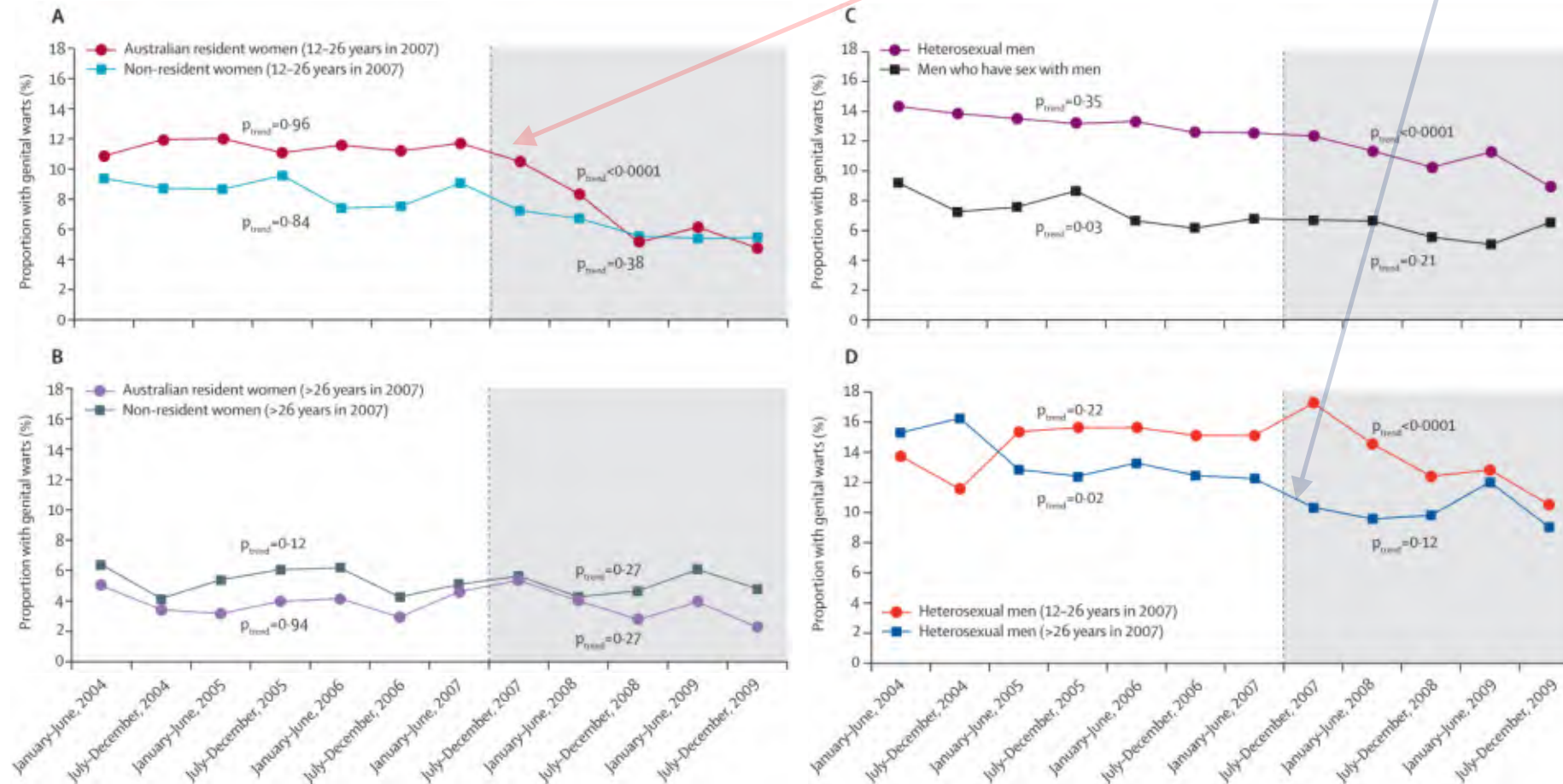
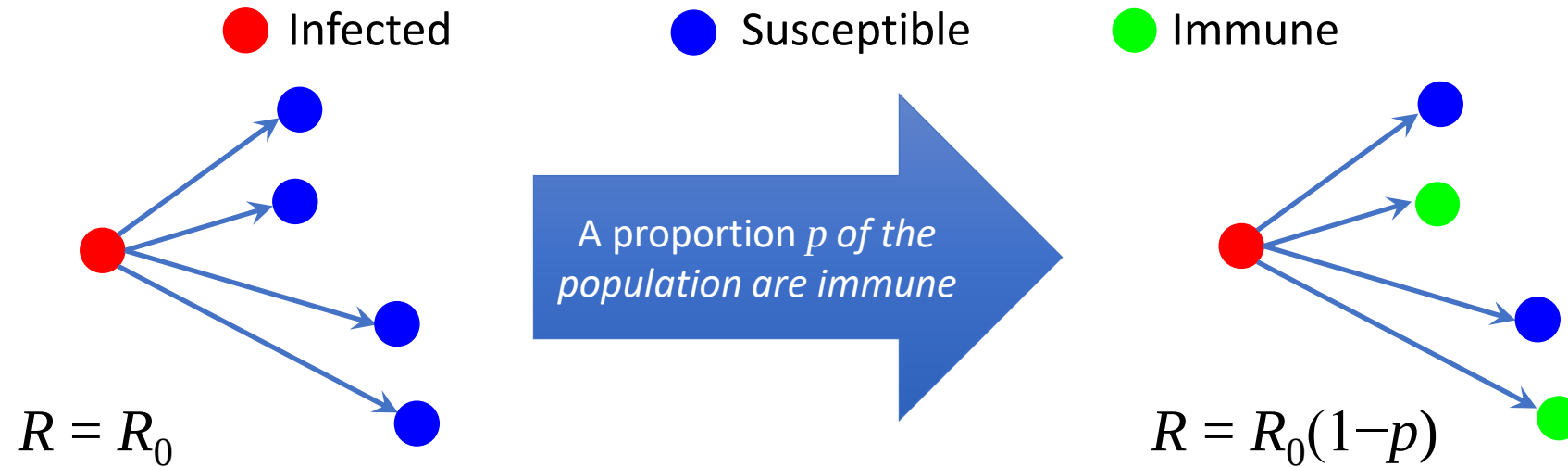


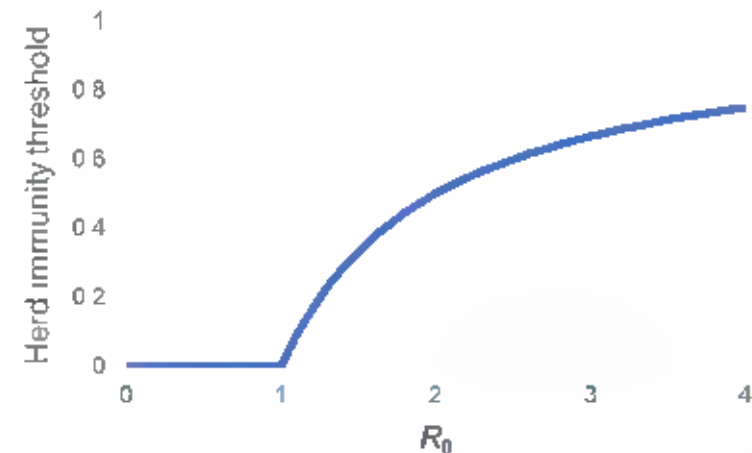
Figure 2: Proportion of people presenting to sexual health services with genital warts, 2004–09
p values for trend are for the prevaccine period or within vaccine period (grey region). (A) Women eligible (aged 12–26 years in July, 2007) for free quadrivalent HPV vaccine in Australia, by residency status. (B) Women not eligible (aged older than 26 years in July, 2007) for free quadrivalent HPV vaccine in Australia, by residency status. (C) Men with genital warts, by sex of sexual partners. (D) Heterosexual Australian men with genital warts, by age group.

Herd immunity threshold and R_0

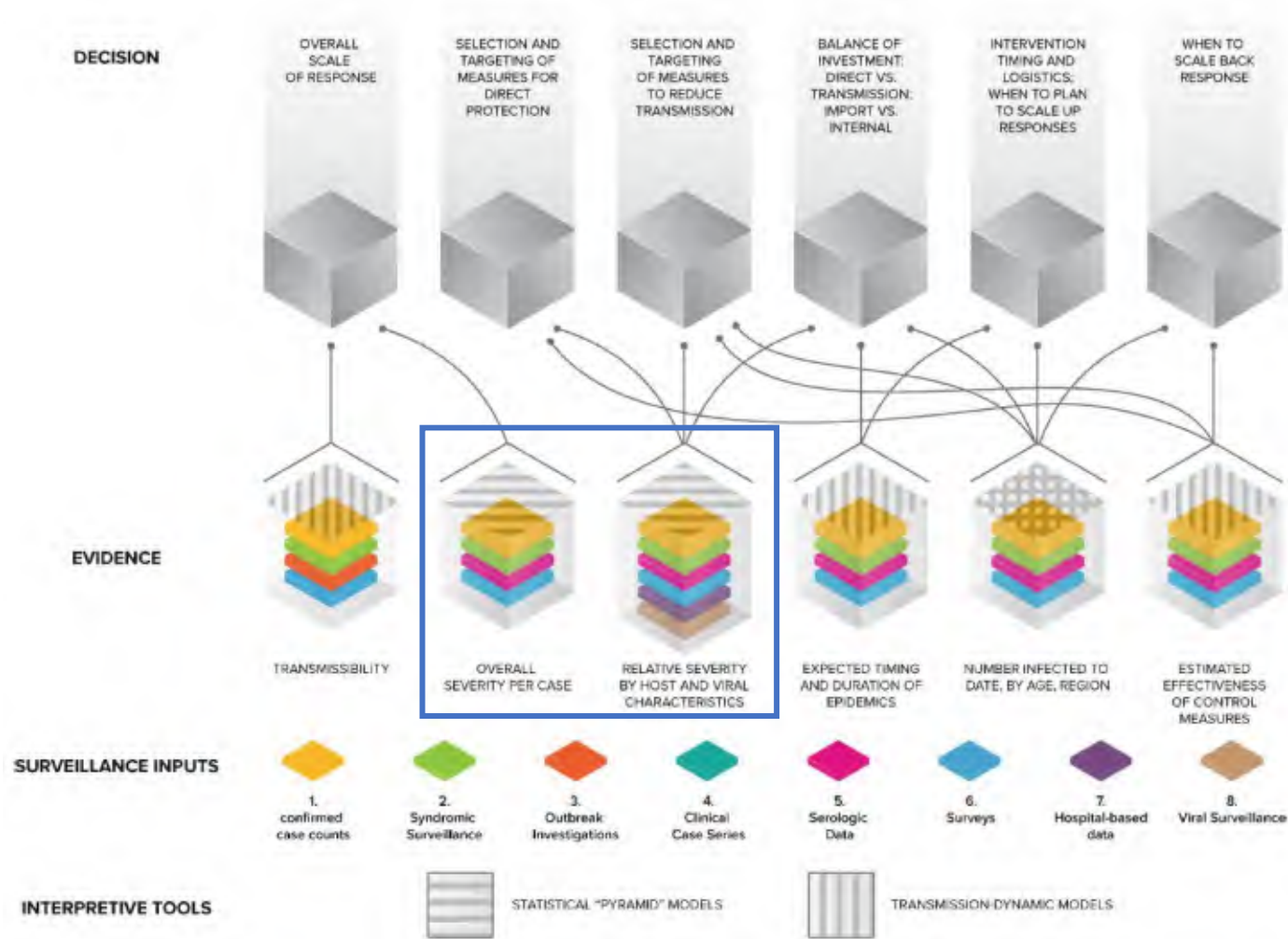


Immunizing a proportion $p > 1 - 1/R_0$ of the population is sufficient to halt an epidemic

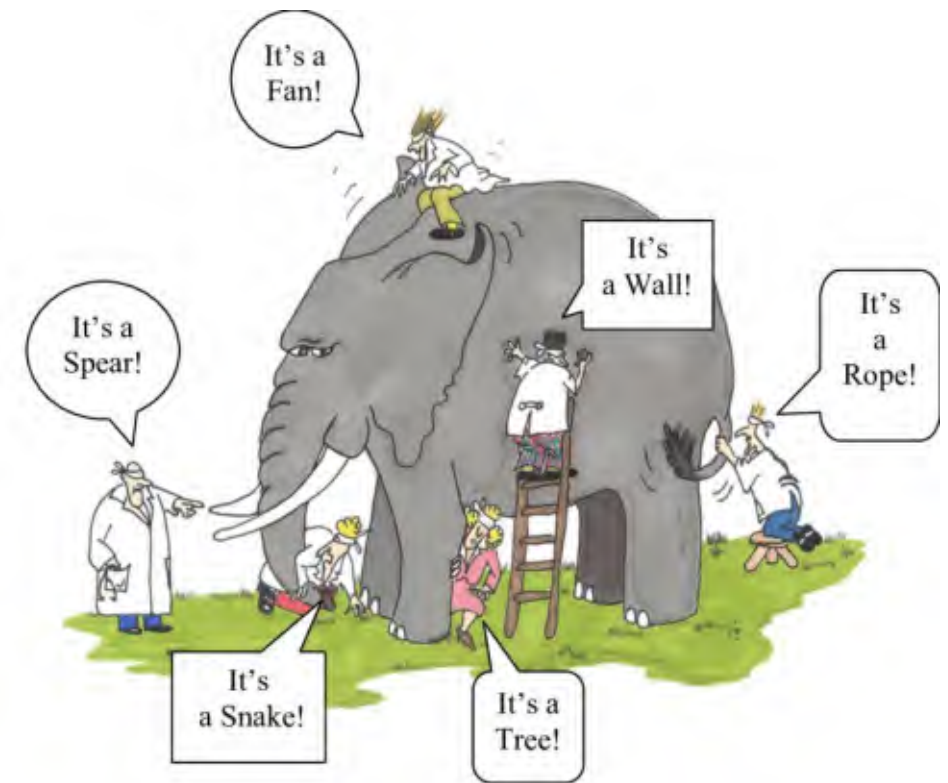
$$R = (1 - p)R_0 < 1 \quad \Leftrightarrow \quad p > 1 - 1/R_0$$



The context



The Blind Men and the Elephant



Why are severity estimates important?

$$\text{Probability of severe outcome per case} = \frac{\text{Total number of severe outcomes}}{\text{Total number of cases}}$$

- Project how health care demand and deaths would scale with epidemic size
- Help health officials strike the optimum balance between the socioeconomic costs of control measures and the health threat posed by an unmitigated epidemic

Difficulties in assessing severity

1. Case definition may vary across time and jurisdictions
 - Clinical vs. lab-confirmed vs. all infections
 - Hospitalized vs. all cases
2. Ascertainment ratio may vary across time and jurisdictions
 - Healthcare seeking behavior
 - Sentinel coverage
 - Laboratory capacity
3. As an epidemic grows rapidly, a substantial proportion of cases still have their clinical outcomes unresolved (e.g. death vs. survival among those hospitalized)

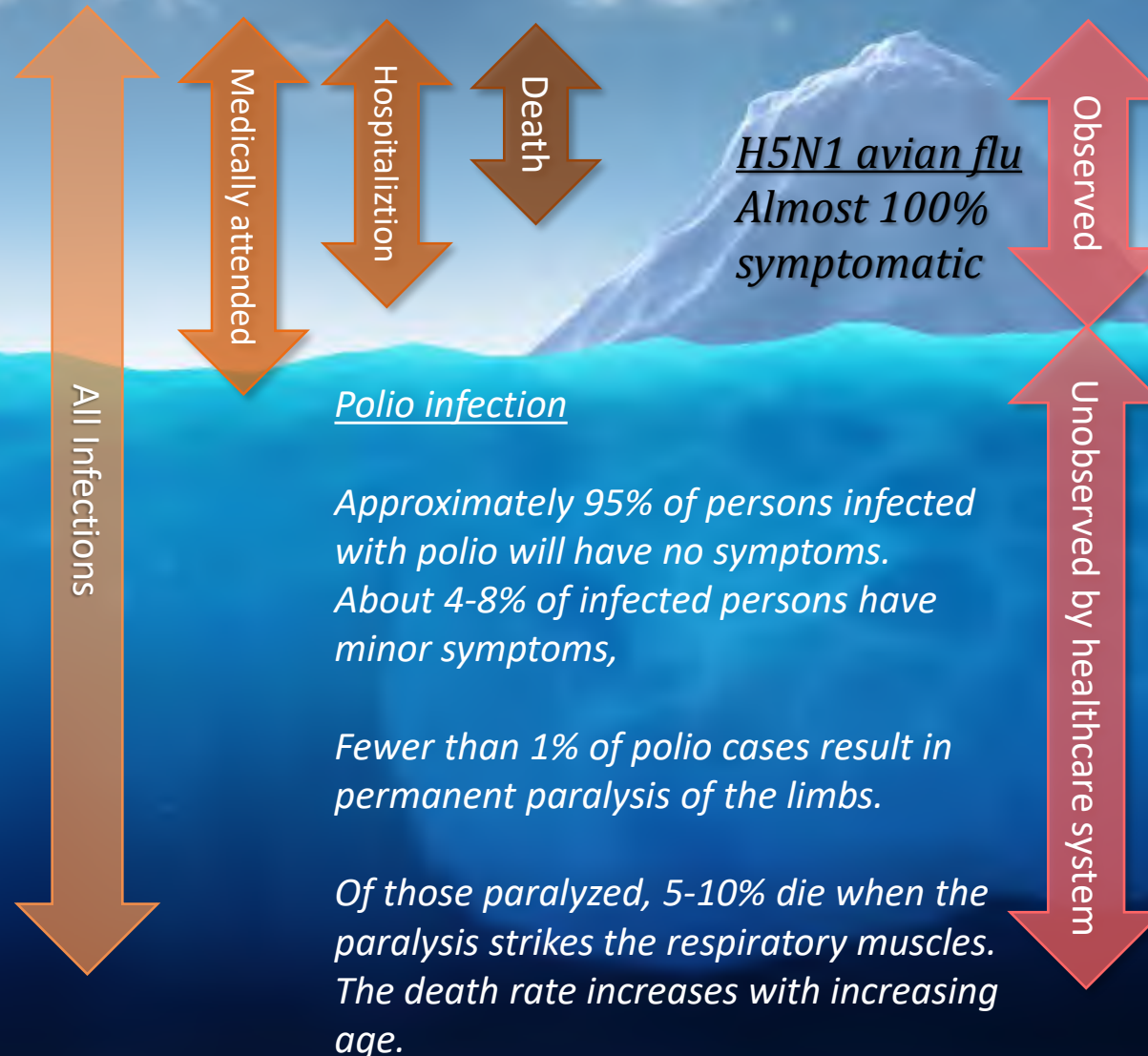


“The absence of a consistent, measurable and understandable depiction of severity of the pandemic” was a major shortcoming of the global response to the 2009 influenza pandemic

“Clinical Iceberg”

Morbidity and mortality observed in the clinical settings often constitute only a small proportion of all infections

Asymptomatic or subclinical infection carriers are common for many infectious diseases



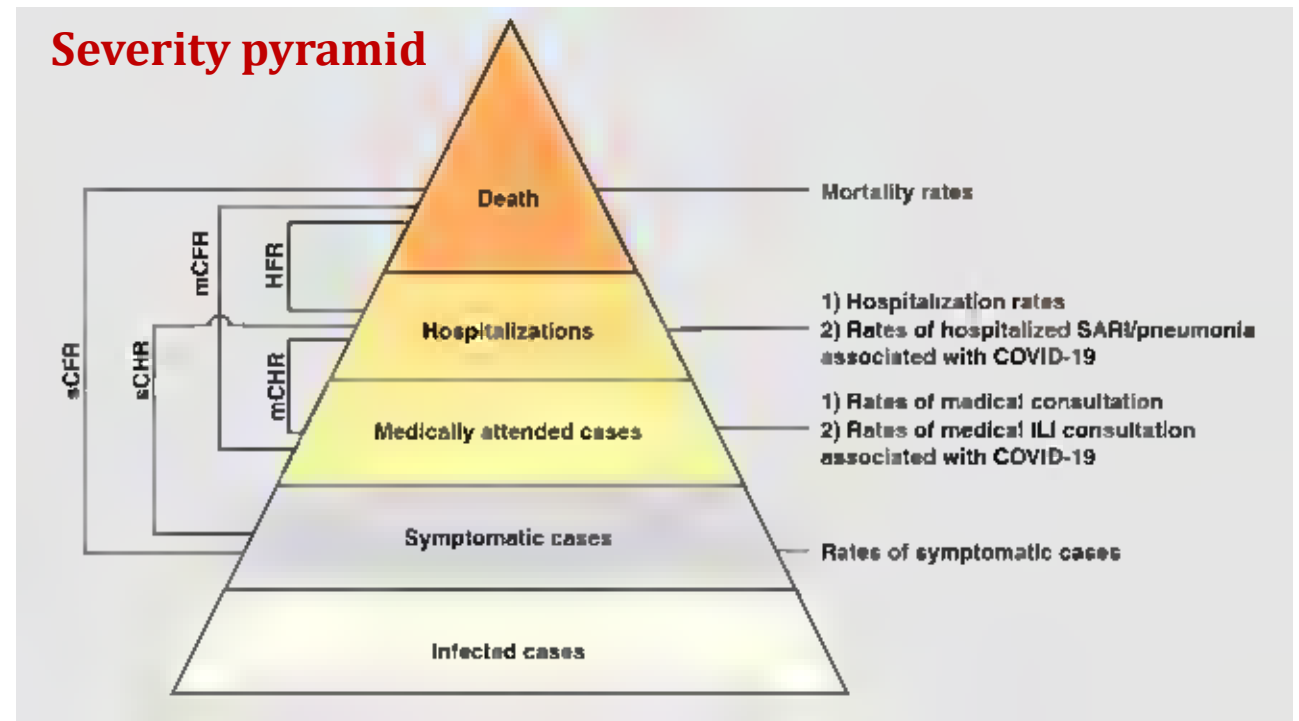
Severity

$$\text{Probability of severe outcome per case} = \frac{\text{Total number of severe outcomes}}{\text{Total number of cases}}$$

Application of severity estimates

- Project how health care demand and deaths would scale with epidemic size
- Help health officials strike the optimal balance between the socioeconomic costs of control measures and the health threat posed by an unmitigated epidemic
- Identify risk factors for increased severity (e.g. case-fatality risk) to help guide prioritization of high-risk groups for vaccines and treatments
- Inform the public on health benefits vs risks of vaccination
- Risk communication

HFR: Hospitalization-fatality risk
sCFR: Symptomatic case-fatality risk
CFR: Case-fatality risk
IFR: Infection-fatality risk

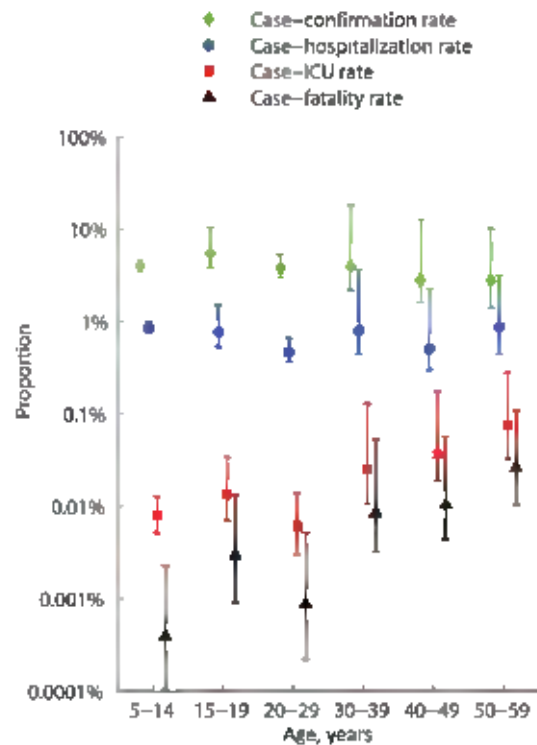


Determinants of Severity

Severity may depend on host factors (age, comorbidities, genetics)

The Infection Attack Rate and Severity of 2009 Pandemic H1N1 Influenza in Hong Kong

Joseph T. Wu,¹ Edward S. K. Ma,² Cheuk Kwong Lee,³ Daniel K. W. Chu,² Po-Lai Ho,² Angela L. Shen,⁷ Andrew Ho,¹ Ivan F. N. Hung,² Steven Riley,¹ Lai Ming Ho,¹ Che Kit Lin,² Thomas Tsang,⁶ Su-Vui Lo,^{7a} Yu-Lung Lau,⁴ Gabriel M. Leung,¹ Benjamin J. Cowling,^{1a} and J. S. Malik Peiris^{2,8a}



Wu et al *CID* 2010

LETTERS

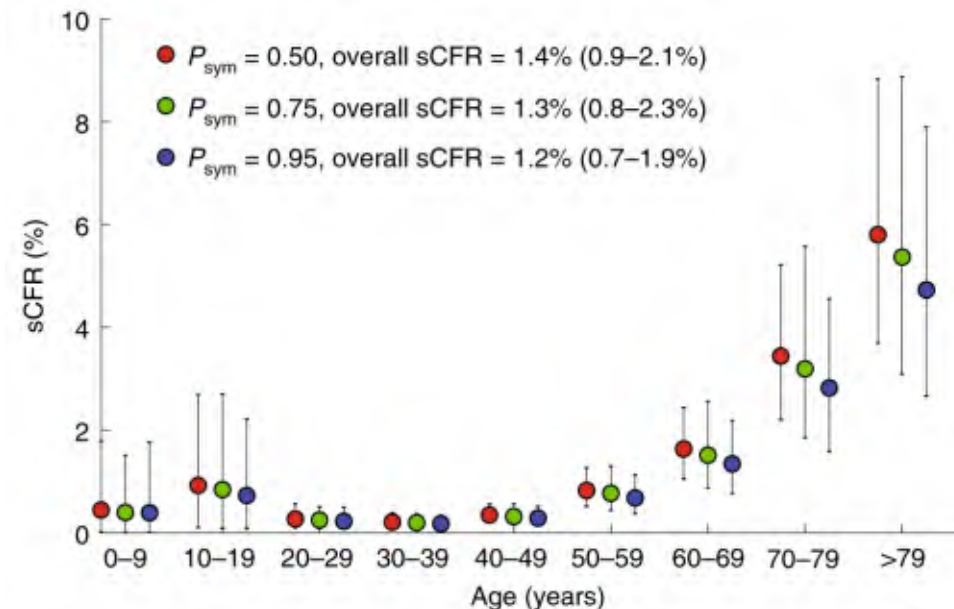
<https://doi.org/10.1038/s41591-020-0822-7>

nature
medicine

Check for updates

Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China

Joseph T. Wu^{1,2,3}, Kathy Leung^{1,3}, Mary Bushman², Nishant Kishore², Rene Niehus², Pablo M. de Salazar², Benjamin J. Cowling¹, Marc Lipsitch² and Gabriel M. Leung¹



Wu et al *Nat Med* 2020

Vaccine Efficacy and Effectiveness

The reduction in the risk of the outcome (infection, symptoms, hospitalization, death) among vaccinated compared to unvaccinated:

$$VE = \frac{Risk_{Unvaccinated} - Risk_{Vaccinated}}{Risk_{Unvaccinated}}$$

Vaccine efficacy measures the direct effect of vaccination **during vaccine trials**.

Vaccine effectiveness measures both the direct and indirect effects of vaccination **in the real world**.

Vaccine efficacy and effectiveness for which endpoint/outcome?

- Susceptibility to infection (VE_S)
- Disease progression (e.g. symptoms onset and severity) given infection (VE_P)
- Infectiousness (e.g. expected number of infectees) given infection (VE_I)
- Hospitalization or death (VE_{HD})

What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

Susanne H Hodgson, Kushal Mansatta, Garry Mallett, Victoria Harris, Katherine RW Emary, Andrew J Pollard



Figure 1: Potential endpoints of an efficacious COVID-19 vaccine

An efficacious COVID-19 vaccine could reduce the likelihood of infection of an individual, severity of disease in an individual or degree of transmission within a population

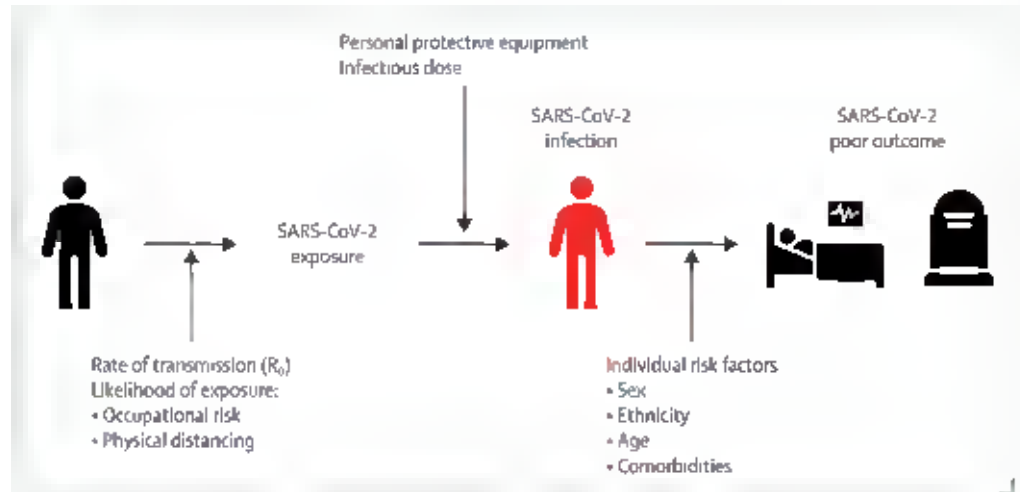


Figure 2: Key variables for SARS-CoV-2 exposure, infection, and poor outcome

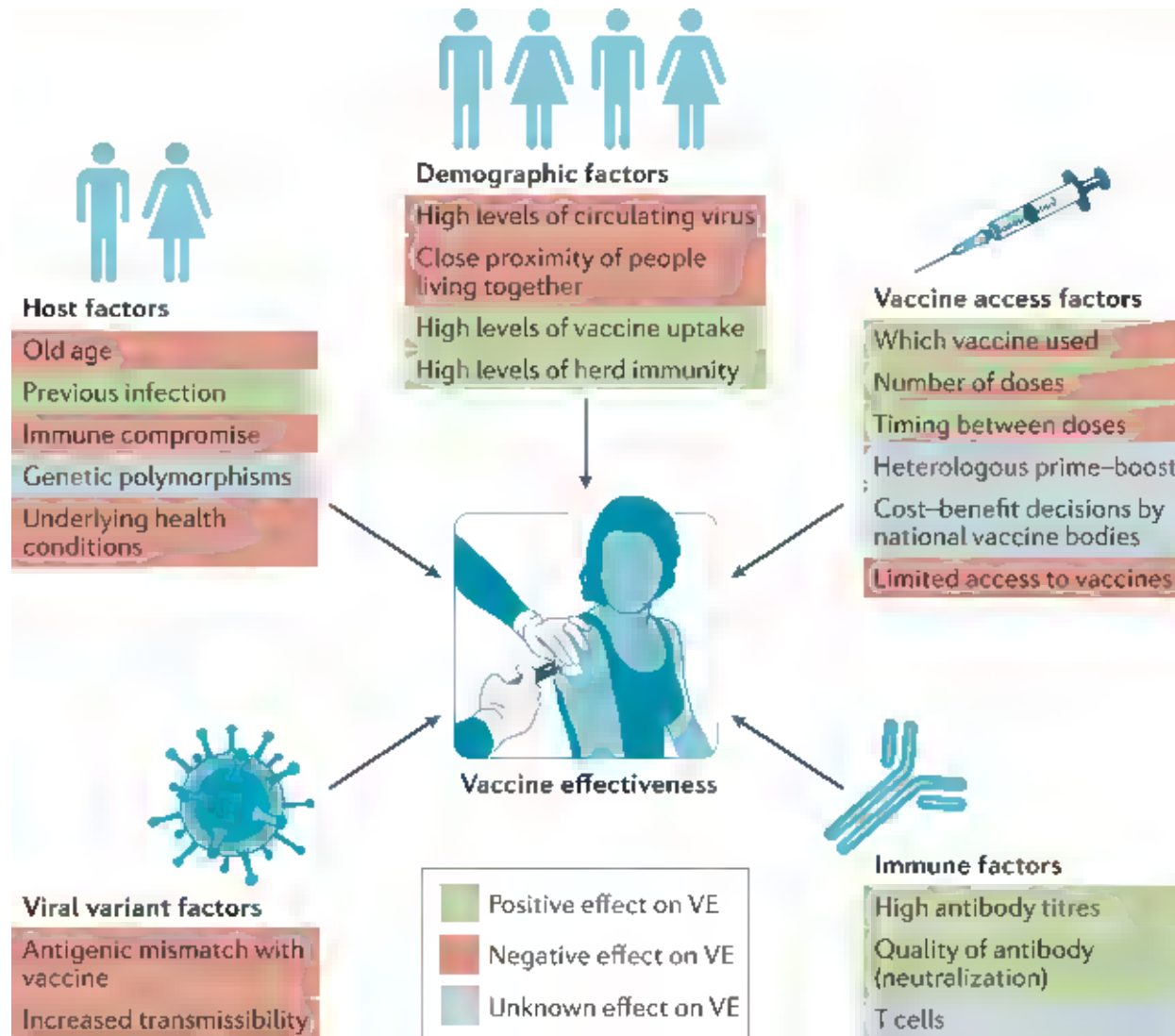
	Infection	Symptomatic infection	Hospital admission	Death
0-12 infections per 1000 people per day over 6 months*				
20-29 years	1880	3154	183 930	619 130
>80 years	1880	3154	10 364	24 494
0-013 infections per 1000 people per day over 6 months†				
20-29 years	17 876	29 816	1722 106	5 796 166
>80 years	17 876	29 816	97 304	229 584

Data are n. Calculations assume no clustering and that participants are randomly assigned to either a SARS-CoV-2 vaccine or a comparator or placebo in a 1:1 ratio, with 80% power to detect 70% vaccine efficacy within 6 months of follow-up and with 5% significance, for various primary efficacy endpoints. Calculations assume that incidence is unchanged over the follow-up period, there is no difference in rates of infection on exposure according to age, and 60% of infected individuals become symptomatic.¹⁷ Hospital admission rates related to age and infection fatality ratio are taken from Verity and colleagues.¹⁸ Each scenario presumes participants aged only either 20-29 years or >80 years are enrolled in the vaccine efficacy trial. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

*Incidence of SARS-CoV-2 infection at peak of transmission in the UK (April, 2020; derived from UK Office of National Statistics data reporting 4793 RT-PCR positive cases per day, which are presumed to only include symptomatic cases).¹⁸ †Incidence of SARS-CoV-2 infection post peak in the UK (July, 2020; derived from UK Office of National Statistics data reporting 512 RT-PCR positive cases per day, which are presumed to only include symptomatic cases).¹⁸

Table 1: Illustrative sample size calculations for a randomised controlled trial to assess efficacy of a SARS-CoV-2 vaccine candidate, calculated according to incidence of SARS-CoV-2 infection and age of participants

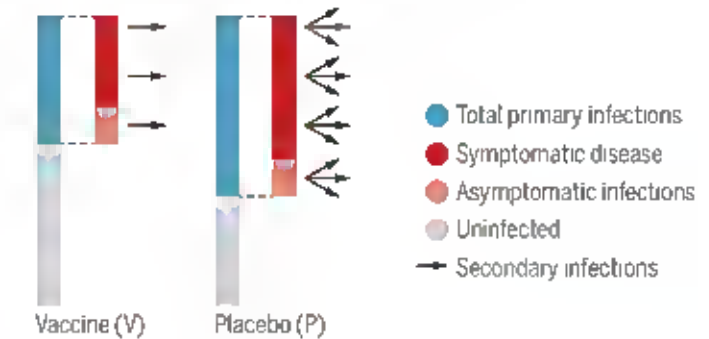
Vaccine Effects and Their Determinants



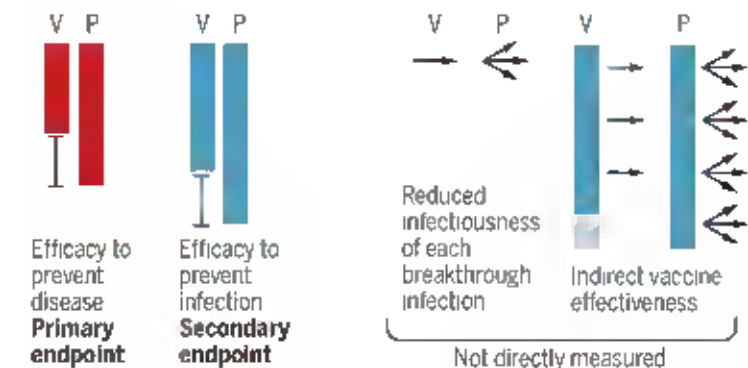
Vaccine effects

Vaccines provide direct protection by reducing susceptibility to disease or infection. Vaccines provide indirect protection by reducing the number of people infected in a population or their infectiousness. These vaccine effects can be assessed in clinical trials by measuring the efficacy to prevent disease, to prevent infection, and to reduce infectiousness, as well as in studies to assess indirect effects of the vaccine (15).

Individually randomized vaccine efficacy trial



Vaccine effects



Pain Points in Tracking and Evaluating Different Endpoints

Hospitalization/death

- Admission criteria might vary across subjects, time and populations

Symptomatic disease

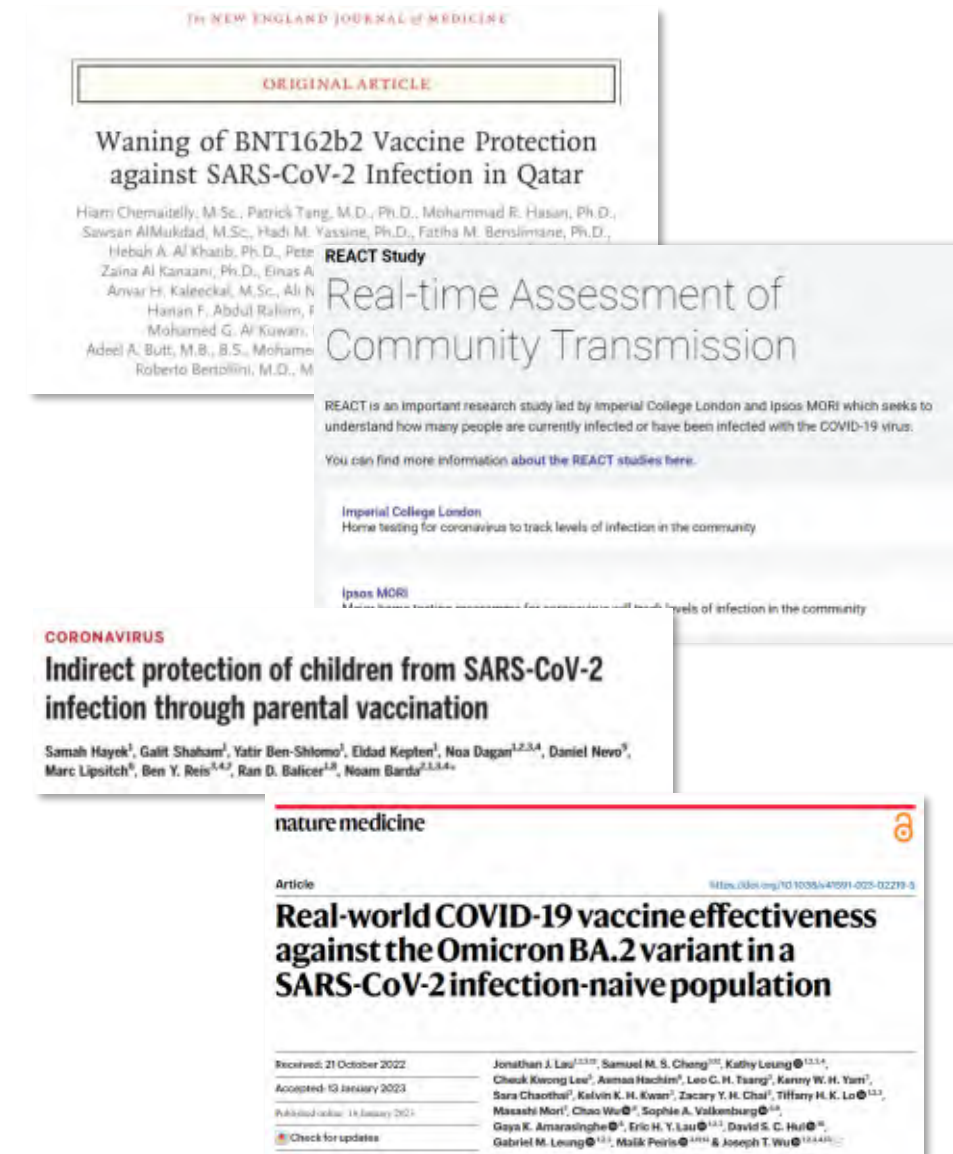
- Test sensitivity may vary depending on time since infection and clinical severity
- Test-negative design is susceptible to bias arising from differences in healthcare-seeking behavior between vaccinated and unvaccinated persons.

Infections (irrespective of symptoms)

- Asymptomatic infections are difficult to detect without prevalence survey, frequent (at least weekly) sampling or proxies associated with past infection (e.g. serological markers that can differentiate infection-induced response from vaccine-induced response)

Infectiousness

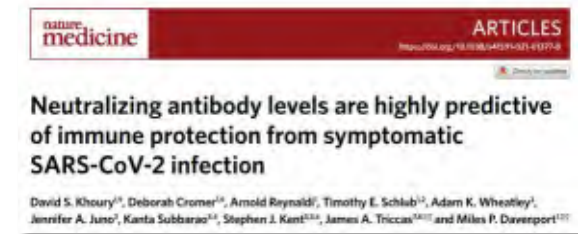
- Need to detect as many infections as possible with longitudinal data on viral shedding, clinical severity and social mixing
- Data analytics for transmission modeling (e.g. within-household transmission)



Correlates of Protection

Immune measures (serological assay titers) that are statistically associated with protection against clinical outcomes (infection, disease, death)

VE studies are resource-intensive, time-consuming and retrospective
Correlates of protection allows VE prediction in the absence of incidence data



Low neutralization titer does not necessarily mean low VE

Vaccine effectiveness of one, two, and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: a population-based observational study

Martina E McMenamin, Joshua Nealon, Yun Lin, Jessica Y Wong, Justin K Cheung, Eric H Y Lau, Peng Wu, Gabriel M Leung, Benjamin J Cowling



3 doses of CoronaVac

Titer against BA.2 below protective threshold but 97% VE against severe disease and death

CoronaVac presents multiple viral proteins to the host immune system that may protect via multiple pathways other than neutralizing antibodies, such as T cell immunity and antibody-dependent cytotoxicity

Vaccination Strategies

If there are not enough vaccines for everyone, what proportion of each age group to vaccinate? Take influenza as an example:

- Schoolchildren is the core group for transmission.
- The elderly has higher risk of severe complications if infected.

Given supply constraints, how to optimize vaccination strategy to maximize population health benefits (e.g. number of infections, number of deaths, life-years saved, quality adjusted life years)?

Optimizing Influenza Vaccine Distribution

Jan Medlock^{1,2*} and Alison P. Galvani¹

The criteria to assess public health policies are fundamental to policy optimization. Using a model parametrized with survey-based contact data and mortality data from influenza pandemics, we determined optimal vaccine allocation for five outcome measures: deaths, infections, years of life lost, contingent valuation, and economic costs. We find that optimal vaccination is achieved by prioritization of schoolchildren and adults aged 30 to 39 years. Schoolchildren are most responsible for transmission, and their parents serve as bridges to the rest of the population. Our results indicate that consideration of age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines. We also found that previous and new recommendations from the U.S. Centers for Disease Control and Prevention both for the novel swine-origin influenza and, particularly, for seasonal influenza, are suboptimal for all outcome measures.

Medlock and Galvani *Science* 2009

CORONAVIRUS

Model-informed COVID-19 vaccine prioritization strategies by age and serostatus

Kate M. Bubar^{1,2*}, Kyle Reinholt³, Stephen M. Kissler⁴, Marc Lipsitch^{4,5}, Sarah Cobey⁶, Yonatan H. Grad⁴, Daniel B. Larremore^{3,7*}

Limited initial supply of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine raises the question of how to prioritize available doses. We used a mathematical model to compare five age-stratified prioritization strategies. A highly effective transmission-blocking vaccine prioritized to adults ages 20 to 49 years minimized cumulative incidence, but mortality and years of life lost were minimized in most scenarios when the vaccine was prioritized to adults greater than 60 years old. Use of individual-level serological tests to redirect doses to seronegative individuals improved the marginal impact of each dose while potentially reducing existing inequities in COVID-19 impact. Although maximum impact prioritization strategies were broadly consistent across countries, transmission rates, vaccination rollout speeds, and estimates of naturally acquired immunity, this framework can be used to compare impacts of prioritization strategies across contexts.

Bubar et al *Science* 2021

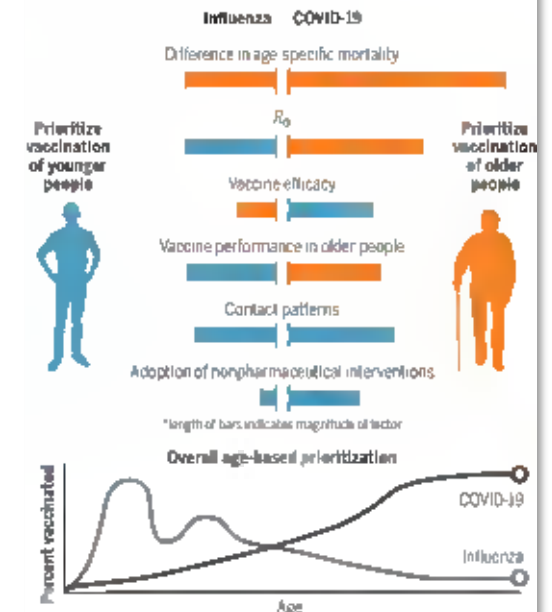
CORONAVIRUS

Optimizing age-specific vaccination

Vaccination strategies are not one-size-fits-all

Key determinants of age-based vaccination

Epidemiological factors drive age-based vaccine optimization for Influenza and COVID-19 with varying influence according to the mechanism and magnitude of the factor. When there are stark differences in mortality risk with age or when the reproductive number R_0 is high, older people are more likely to be prioritized for vaccination. By contrast, high vaccine efficacy, the amount of social contact among younger people, and widespread adherence to nonpharmaceutical interventions can shift prioritization toward younger ages.



Fitzpatrick and Galvani *Science* 2021



Fractional dosing of yellow fever vaccine to extend supply: a modelling study

Joseph T Wu, Corey M Peak, Gabriel M Leung, Marc Lipsitch

Summary

Background The ongoing yellow fever epidemic in Angola strains the global vaccine supply, prompting WHO to adopt dose sparing for its vaccination campaign in Kinshasa, Democratic Republic of the Congo, in July–August, 2016. Although a 5-fold fractional-dose vaccine is similar to standard-dose vaccine in safety and immunogenicity, efficacy is untested. There is an urgent need to ensure the robustness of fractional-dose vaccination by elucidation of the conditions under which dose fractionation would reduce transmission.

Methods We estimate the effective reproductive number for yellow fever in Angola using disease natural history and case report data. With simple mathematical models of yellow fever transmission, we calculate the infection attack rate (the proportion of population infected over the course of an epidemic) with various levels of transmissibility and 5-fold fractional-dose vaccine efficacy for two vaccination scenarios, ie, random vaccination in a hypothetical population that is completely susceptible, and the Kinshasa vaccination campaign in July–August, 2016, with different age cutoff for fractional-dose vaccines.

Findings We estimate the effective reproductive number early in the Angola outbreak was between 5.2 and 7.1. If vaccine action is all-or-nothing (ie, a proportion of vaccine recipients receive complete protection [VE] and the remainder receive no protection), n -fold fractionation can greatly reduce infection attack rate as long as VE exceeds $1/n$. This benefit threshold becomes more stringent if vaccine action is leaky (ie, the susceptibility of each vaccine recipient is reduced by a factor that is equal to the vaccine efficacy). The age cutoff for fractional-dose vaccines chosen by WHO for the Kinshasa vaccination campaign (2 years) provides the largest reduction in infection attack rate if the efficacy of 5-fold fractional-dose vaccines exceeds 20%.

Interpretation Dose fractionation is an effective strategy for reduction of the infection attack rate that would be robust with a large margin for error in case fractional-dose VE is lower than expected.

Funding NIH MIDAS, HMRF Hong Kong.

Lancet 2016; 388: 2904–11

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See Comment page 2847

WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China (J T Wu PhD,

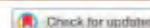
Prof G M Leung MD), Center for Communicable Disease Dynamics, Department of Epidemiology, (C M Peak MS, Prof M Lipsitch PhD), and Department of Immunology and Infectious Diseases, (Prof M Lipsitch), Harvard T H Chan School of Public Health, Boston, MA, USA

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BRIEF COMMUNICATION

<https://doi.org/10.1038/s41591-022-01736-z>

nature
medicine



OPEN

Modeling comparative cost-effectiveness of SARS-CoV-2 vaccine dose fractionation in India

Zhanwei Du^{1,2,8}, Lin Wang^{3,8}, Abhishek Pandey⁴, Wey Wen Lim⁵, Matteo Chinazzi⁵, Ana Pastore y Piontti⁵, Eric H. Y. Lau^{1,2}, Peng Wu^{1,2}, Anup Malani⁶, Sarah Cobey^{6,7} and Benjamin J. Cowling^{1,2}✉

Given global Coronavirus Disease 2019 (COVID-19) vaccine shortages and inequity of vaccine distributions, fractionation of vaccine doses might be an effective strategy for reducing public health and economic burden, notwithstanding the emergence of new variants of concern. In this study, we developed a multi-scale model incorporating population-level transmission and individual-level vaccination to estimate the costs of hospitalization and vaccination and the economic benefits of reducing COVID-19 deaths due to dose-fractionation strategies in India. We used large-scale survey data of the willingness to pay together with data of vaccine and hospital admission costs to build the model. We found that fractional doses of vaccines could be an economically viable vaccination strategy compared to alternatives of either full-dose vaccination or no vaccination. Dose-sparing strategies could save a large number of lives, even with the emergence of new variants with higher transmissibility.

began its COVID-19 vaccination program on 16 January 2021 and, by 14 January 2022, had administered 837 million doses, with 46% of the population partially vaccinated and 18% fully vaccinated¹. As of 14 January 2022, nine COVID-19 vaccines, including ChAdOx1 (Covishield, AstraZeneca), BECOV2A (Corbevax, Biological E. Limited), BBV152 (Covaxin, Bharat Biotech), Gam-COVID-Vac (Sputnik V, Gamaleya) and mRNA-1273 (Spikevax, Moderna), have received emergency use authorization in India^{2,3}.

Given global vaccine shortages, dose fractionation of vaccines has been proposed as a potential strategy to accelerate the accrual of population immunity through vaccination⁴. Assuming that vaccines approved in India face a shortfall in the total number of full doses available, we evaluated the economics of potential costs and benefits of dose fractionation of COVID-19 vaccines. Studies of COVID-19 mRNA vaccines indicate that fractional doses could still provide a robust immune response against COVID-19 (ref. ⁵). For the mRNA-1273 vaccine, two doses of 25 µg elicited about half the

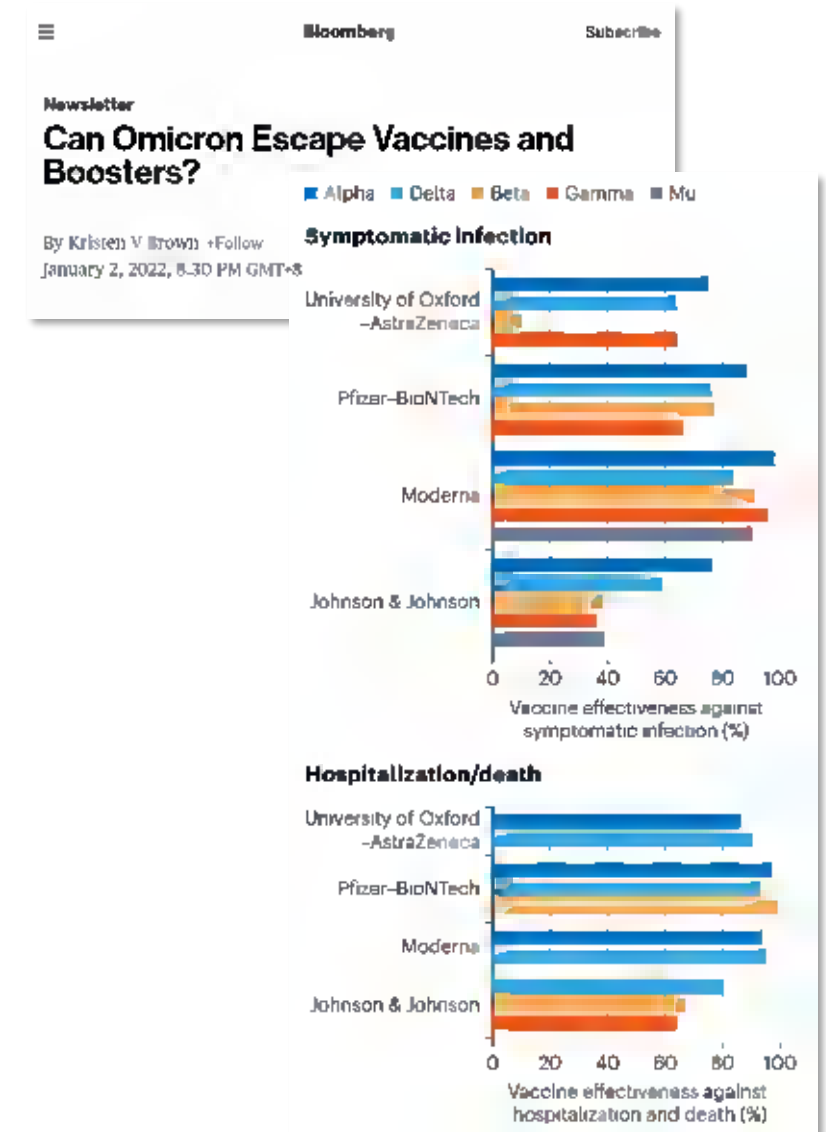
Strain/serotype Replacement

Many infectious diseases comprise strains/serotypes that are:

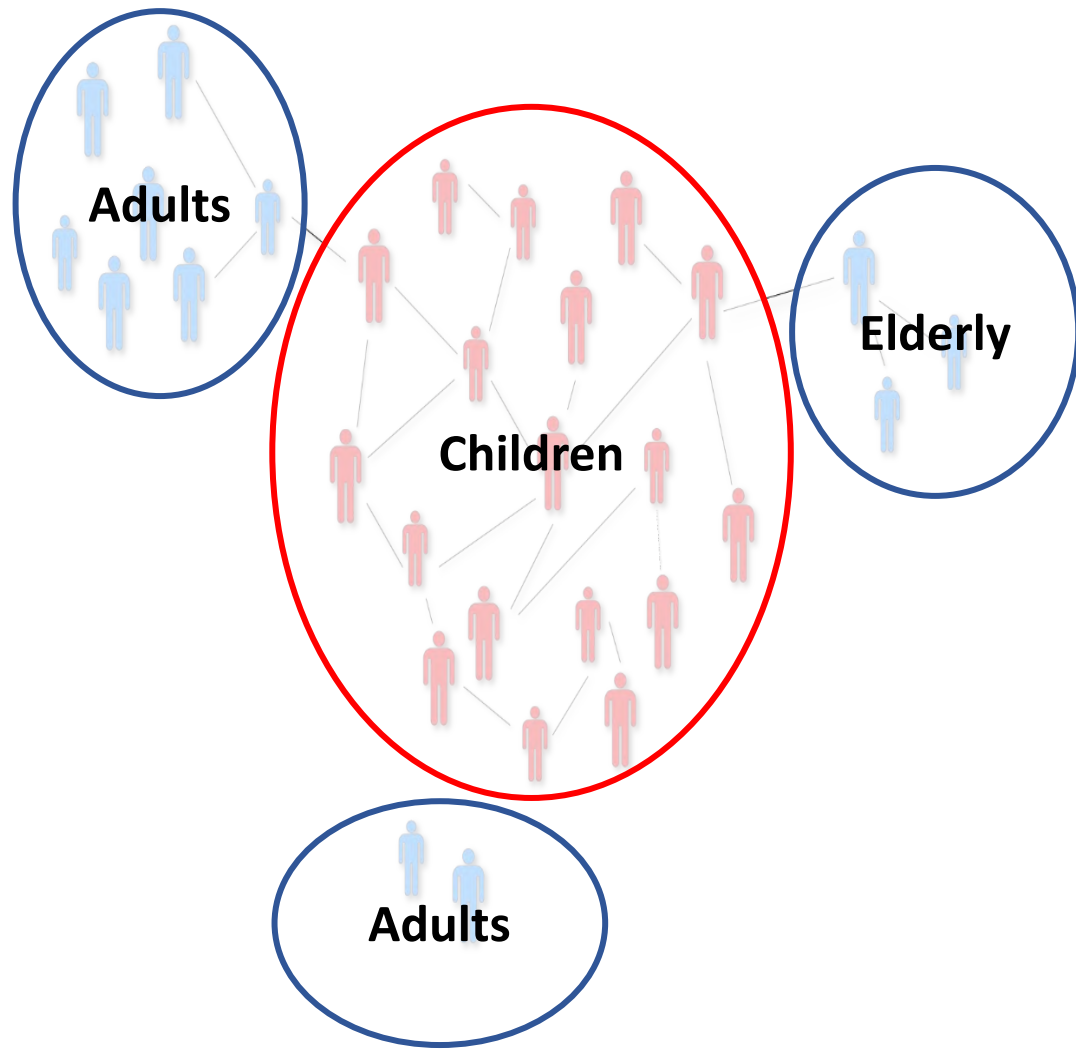
- Collectively similar in terms of their ecology and evolutionary biology
- Individually distinct in terms of their antigenicity, virulence, prevalence

Examples: Influenza, pneumococcal diseases, HPV

Because of these similarities and differences, vaccination efficacious against one strain/serotype (usually the dominant one in terms of prevalence or severity) may increase the prevalence of other strains/serotypes in the same disease category



Optimizing vaccination strategies



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PLOS MEDICINE

Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study

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Abstract

Background: Influenza vaccine policies that maximise health benefit through efficient use of limited resources are needed. Generally, influenza vaccination programmes have targeted individuals 65 y and over and those at risk, according to World Health Organization recommendations. We developed methods to synthesise the multiplicity of surveillance datasets in order to evaluate how changing target populations in the seasonal vaccination programme would affect infection rate and mortality.

Methods and Findings: Using a contemporary evidence-synthesis approach, we use virological, clinical, epidemiological, and behavioural data to develop an age- and risk-stratified transmission model that reproduces the strain-specific behaviour of influenza over 14 seasons in England and Wales, having accounted for the vaccination uptake over this period. We estimate the reduction in infections and deaths achieved by the historical programme compared with no vaccination, and the reduction had different policies been in place over the period. We find that the current programme has averted 0.39 (95% credible interval 0.34–0.45) infections per dose of vaccine and 1.74 (1.16–3.02) deaths per 1,000 doses. Targeting transmitters by extending the current programme to 5–16-y-old children would increase the efficiency of the total programme, resulting in an overall reduction of 0.70 (0.52–0.81) infections per dose and 1.95 (1.28–3.39) deaths per 1,000 doses. In comparison, choosing the next group most at risk (50–64-y-olds) would prevent only 0.43 (0.35–0.52) infections per dose and 1.77 (1.15–3.14) deaths per 1,000 doses.

Conclusions: This study proposes a framework to integrate influenza surveillance data into transmission models. Application to data from England and Wales confirms the role of children as key infection spreaders. The most efficient use of vaccine to reduce overall influenza morbidity and mortality is thus to target children in addition to older adults.

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