An Overview of Mathematical Modeling for Pandemic Control

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Why are infectious diseases different?

1. Communicability: a case is also a risk factor
   - Some cases will be unrecognized + pre-symptomatic transmission

2. In models, communicability manifests as "**positive feedback**"
   - The more cases you have the more cases you get

3. Control depends on the "herd", not just individuals

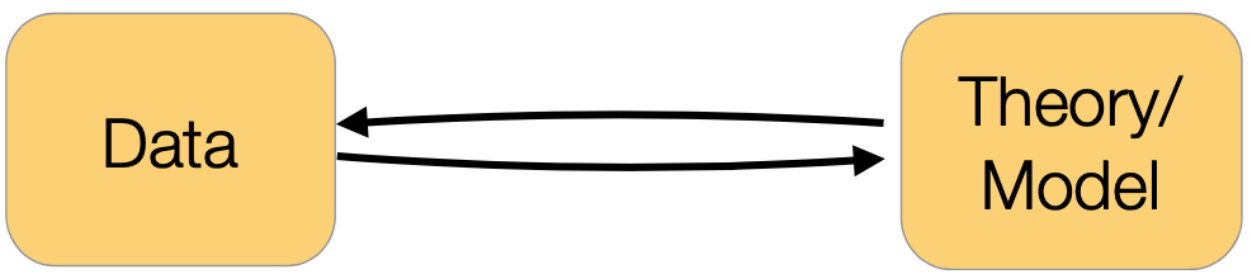
An important distinction

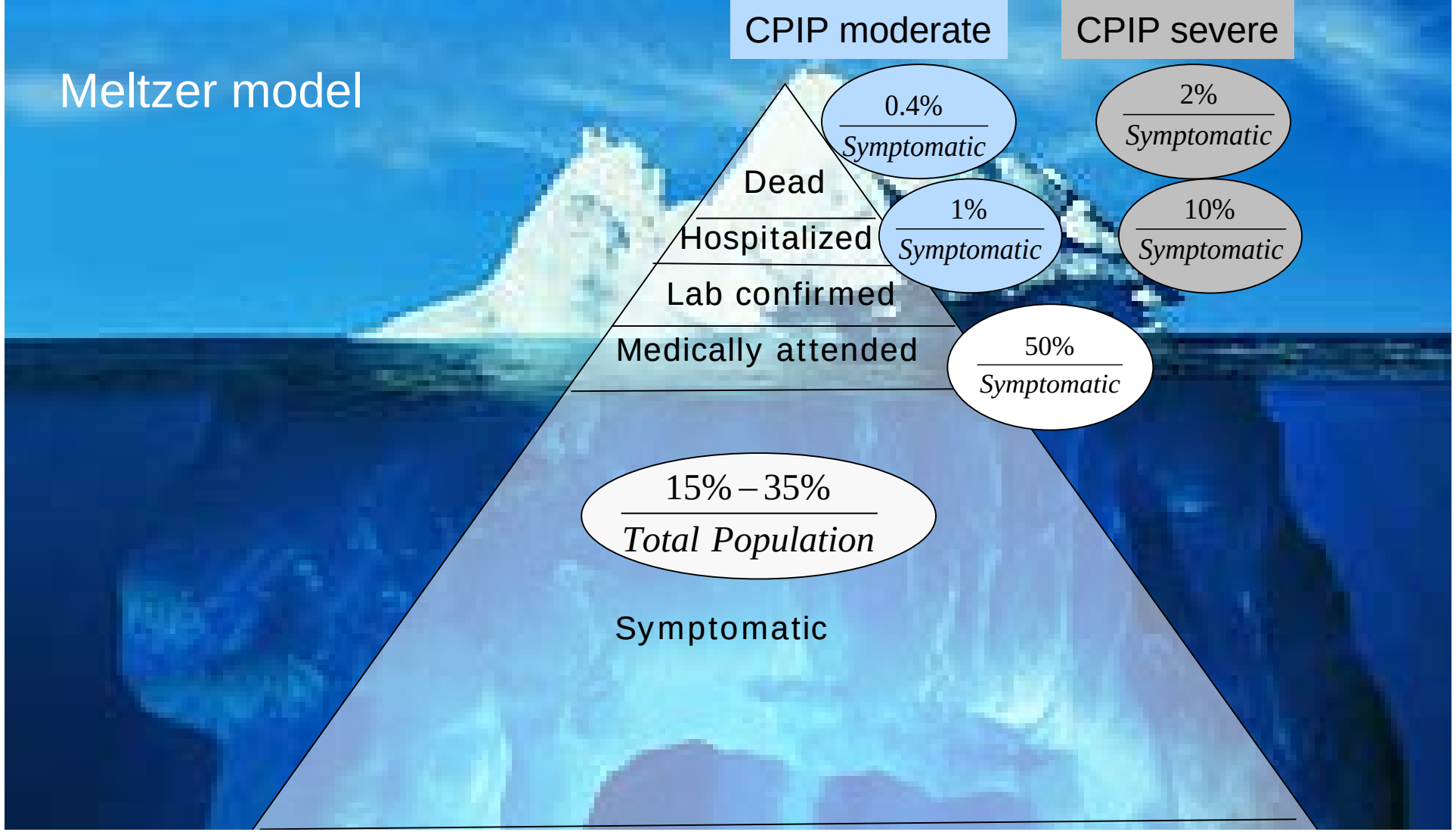
Statistical Models

- describe associations between variables
- used to derive parameter estimates from empirical data

Mathematical Models

- provide a framework that represents the proposed causal pathways
- Describe mechanisms that link exposures, interventions, infection and/or disease
- Used to make projections/ predictions





Intuitive, static, linear: simple multipliers implemented by a spreadsheet.

Disadvantages:

- no consideration of disease transmission
- no consideration of interventions

Epidemiologic parameters for infectious diseases

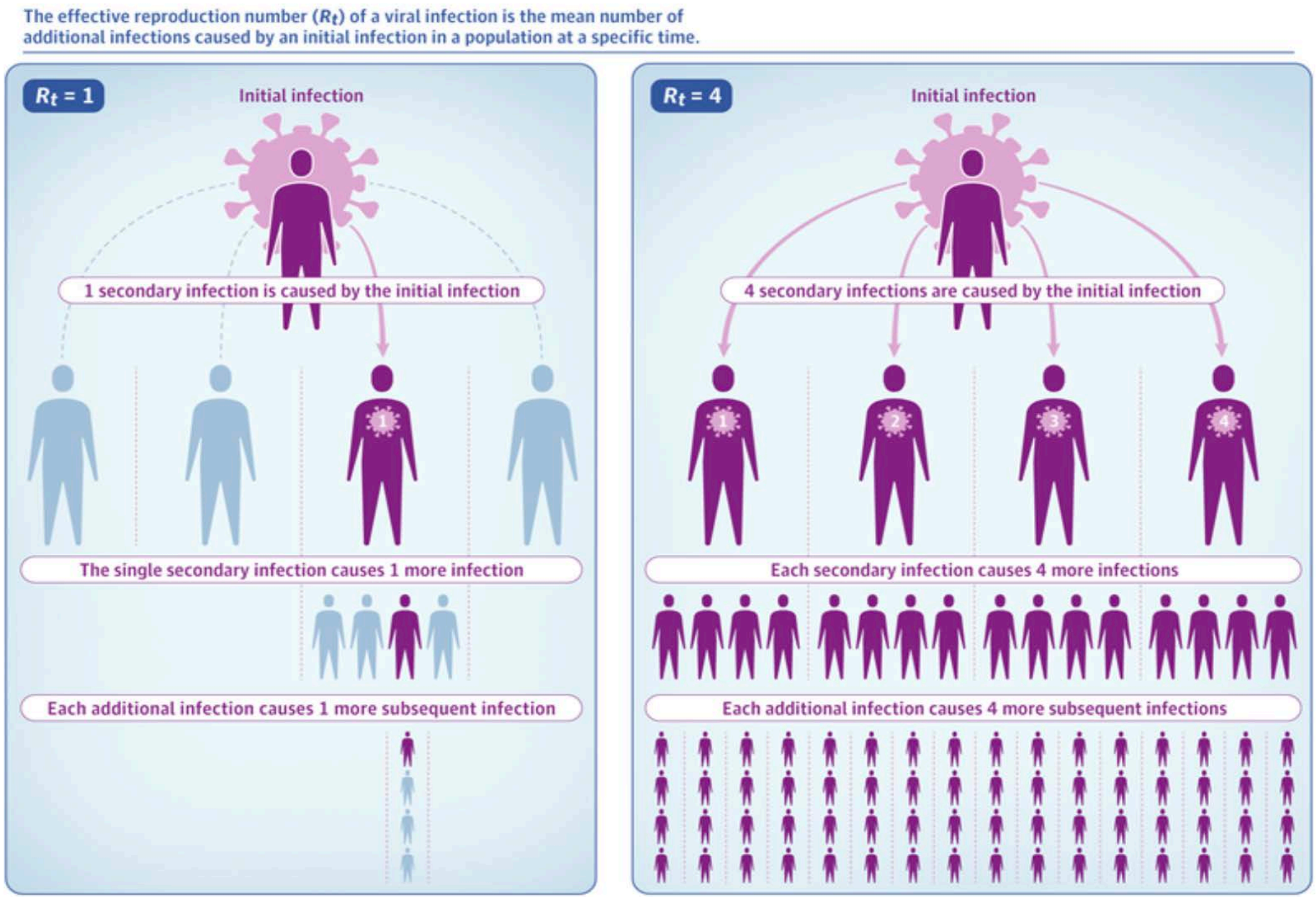
- Basic reproductive number (R_0) – number of secondary infections when a single infectious case is introduced into a completely susceptible population

- Effective reproductive number (R_e): number of secondary infections produced by each primary infectious individual

When R0 > 1, can have an epidemic

When R = 1, disease stays endemic

Figure 1. Concepts of the Effective Reproduction Number



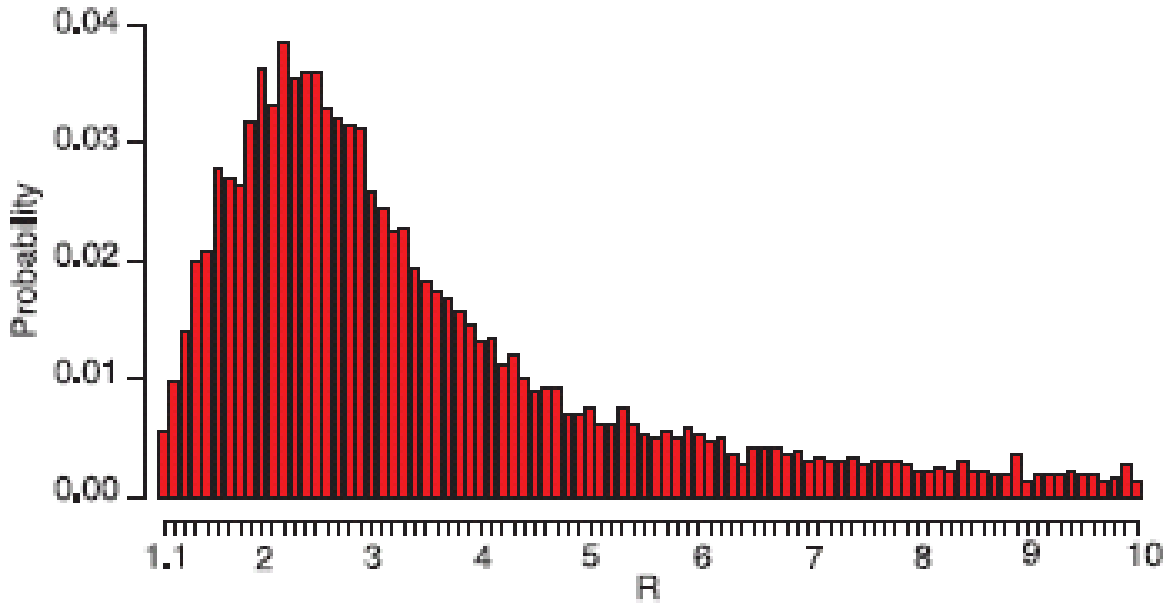
Inglesby. 2020

Select estimates of R_0

Pathogen	Estimated R_0
SARS-CoV-2 (D'Arienzo & Coniglio, 2020, Liu et al. 2020)	**2-3** (1.4-6.49)
SARS (Lipsitch et al. 2003, Anderson et al. 2003)	2-4
Varicella zoster (Brisson & Edmunds, 2000)	10-12
Tuberculosis (Blower, 2000)	~10
Measles (Edmunds et al. 2000)	10-20
Smallpox (Gani & Leach, 2001)	3-5

R_0 as a distribution

- **Heterogeneity** among individual behaviors and infectiousness.
  - R_0 can be thought of as the mean of a **distribution**.



Lipsitch et al., 2003

Heterogeneity of transmission

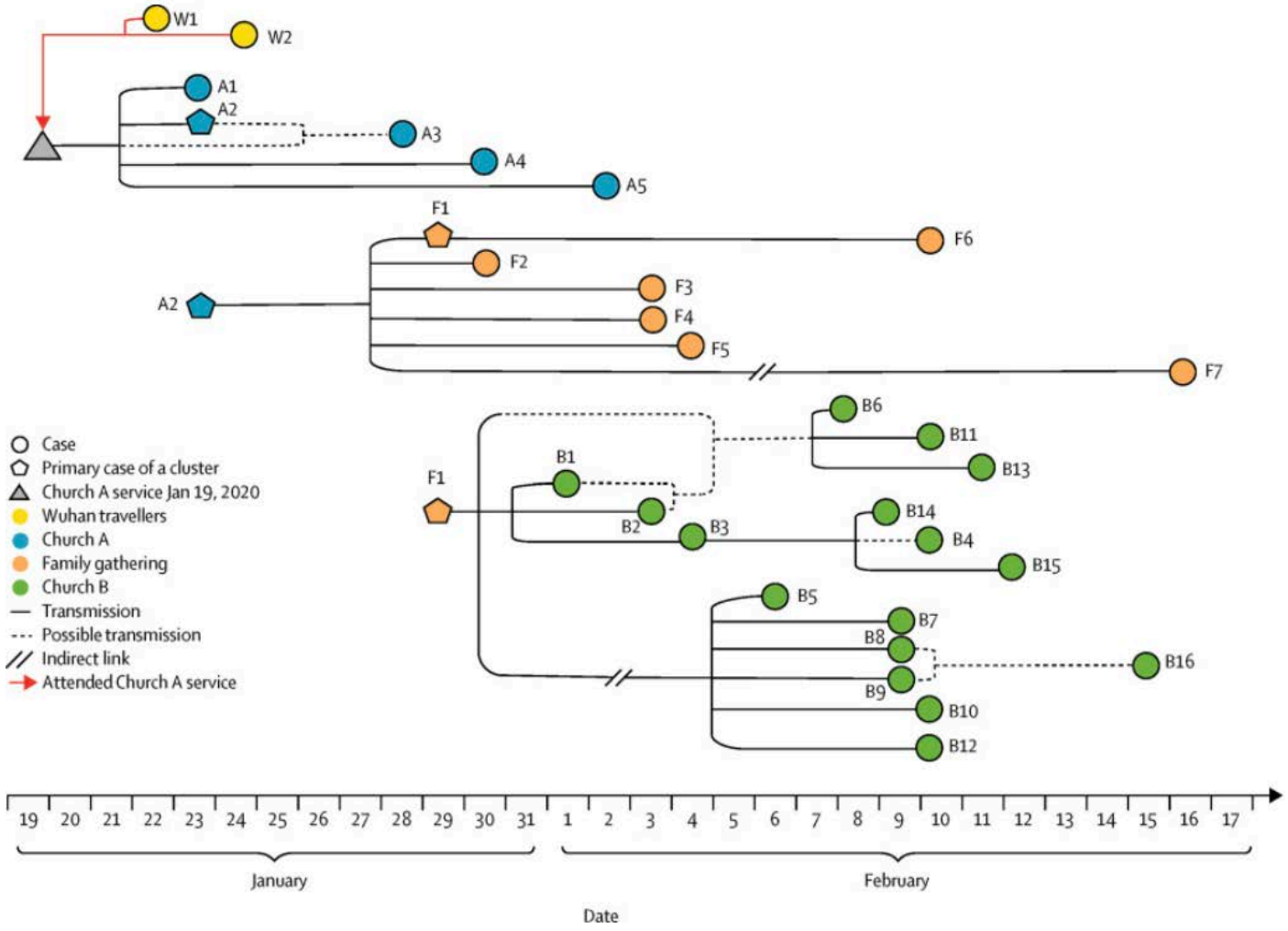


Figure 1 Transmission map of COVID-19

Yong et al. 2020

Derivation of R_0

- Understanding disease dynamics forms the scientific basis for interventions

- Control measures operate by reducing transmission

$$R_0 = c * p * D$$

R_0 = number of secondary cases / primary case in a totally susceptible population

β → c = contact rate

β → p = probability of transmission given an infected contact

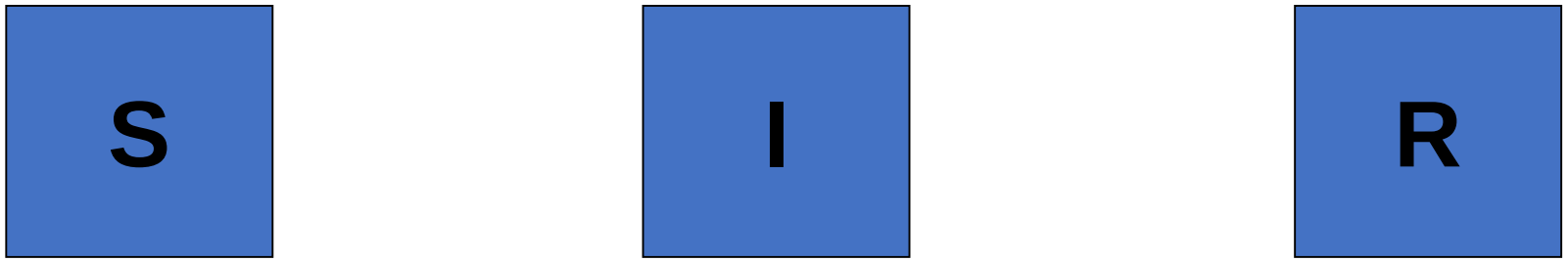
D = duration of infectiousness

What are mathematical models?

- Conceptual tools that explain how an object or system of objects will behave
- Models come in a variety of forms
  - Highly complex or simple (and anywhere in between)
  - Decision of which to use is determined by:
    - Precision / generality required
    - Available data
    - Time frame for getting results
  - Even the most complex models make simplifying assumptions
- Hope to capture the essential features

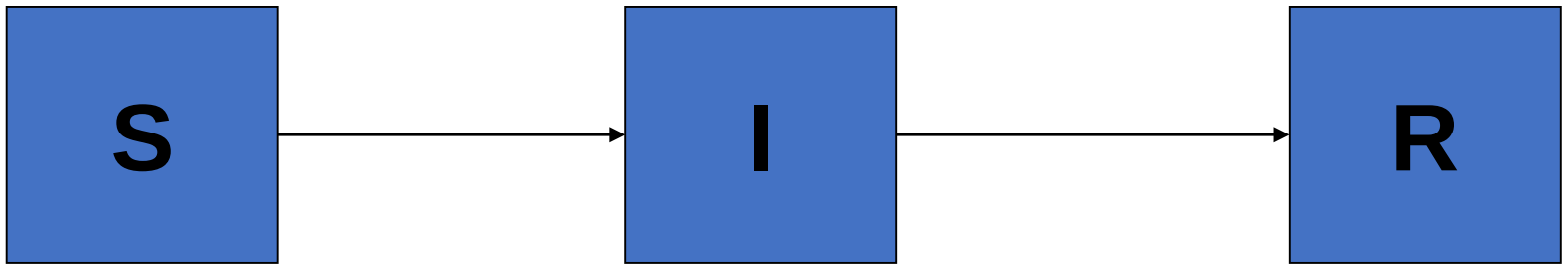
Translating a process into a model

1. Define host population of interest
2. Define the "type" of people who will be in the model compartments



Translating a process into a model

3. What are the transitions in and out of the states?



Translating a process into a model

4. Define how infection incidence depends on exposure to infectious people

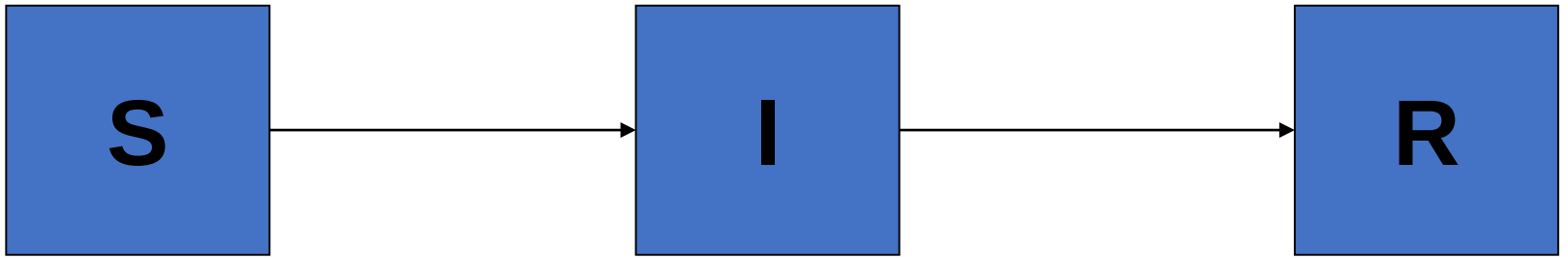
c = Number of contacts / time

p = probability of infection given an exposure

$\beta = c * p$

λ = force of infection = $\beta I / N$ (risk of new infection / time)

R0 = number of secondary infections caused by single infected individual in a wholly susceptible population

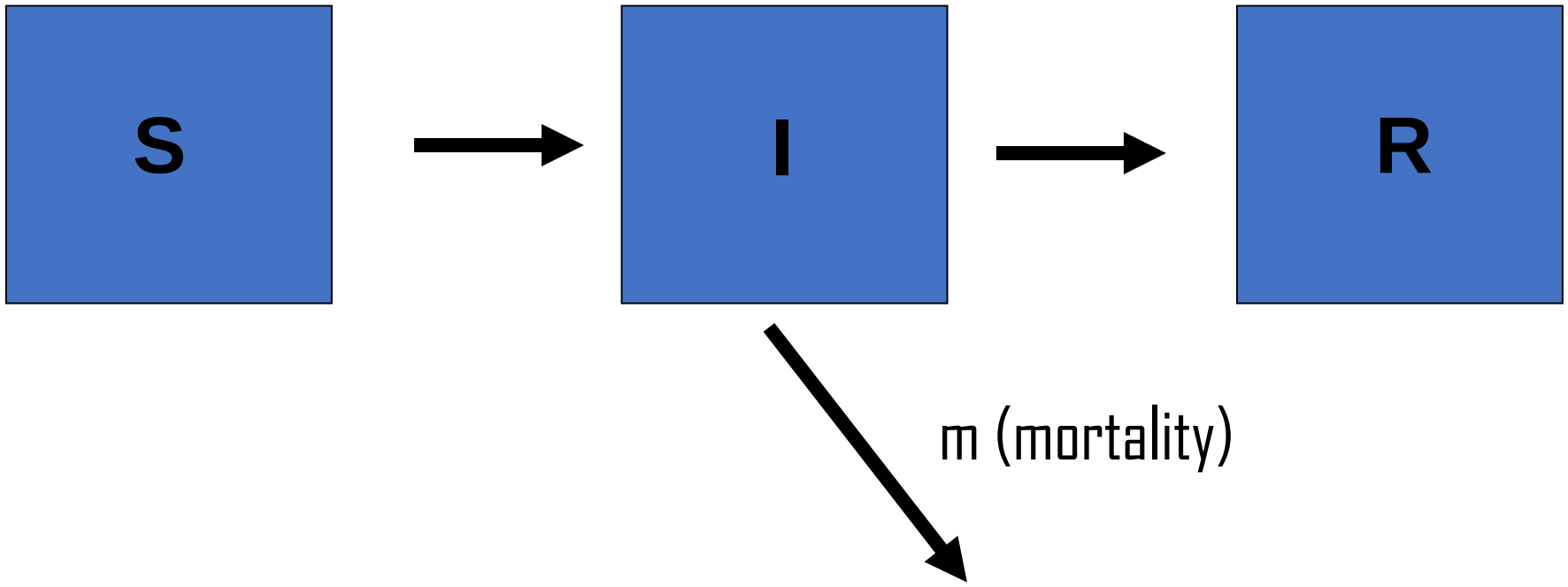


Translating a process into a model

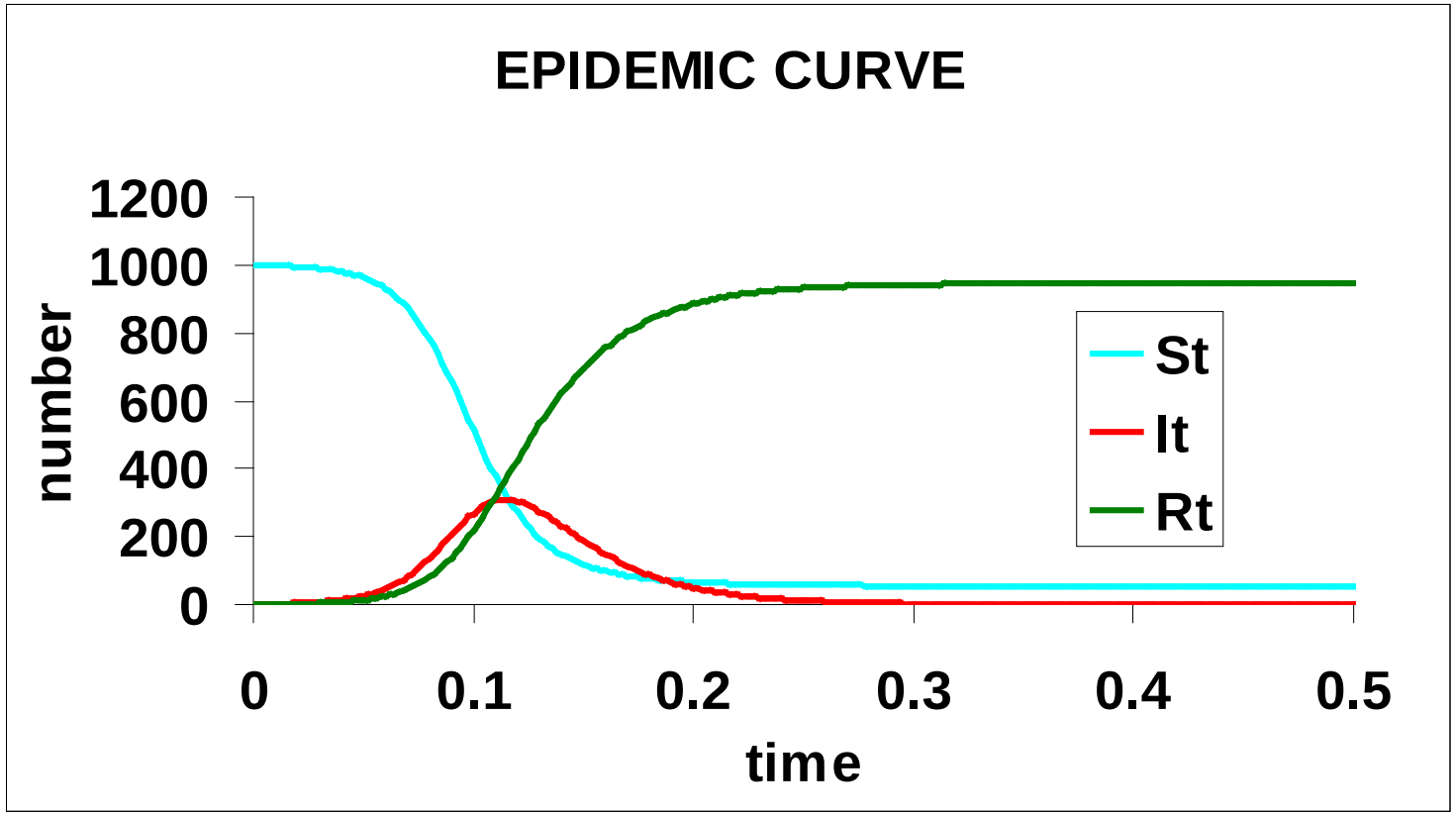
$dS/dt = -\beta SI$

$dI/dt = +\beta SI - I/D - \mu I$

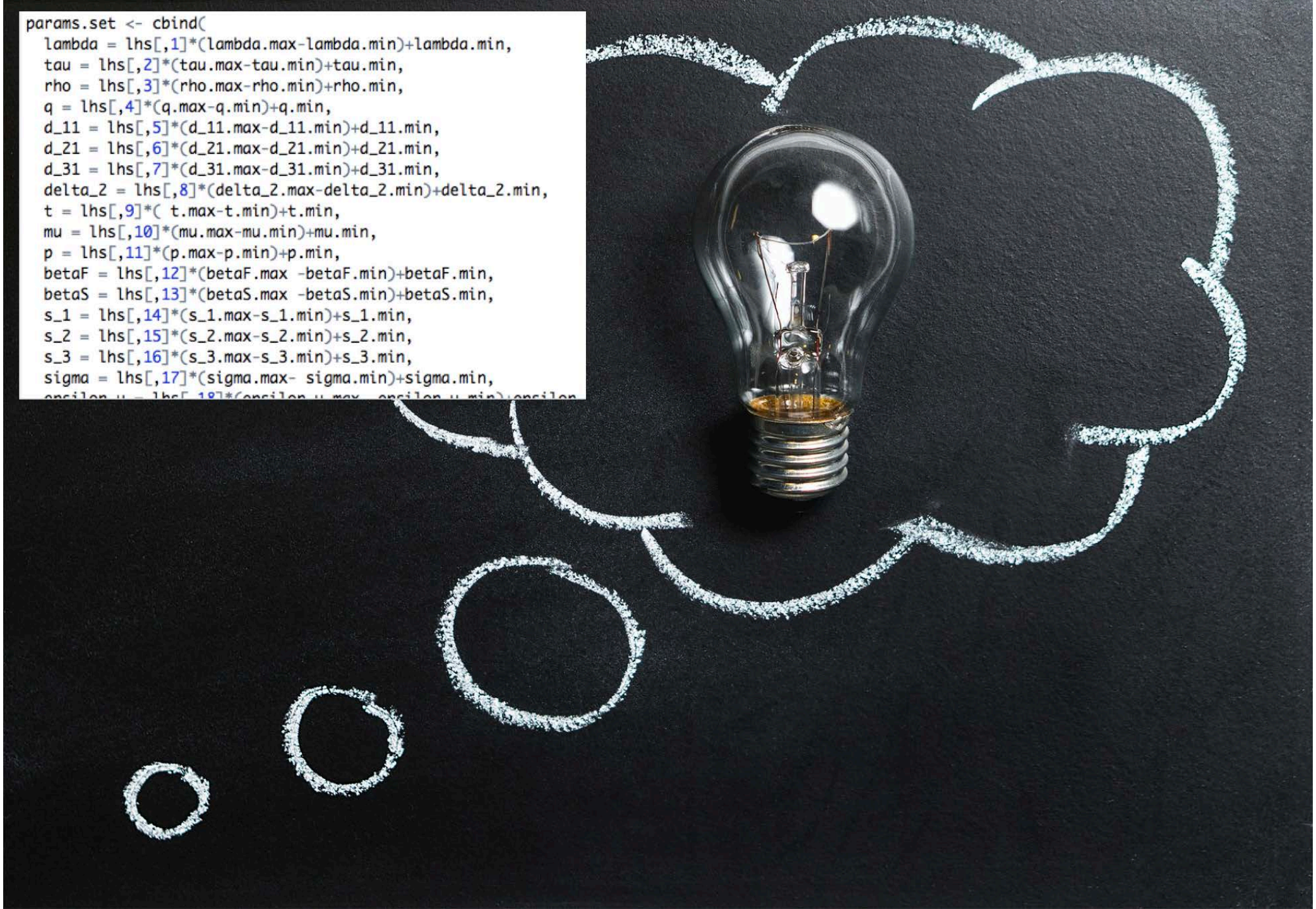
$dR/dt = +I/D$



A simple model, $R_0 = 3$



```
params.set <- cbind(
  lambda = lhs[,1]*(lambda.max-lambda.min)+lambda.min,
  tau = lhs[,2]*(tau.max-tau.min)+tau.min,
  rho = lhs[,3]*(rho.max-rho.min)+rho.min,
  q = lhs[,4]*(q.max-q.min)+q.min,
  d_11 = lhs[,5]*(d_11.max-d_11.min)+d_11.min,
  d_21 = lhs[,6]*(d_21.max-d_21.min)+d_21.min,
  d_31 = lhs[,7]*(d_31.max-d_31.min)+d_31.min,
  delta_2 = lhs[,8]*(delta_2.max-delta_2.min)+delta_2.min,
  t = lhs[,9]*( t.max-t.min)+t.min,
  mu = lhs[,10]*(mu.max-mu.min)+mu.min,
  p = lhs[,11]*(p.max-p.min)+p.min,
  betaF = lhs[,12]*(betaF.max -betaF.min)+betaF.min,
  betaS = lhs[,13]*(betaS.max -betaS.min)+betaS.min,
  s_1 = lhs[,14]*(s_1.max-s_1.min)+s_1.min,
  s_2 = lhs[,15]*(s_2.max-s_2.min)+s_2.min,
  s_3 = lhs[,16]*(s_3.max-s_3.min)+s_3.min,
  sigma = lhs[,17]*(sigma.max- sigma.min)+sigma.min,
```



1. What is the benefit?

2. Is it cost-effective?

Verbal description

Mathematical formulation

Verbal dissemination

CMAJ RESEARCH

Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza

Ashleigh R. Tuite MSc MHSc, Amy L. Greer MSc PhD, Michael Whelan MSc,
Anne-Luise Winter BScN MHSc, Brenda Lee MHSc, Ping Yan PhD, Jianhong Wu PhD,
Seyed Moghadas PhD, David Buckeridge MD PhD, Babak Pourbohloul PhD, David N. Fisman MD MPH

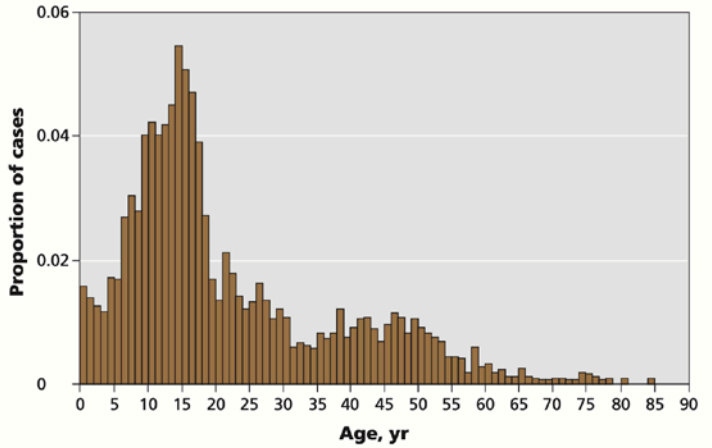
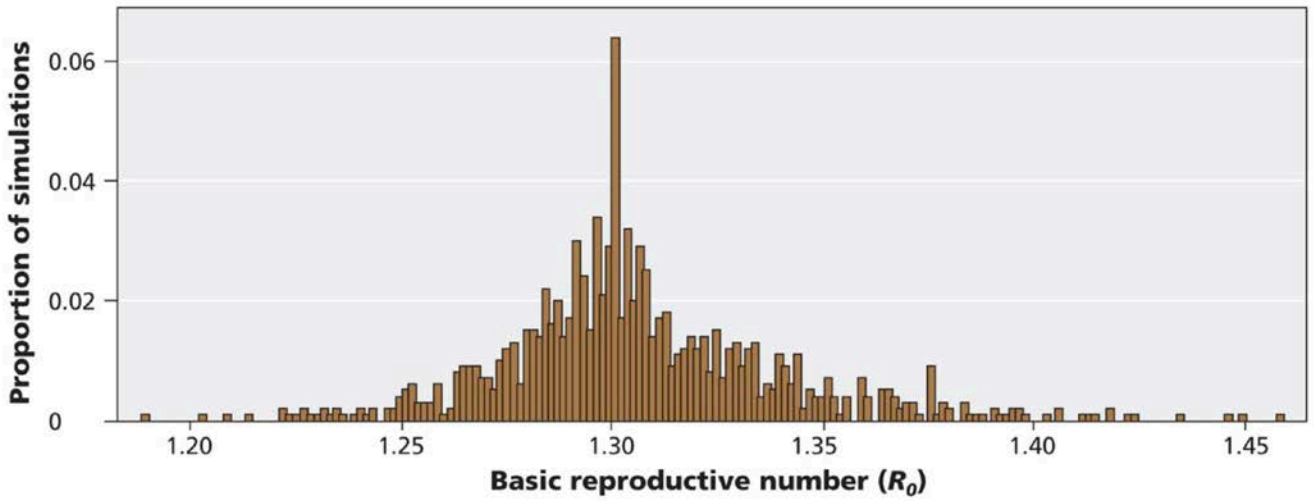


Figure 1: Age distribution of 3152 laboratory-confirmed cases of pandemic H1N1 influenza in the province of Ontario with onset of symptoms between Apr. 13 and June 20, 2009.



Tuite et al. 2010

The emergence and spread of SARS-CoV-2

Dec. 31, 2019 — China alerts World Health Organization (WHO) to several cases of pneumonia with no known cause in Wuhan. The disease goes on to be named COVID-19.

Jan. 7 — WHO officials announce they have identified a new virus named SARS-CoV-2 that causes COVID-19. It belongs to the coronavirus family, which includes viruses that cause SARS, MERS and the common cold.

Jan. 11 — China announces the first death linked to COVID-19.

Jan. 13 — WHO reports the first case outside of China in Thailand.

Feb. 26 — National Institutes of Health (NIH) begin the first clinical trial in the U.S. for a potential COVID-19 treatment, remdesivir, an antiviral drug originally developed to treat Ebola.

Feb. 29 — The FDA took steps to expand novel coronavirus testing to hospital clinical microbiology laboratories.

Mar. 11 — WHO declares COVID-19 a pandemic, with more than 100,000 cases and 4,000 deaths in 114 countries.

Apr. 2 — Confirmed cases of COVID-19 top 1 million worldwide.

Apr. 10 — Global deaths due to COVID-19 top 100,000.

www.asm.org

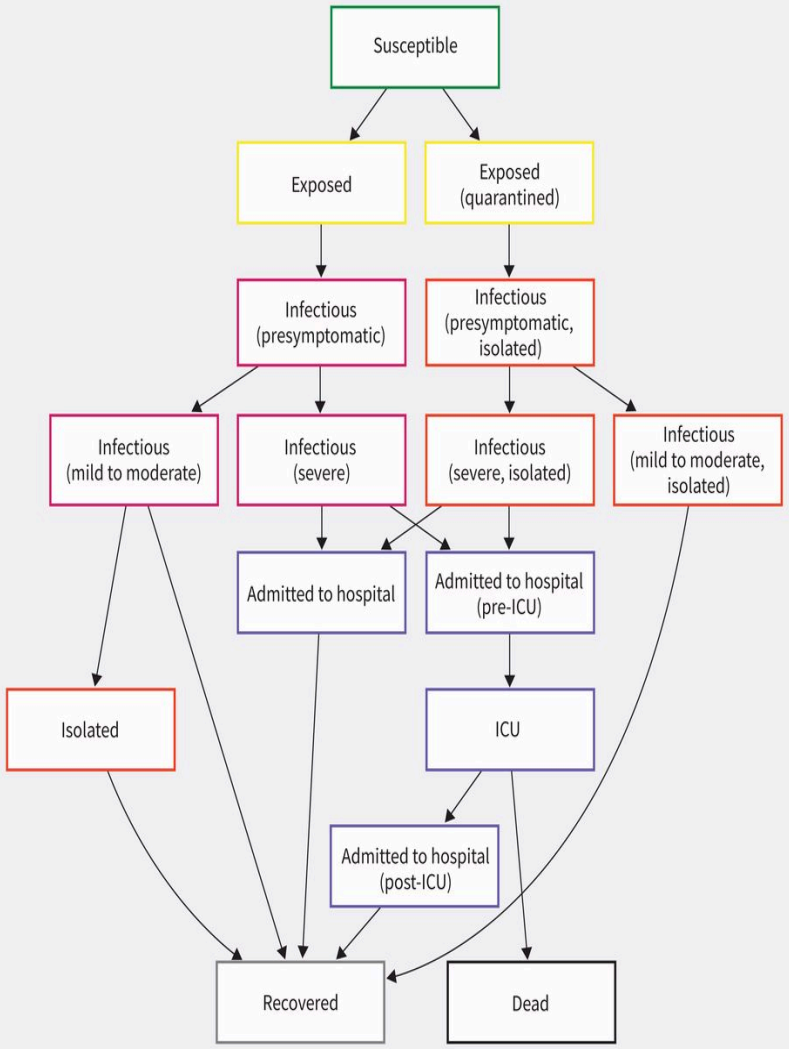
	SARS-CoV-2	SARS-CoV	Pandemic influenza 1918	Pandemic influenza 2009	Interpretation
Transmissibility, R_0	2·5	2·4	2·0	1·7	SARS-CoV-2 has the highest average R_0
Incubation period, days	4–12	2–7	Unknown	2	Longer incubation period; SARS-CoV epidemics form slower
Interval between symptom onset and maximum infectivity, days	0	5–7	2	2	SARS-CoV-2 is harder to contain than SARS-CoV
Proportion with mild illness	High	Low	High	High	Facilitates undetected transmission
Proportion of patients requiring hospitalisation	Few (20%)	Most (>70%)	Few	Few	Concern about capacity in the health sector
Proportion of patients requiring intensive care	1/16 000	Most (40%)	Unknown	1/104 000	Concern about capacity in the health sector
Proportion of deaths in people younger than 65 years out of all deaths	0·6–2·8%	Unknown	95%	80%	SARS-CoV-2 might cause as many deaths as the 1918 influenza pandemic, but fewer years of life lost and disability-adjusted life-years, as deaths are in the older population with underlying health conditions
Risk factors for severe illness	Age, comorbidity	Age, comorbidity	Age (<60 years)	Age (<60 years)	..

Data from the following references.[2,3,5-36] MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 1: **Characteristics of SARS-CoV-2, SARS-CoV, and pandemic influenza**

Petersen et al. 2020

What would a model of SARS-CoV-2 look like?



Parameter	Age group, yr	Health status	Value	Details	Source
Latent period, d	All	All	2.5	Time from exposure to onset of infectiousness	References 18–20
Presymptomatic infectious period, d	All	All	1	Duration of infectiousness before symptom onset	References 18–20
Infectious period (mild to moderate), d	All	All	6	Symptomatic infectious period for mild-to-moderate cases (in absence of isolation)	References 18–20
Infectious period (severe), d	All	All	6	Symptomatic infectious period for infectiousness for severe cases; assumed equal to time to hospital admission	References 18–20
Basic reproduction number	All	All	2.3	Average number of secondary infections derived from a primary infection in a susceptible population	Reference 6
Time in quarantine, d	All	All	14	Duration of quarantine for exposed cases	Current policy
Relative risk of transmission for cases in isolation	All	All	0.1	Isolated cases are assumed to have reduced transmission relative to unrecognized cases	Assumption
Average length of stay in hospital for cases not requiring ICU care, d	All	All	10		Reference 21
Average length of stay in hospital before ICU admission, d	All	All	3	For severe cases requiring ICU care	Reference 21
Average length of stay in ICU, d	All	All	21	For severe cases requiring ICU care	Reference 22
Average length of stay in hospital after ICU, d	All	All	21	For severe cases requiring ICU care	Reference 22
Probability of severe infection				Severe infections requiring hospital admission	Reference 21
	< 15	No comorbidities	0.01		
	15–49	No comorbidities	0.03		
	50–69	No comorbidities	0.12		
	≥ 70	No comorbidities	0.35		
	< 15	Comorbidities	0.02		
	15–49	Comorbidities	0.06		
	50–69	Comorbidities	0.25		
	≥ 70	Comorbidities	0.76		
Probability severe case requires admission to ICU	All	All	0.26		Reference 21
Probability of death in cases admitted to ICU					Reference 22
	< 15	No comorbidities	0		
	15–49	No comorbidities	0.2		
	50–69	No comorbidities	0.36		
	≥ 70	No comorbidities	0.58		
	< 15	Comorbidities	0		
	15–49	Comorbidities	0.53		
	50–69	Comorbidities	0.9		
	≥ 70	Comorbidities	1		

Note: ICU = intensive care unit.
*A full model description is provided in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200476/-/DC1). Age group and health status refer to the population groups to which the parameter value was applied.

Tuite, Fisman, & Greer, 2020

Working with knowledge users and stakeholders

- Formulating the research question
- Developing a plan regarding the most suitable methodology & type of model

STRATEGIC MODELS

- make many assumptions to draw general conclusions
- appear "over-simplified"
- results tend to be more qualitative
- may not be readily applied to specific questions

TACTIC MODELS

- specific research question
- look more "realistic"
- results tend to be more quantitative
- limited relevance beyond the question of interest

Working with knowledge users and stakeholders

Parameter values

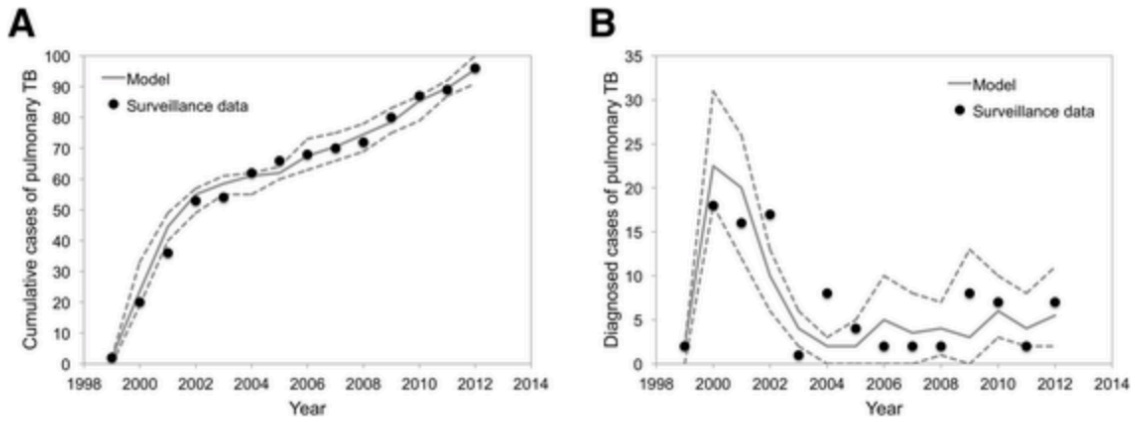
- Definitions, values, ranges, and where the values come from (observation, extracted from previous studies, or estimated by fitting to data?)
- What values are being fit in the model (not independently measured)?

Assumptions

- What are they and how realistic are they?

Assessment of model predictions with data

- Can the model reproduce the observed data?
- If the data are limited different sets of parameters might fit equally well
- Quantifying this uncertainty is important: uncertainty in parameterization can result in uncertainty in intervention effectiveness



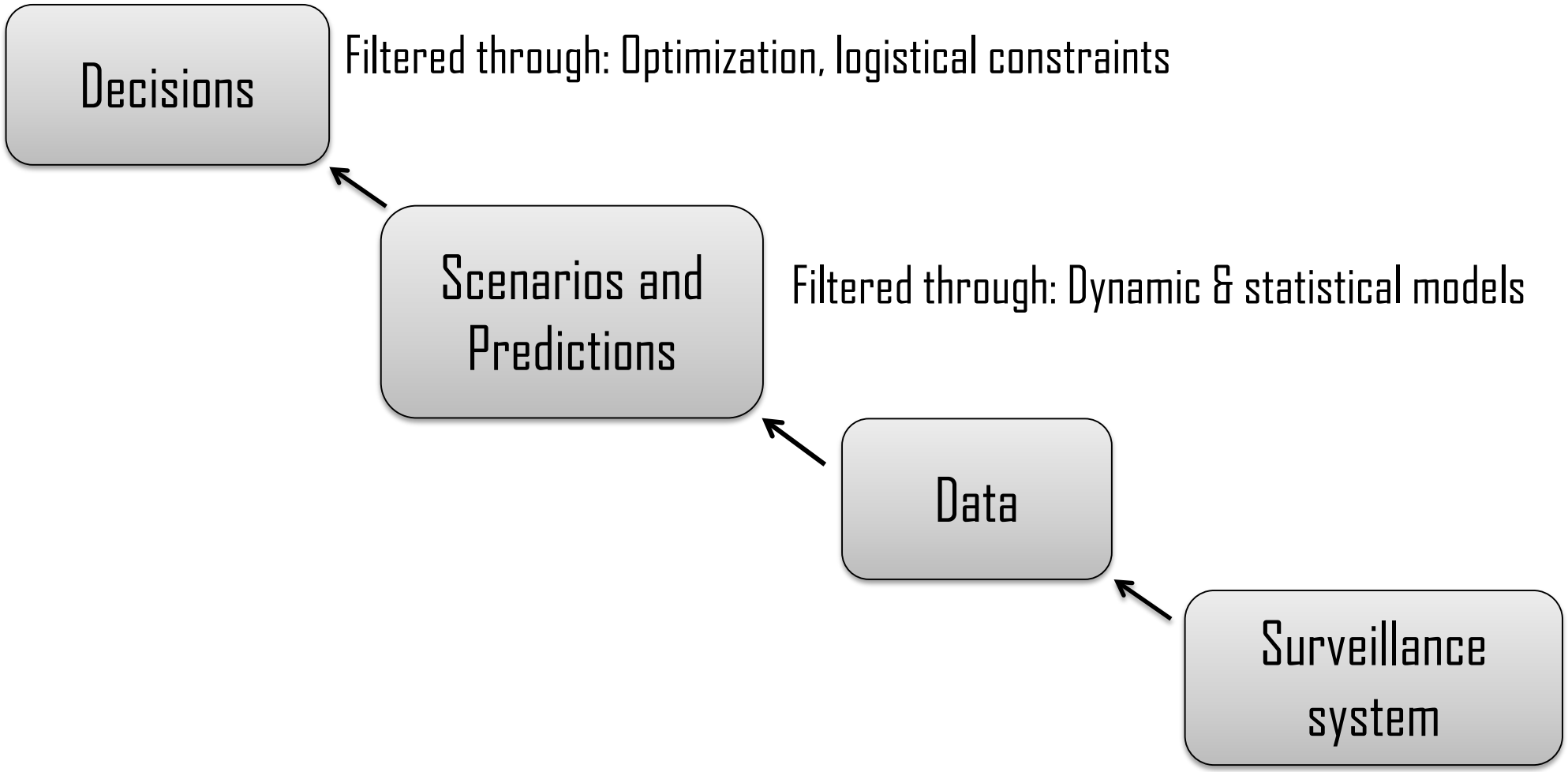
Model calibration. Model-projected (**a**) cumulative and (**b**) annual cases of pulmonary TB (median: solid line; minimum/maximum: dashed lines) compared to surveillance data for the Kivalliq region of Nunavut. Results represent the 10 best-fit model realizations, assuming that 5% of respiratory contacts sufficient for transmitting TB occur within the community. Results are similar for 1% and 15% of respiratory contacts in the community

Tuite et al. 2017

Important considerations

1. The real world cannot be fully captured by a series of equations
   - parameter values and simplifying assumptions, spatial heterogeneity, concurrent mitigation strategies
2. The models do not have the ability to identify the likelihood that a given scenario will or will not occur.
3. Models are meant to complement public health experience, expertise and common sense
   - constantly evolving landscape (e.g. lab testing, surveillance data, and reporting bias)

An idealized decision-making framework



Based on a slide from: M. Lipsitch during the 2009 influenza A (H1N1) pandemic

Decision making in times of public health crisis

- In most cases perfect data is not available and yet decisions need to be made.

Defining our roles

Garnett et al. 2011

Modeler

- Explain the models clearly
- Be rigorous in quality assurance
- Provide full documentation
- Strive to excel in both communication and technical skills
- Provide transparent analyses that can be replicated by others

"Non-modellers"

- Formulate the questions systematically
- Engage with modelling
- Sufficient consideration to the technical difficulties
- Be aware of the time and resources required

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