En Route to Reliable Policymaking Tools: Models as Hypotheses

Mathematical Modeling† of Infectious Diseases: Dynamics and Control

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†"And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand." Sir Ronald Ross

Outline

1. Philosophical underpinnings of my modeling, and natural science
2. Mathematical basics (if earlier speakers have covered them, we can spend more time on applications)
3. First application: 1997 Measles Outbreak in São Paulo, Brazil

Beliefs†

- Beliefs entail disposition to act when challenged, if only to affirm them
- Can know that some are true, but others begin as conjectures, …
- Non-belief, or suspension of judgment, lies between belief and disbelief

†Quine, WV and JS Ullian 1970. *The Web of Belief*. Random House, NY, 95 pp.

Hypotheses

- Explanations for existing beliefs or contemporary observations, but …
- Framed to predict the future or past, often under alternative scenarios
- By induction, a poorly-understood process of generalization
- Evidence lies in the extent to which consequences are realized

Some Virtues

- Conservatism – include antecedent beliefs
- Generality – reproducible under conditions that may differ somewhat
- Simplicity – subjective, but …
- Refutability – observations that would refute hypotheses must be imaginable
- Modesty – the less explained the better
- Precision – affirmation of predictions unlikely coincidental

Affirmation and Refutation

- Because hypotheses are generalizations arrived at via induction, …
- Predictions are instances
- Consistent observations affirm – but do not cinch – hypotheses, …
- Strengthening our belief
- But single disparate observations suffice to refute them

Evaluation

- Facilitated by objective criteria, chosen beforehand
- Contradictions, disparities between predictions and observations, …
- Are resolved by replacing least reliable element(s) underlying false predictions
- With evidence, and consistency with other beliefs, determining reliability
- Reevaluate

Persuasion

- Depart from common beliefs using observations and logic
- Induce people to observe for themselves or convey via testimony of credible witnesses
- Convert non-believers, overwhelm disbelievers or undermine their contrary beliefs
- Occasionally, alternatives may be ably defended, persuading us …

Ensure that CDC Models …

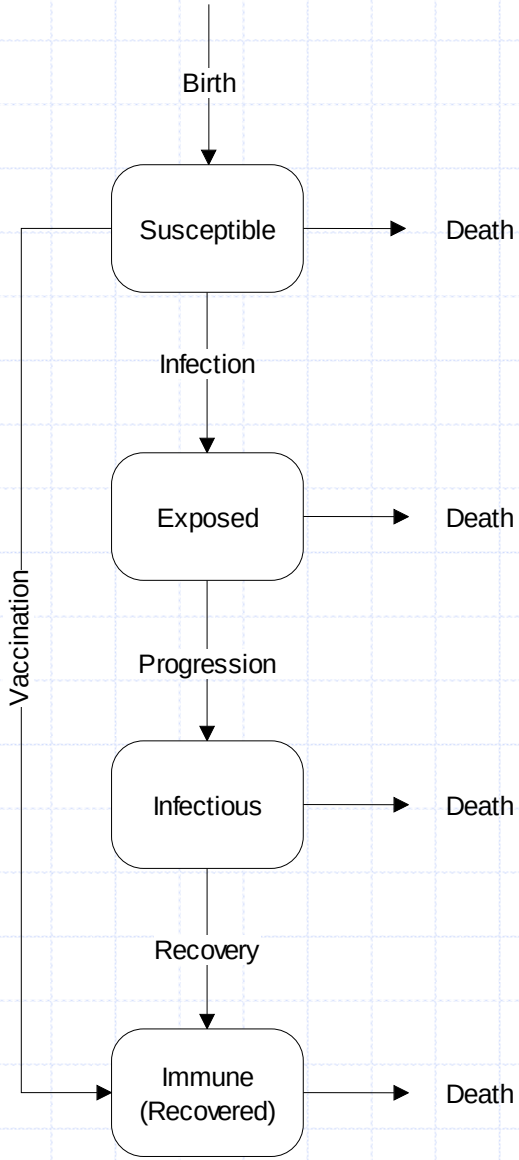
- Consistent with experts' understanding of transmission in human populations
- Have parameters estimated from the literature, accessible data or expert opinion
- Fit historical observations, if available from the setting of interest
- Assist in the design, evaluation and improvement of vaccination policy

Mathematical Basics

- The simplest model that has the features required for my work, most of which involves vaccination
- That described yesterday doesn't, but …
- Realistic models may be very complex, obscuring ideas that are more easily illustrated via simpler ones

SEIRV Model

- SIR, SIS, SEIR, SEIRV, … are classic models
- But Grenfell, BT and BM Bolker (1994. Population Dynamics of Measles, pp. 219-33 in *Parasitic and Infectious Diseases*, Academic Press) provide a lucid description of the SEIRV model



Their equations actually correspond to a slightly different diagram

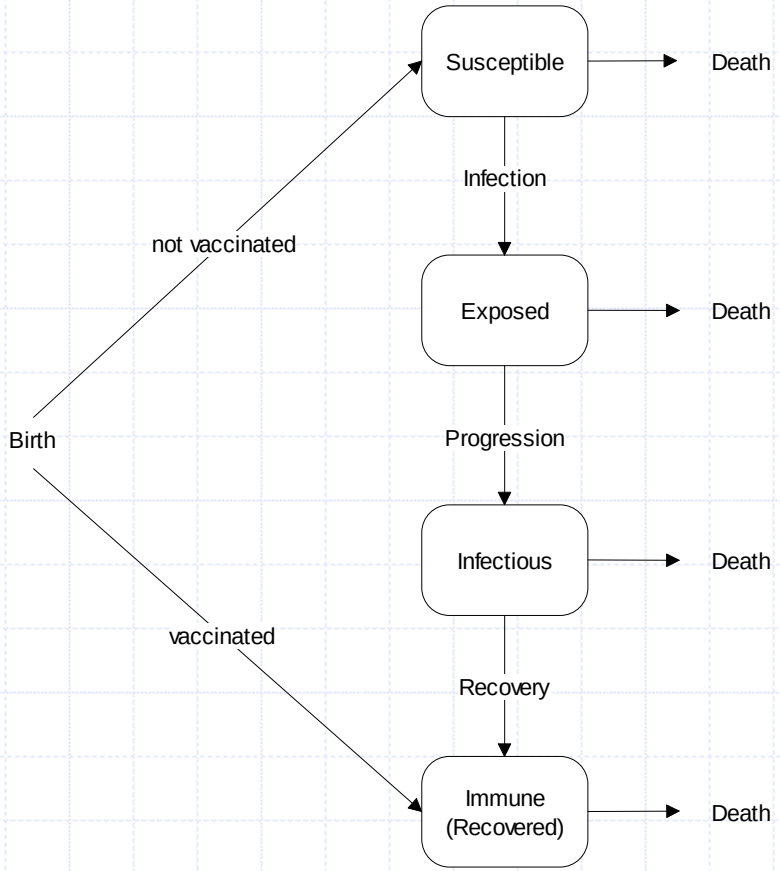
$$\frac{dS}{dt} = \mu N(1-p) - (\mu + \beta I)S$$

$$\frac{dE}{dt} = \beta IS - (\mu + \sigma)E$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I$$

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

$$N = S + E + I + R$$



What is R_0?

- The number of secondary cases a newly infectious person would cause on introduction to a wholly susceptible population
- As no population is wholly susceptible, except possibly to a pathogen causing a new human disease, contacts with people who would be infected if susceptible is more intuitive
- Derive from SEIRV model and use to facilitate understanding of control and related concepts (e.g., herd immunity threshold)

Some algebra

Setting the first DE to zero, we determine conditions under which I > 0:

$$0 = \mu N(1-p) - (\mu + \beta I)S \Rightarrow \mu N(1-p) = \mu S + \beta IS$$

$$\mu N(1-p) - \mu S = \beta IS \Rightarrow I = \frac{1}{\beta S}\left[\mu N(1-p) - \mu S\right]$$

$$I > 0 \Leftrightarrow \mu N(1-p) > \mu S \Leftrightarrow \frac{N(1-p)}{S} > 1$$

N and p are constant, but we must solve for the equilibrium value of S, denoted S*

More …

Setting the second and third DEs to zero, solving for E and I, and substituting the equation for one into that for the other,

$$0 = \beta IS - (\mu + \sigma)E \Rightarrow E = \frac{\beta IS}{(\mu + \sigma)}$$

$$0 = \sigma E - (\mu + \gamma)I \Rightarrow I = \frac{\sigma E}{(\mu + \gamma)}$$

$$I = \frac{\sigma}{(\mu + \gamma)} \cdot \frac{\beta IS}{(\mu + \sigma)} \Leftrightarrow \frac{(\mu + \sigma)}{\beta S} = \frac{\sigma}{(\mu + \gamma)}$$

$$S* = \frac{(\mu + \sigma)(\mu + \gamma)}{\sigma\beta}$$

Reproductive Numbers

Defining N(1-p)/S* as R, or N/S* as R_0, and substituting, we have

$$R = \frac{\sigma\beta N(1-p)}{(\sigma+\mu)(\gamma+\mu)} = R_0(1-p),$$

where σ and γ are reciprocals of the latent and infectious periods, β is the infection rate, N the effective population size, p proportion immune, and μ is the reciprocal of the mean lifespan

Table 3.1, Anderson and May 1991. *Infectious Diseases of Humans: Dynamics and Control*. Oxford, 757 pp.

Disease	Incubation	Latent	Infectious
Measles	8-13	6-9	6-7
Mumps	12-26	12-18	4-8
Pertussis	6-10	21-23	7-10
Rubella	14-21	7-14	11-12
Diphtheria	2-5	14-21	2-5
Varicella	13-17	8-12	10-11
Hepatitis B	30-80	13-17	19-22
Poliomyelitis	7-12	1-3	14-20
Influenza	1-3	1-3	2-3
Smallpox	10-15	8-11	2-3
Scarlet Fever	2-3	1-2	14-21

Still more …

The condition for control is $R=R_0(1-p)<1$. We can solve for the p at which R=1, denoted p_c:

$$R_0(1-p_c)=1 \Rightarrow 1-p_c=\frac{1}{R_0} \Rightarrow p_c=1-\frac{1}{R_0}$$

For measles, R_0 = 5-18, so p_c = 0.8-0.94.

- Everyone needn't be immune to control measles. Why? What is this phenomenon called?
- Ignoring naturally-acquired immunity, control may require virtually everyone receiving a 95% efficacious vaccine
- This is essentially impossible via a single opportunity

Table 4.1 of Anderson and May 1991 includes estimated values of R_0 for various diseases, locations, and epochs.

Disease	Location	Period	R_0
Measles	Cirencester, England	1947-50	13-14
	England and Whales	1950-69	16-18
	Kansas, USA	1918-21	5-6
	Ontario, Canada	1912-13	11-12
	Willesden, England	1912-13	11-12
	Ghana	1960-68	14-15
	Eastern Nigeria	1960-68	16-17

Given two opportunities, what proportion must be vaccinated?

- The value of x that satisfies $x+x(1-x) = 0.94$ is ° 0.76. Defining x = coverage*efficacy, where efficacy is 0.95, coverage must be 0.79
- When first opportunities occur during infancy, maternal antibodies may reduce efficacy, so one could solve $C_1*E_1+ C_2*E_2(1-C_1*E_1) = 0.94$ for the requisite coverage, C_2, given C_1, E_1 and E_2
- C_2 of those who either don't avail themselves of the first opportunity or don't respond, $1-C_1*E_1$, avail themselves of the second, and E_2 respond

Effect of coverage on R (average number of secondary infections)

- Simplest calculation (i.e., 2 opportunities), VE= 0.95
- Consequences of reduced coverage due to safety concerns
- Depending on R_0, threshold (R>1) is between 0.7 and 0.75

Coverage	R_0=12	R_0=15
0.85	0.44	0.56
0.8	0.6	0.86
0.75	0.99	1.24
0.7	1.35	1.68

In the US, we have two doses …

- Reformulate to $C_1E_1+C_2E_2*C_1*(1-E_1)$, where only those who received the first dose, C_1, are eligible for the second. This gives C_2 of the $C_1*(1-E_1)$ who failed to respond another opportunity, to which E_2 will respond
- If C = 0.9, E = 0.95, and immunity doesn't wane, this would increase immunity by ~ 3.85%. A second opportunity, in contrast, would boost immunity by ~ 12.4%, a threefold increase
- Do we want multiple doses or opportunities? Doses reach the same children, by definition, but if the first opportunity is well-child care and second a mass campaign, different children may be reached

Another Model

- Whittle et al. (1999. Pediatric Infect Dis J 18:53-57) found low Ab titers among West African children 5-7 yrs post-vaccination
- Suggested multiple-dose regimen might be needed absent boosting, possibly because of malaria, which increases Ig turnover