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Chapter 26

Transmission Modeling To Enhance Surveillance System Function

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Models of how infection flows through populations are increasingly being used to inform disease control decisions. Technological advances discussed in previous chapters that allow for more and better data are improving how models can relate to reality. Better technology, in terms of software and computers, is also making models more usable and useful. New technologies make it easier to add realism to models and to explore what aspects of a model determine its behavior, which facilitate the formulation of hypotheses and theory about what is determining the behavior of the real world. Better technology also helps test hypotheses and theory by fitting models to surveillance data. Nonlinear dynamics of complex real world systems generate the patterns seen in surveillance data. Fitting these nonlinear dynamic models to data has been a challenge that is, bit by bit, being met by new algorithms and new hardware.

A major theme of this chapter is the logic of how to use such model fitting to improve disease control decisions. The logic presented demands particular forms of coordination between surveillance personnel, modelers, and policy makers. Accordingly, structured steps are presented in this chapter to improve this coordination. To illustrate the general concepts presented, a real-world example is presented about proceeding to use surveillance data and transmission models to inform polio eradication endgame policies by helping to monitor levels of non-paralytic poliovirus infections that are difficult to observe and count directly.

Transmission modeling and broader analytic contexts

Two recent analytic advances, data mining and fitting of transmission models to data, help public health surveillance to incorporate more complex data and methods for guiding disease control decisions. The focus in this chapter is on inferring control action effects from surveillance data using causal system models of infection transmission.

Data mining is a different approach to complexity that, like classical risk factor analyses, assumes away all system control loops while providing a better way to perceive complex risk factor effects.

Currently both data mining and transmission modeling are applied as special analyses of surveillance data that were not gathered for these purposes. In the future, data mining and transmission modeling have the potential to transform surveillance if they evolve within systems that guide disease control and feedback is provided by surveillance system users on the effectiveness of their guidance. All surveillance systems need such feedback. Data mining involves machine learning of how sets pf factors lead to other sets of factors and the feedback needed is whether the machine is focusing on the right things to learn. Causal system analyses, like those using infection transmission models, build theoretical system models and feedback is needed on whether those models are adequate to guide public health actions.

Data mining

Data mining uses computer programs to progressively learn from massive and diverse data about how patterns of single variables or combinations of variables relate to patterns of disease. Diverse strategies and algorithms have been developed for data mining, and new approaches are evolving rapidly. Since our main purpose in mentioning data mining here is to make broad contrasts with transmission modeling, we will not discuss these specific approaches. Data mining either retrieves answers to narrow questions or describes relationships. The relationships of interest might be about how words like “flu” in internet communications or purchases of particular types of medications from pharmacy records indicate disease patterns of infection or disease variables. Or they may be about how patterns of risk factors such as behaviors, genetics, or physiological states relate to patterns of disease. Data mining mostly examines the type of associations that have been the core of mainstream epidemiology since John Snow linked water sources and cholera, but it pursues more complex relationships between predictor variables than is feasible with traditional methods. Data mining is mostly “theoryless” (Vaillant 2013) in that it does not currently use mathematically expressed theory about the complex system processes through which disease states at the individual or population level are generated.

The learning programs used by many data mining methods are like those that enabled the IBM computer named Watson to beat the best Jeopardy contestants (Ferrucci, Brown et al. 2010) and represent significant advances in learning theory. These programs can “learn” more effectively if they get feedback as to whether the analyses performed provided an informative inference or not. In traditional epidemiology, analysts do the learning themselves rather than having a machine do the learning. In data

mining, analysts direct a computer to learn and then guide the computer to learn more effectively by providing feedback on whether it is learning helpful things about risk factors or generating gibberish.

Infection transmission system modeling

Mechanistic, causal models of infection transmission systems (called transmission models for short hereafter) are used to analyze the dissemination of infections through populations. They differ from risk factor epidemiology models and most data mining models by using systems theory to formulate mechanistic feedbacks between variables and the individuals or populations modeled. Such feedbacks generate nonlinear dynamics that cause the outcomes experienced by some individuals to change the risks experienced by other individuals. Traditional analyses and data mining, in contrast, describe data (not theory) using dynamically linear models of relationships in the data in a manner that preserves the independence between outcomes in different individuals.

One source of a positive system feedback in a transmission model is risk factors for infection transmission, such as drinking from an unsafe water supply. Early in an epidemic, with each new infection there is a new source of contamination for the unsafe water, causing the risk from drinking unsafe water to increase. On the other hand, late in an epidemic or during endemic transmission, immunity acquired from previous infections related to risk factor exposures provides a negative feedback. Those who drank unsafe water have more immunity and lower risks of infection. This might make an exposure like drinking from an unsafe water supply look like a protective factor in a study of endemic infection where individuals' immunity levels are not measured. A transmission model that captures the risk of drinking contaminated water would include variables that specify individuals' immunity status and parameters that govern the risk of infection by immunity status and exposure status. Such a model would require specifying immunity status in the model, even though there might not be such data available. When the model parameters are fitted adequately to exposure and disease experience data, it would make more accurate predictions of ongoing risk than a risk difference because it captures the effects of exposures and immunity.

Traditional surveillance systems describe surveillance data by time, place, and person. These descriptions may identify risk factors directly or stimulate special investigations that identify risk factors. Odds ratios, risk ratios, risk differences, and other epidemiologic measures are used for risk factor identification. For infectious diseases, however, these measures can provide bad predictions of future risk because of the system feedbacks generating nonlinear dynamics such as those arising from risk factors in the previous paragraph. With regards to the positive risk factor example, the traditional measures miss the new infections generated by the person getting the infection from risk factor exposure. The negative risk factor example made a factor that

is disseminating infection look like a protective factor. Because transmission models capture these feedbacks, they are more capable of predicting future infection levels if control actions change risk factors.

When a risk difference is used to predict the effect of eliminating an exposure, the assumptions behind that prediction are often poorly specified and understood. One basic assumption is that the infection or disease outcome from exposure in one individual is independent of outcomes in other individuals. Infection transmission and immunity effects violate that assumption.

The assumptions behind transmission model based predictions are usually better specified than the assumptions behind risk difference based predictions; however, considerable care, experience, and knowledge are required to specify how assumptions in transmission models differ from real world situations being modeled. We propose a set of steps to assess the effects of assumptions on inferences made by analyzing data using transmission models. These will be presented later in sections dealing with inference robustness assessment and identifiability analyses.

Another important difference between traditional surveillance data analysis and transmission model analysis is what determines the variables used in an analysis. Traditional epidemiology and data mining both determine what variables are used in a model by the availability of data for those variables. In contrast, transmission system model variables are determined by what is theoretically needed to understand an infection control issue – whether or not data for a particular variable are available.

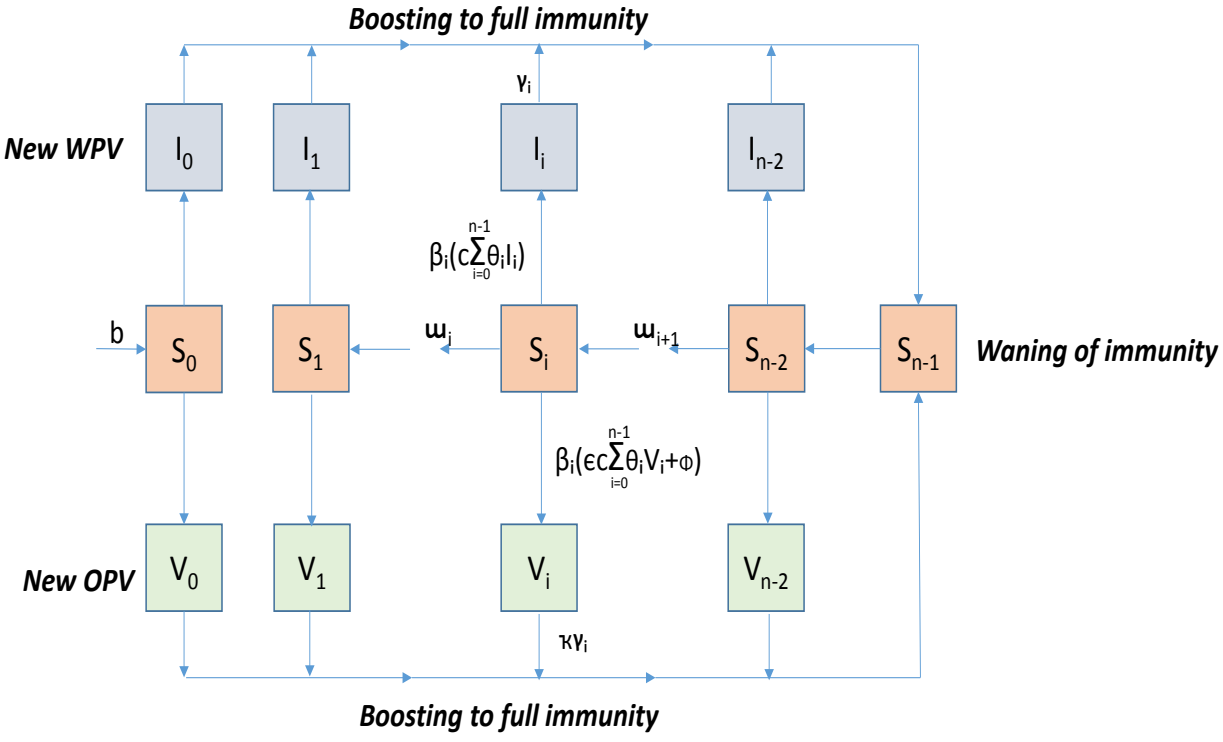
Classes of transmission models

Differential Equation (DE) Models

Compartmental models based on differential equations model continuous populations rather than discrete individuals. They use deterministic approaches that predict expected mean system behavior for very large populations. They break up a population into compartments such as susceptible, infected, or immune, as is the case for the classic SIR (susceptible, infectious, recovered) model and define transmission generating contact patterns between these compartments). DE models assume very large numbers of individuals in compartments so that chance events cannot drive the model behavior. This assumption holds no matter whether the size of the compartment is 1 or 1 billion. because the DE form assumes that population or compartmental sizes are continuous, in the sense that between any two values for a compartment there are an infinite number of intervening values.

An example of a compartmental model can be found in Figure 1. Each box in the figure represents a segment of the population. The "S_n" boxes represent susceptible populations, the "I_n" boxes represent populations infected with wild poliovirus (WPV), and the "V_n" boxes represent those infected with live oral polio vaccine (OPV). The arrows represent transitions between population compartments. All new population comes into compartment S_0. There are n levels of immunity and n different natural histories of infection corresponding to OPV or WPV infection that occur in individuals at each level of immunity. Infection with OPV or WPV can occur out of the S compartments at the 0 through n-2 levels, but no infection can occur at the n-1 level of immunity. When individuals recover from either an OPV or a WPV infection, they recover into the S_{n-1} compartment. This model was used to generate general insights into the dynamics of poliovirus infection and immunity and how these dynamics are altered by increasing transmissibility, speed with which immunity wanes, the transmissibility of OPV, and the timing and extent of coverage of vaccination campaigns (Mayer, Eisenberg et al. 2013). A radically simplifying assumption of this model is that the immunity levels generated by WPV and OPV infection are identical. A single infection with either OPV or WPV gets one to the maximal state of immunity, and if one gets reinfected after immunity has waned, immunity cannot be boosted beyond that achieved after the first infection.

Figure 1. DE polio model



One does not need to know much about the mathematics of differential equations to use this modeling approach. Expertise in the social, epidemiological, and biological

processes involved is the most important factor for developing useful models. Computer programs are then utilized to solve the differential equations tied to the model. Understanding how to translate model assumptions into model structure and equations is a skill almost anyone can acquire, but a capacity to make judgments about the appropriateness or necessity of model assumptions is needed in order to make valid inferences from a model analysis. Gaining such capacity requires experience and a good theoretical foundation of how model structures relate to assumptions. A complete public health surveillance system should include individuals with this capacity.

Agent Based (AB) Models

Instead of continuous population segments, agent based (AB) models use individuals. When an infected and a susceptible individual encounter each other, there is some chance that transmission may take place. Chance plays no role in DE models. AB modeling is one variety of "stochastic" or "chance" modeling. A single run of an AB model provides one possible outcome, but the next outcome might vary greatly from the first. Thus, a model must be run many times to produce a distribution of outcomes in order to make inferences about disease control on the basis of surveillance data. This extra computing work has an important benefit not possible with DE models: one can calculate the chances of different outcomes having different degrees of severity. The real world can be viewed as having experienced such a chance process that might have come from a variety of different distributions; such chance considerations can be an important driver of disease control decisions.

To use the example of polio eradication again, one might want to choose between two different control options that, on average, take the same time and effort to achieve eradication. If one control option has a chance of a very large outbreak that could not be controlled with available resources but the other does not have that chance, the choice of control options may be influenced—such chances could not be evaluated using a purely DE approach.

Just as for DE modeling, a growing body of software facilitates AB modeling without requiring specialized mathematical or programming skills. What is required is experience and a broad disciplinary knowledge base that improves judgment capacity when deciding what to include or ignore in a model to make it as simple as possible, but no simpler. Simple models help make clear inferences relevant to disease control, but models that are simpler than necessary lead to erroneous inferences. Later, we will present an inference robustness strategy for finding simple models that lead to good inferences.

Model complexity and model inferences

Complexity of DE models relates to the total number of compartments in a model as well as the number of interactions between compartments and their variety. Similarly, the complexity of AB models relates to the numbers of individuals, the number of states those individuals might have, and the number and types of things that can happen to individuals, especially the number and type of interactions that might occur between individuals.

Because the social and biological complexities that underlie real world infection transmission systems are so rich, simpler models in general make more unrealistic assumptions about the real world than more complex models. The simplest models assume that all individuals or all population segments behave identically to all others and have equal contact rates with all others. The classical SIR model makes such assumptions. However, if there is a high risk group affecting transmission, and mixing between high and low risk groups affects the spread of infection, then decisions about resource allocation can be dramatically wrong if the model does not capture these complexities (Koopman, Simon et al. 2005).

One relaxes an unrealistic simplifying assumption by making a model more realistically complex. To relax unrealistic assumptions about large population size in DE models, one can keep most assumptions in the DE model but transition to an AB model. Any such transition involves also adding the analytic task of having to examine distributions of model outcomes affected by chance events rather than just deterministic mean model outcomes. Assumptions regarding networks of interactions between individuals are best handled by AB models, as DE models do not have individuals but rather only continuous segments of population. Consequently, DE models intrinsically assume that if one person makes contact with two individuals, those contacts do not affect the chances that those two people will contact each other. In other words, the chance of two people contacting each other is not influenced by whether they both have a common contact as it is in the real world. To relax this unrealistic assumption, one must use an AB model. In general, however, since it is much faster and easier to explore the effects of relaxing assumptions in DE models than in AB models, one should go as far as one can to relax simplifying assumptions in DE models before transitioning to AB models.

Infectious disease modeling: Polio Example

The global strategy for polio eradication is a product of a century of epidemiologic research and 60 years of experience with polio immunization. Since the launch of Polio Eradication Program at the World Health Assembly in 1988, the Global Polio Eradication Initiative (GPEI) has reduced the global incidence of polio by more than 99% and the number of countries with endemic polio from 125 to 3 (GPEI and WHO 2013). Of the three types of WPV (type 1, type 2 and type 3), type 2 WPV transmission

has been successfully stopped (since 1999), and significant progress has been made towards eradicating type 1 and type 3 WPV (WHO 2013).

Until recently, polio transmission modeling has not been very important in guiding control decisions. The polio eradication effort has used an empirical strategy that detects acute flaccid paralysis (AFP) cases and diagnoses polio infections among these. Even though only a small fraction of poliovirus infections result in paralysis, eradication efforts have assumed that AFP surveillance sufficiently detects all places with poliovirus transmission. However, now, in the final stages of eradication, this assumption may no longer be appropriate.I It is thus becoming more important to understand what can sustain poliovirus transmission in the absence of paralytic cases and not just what immunization program deficiencies create risks of paralytic poliomyelitis cases. To ensure eradication, it may be necessary to make inferences about whether waning immunity is allowing previously infected individuals to sustain transmission. Before vaccination efforts begin in high transmission areas, waning immunity is continuously boosted by WPV infections that immunity aborts before they become contagious. A major value of OPV transmission is that it allows waning immunity in older individuals to be boosted by OPV infections. But some individuals, due to better sanitation, hygiene, and less crowded living conditions, will not be boosted by OPV transmission. These individuals' immunity will wane so that if they get infected with WPV, their infections will last longer and they will excrete enough virus to be more capable of transmitting.

Immunity affecting transmission wanes much more quickly than immunity against paralysis. Thus, waning immunity could result in reinfected cases transmitting enough to sustain WPV circulation without there ever being paralytic poliomyelitis cases. It is not practical to make observations about WPV transmissions from people who have waned to different immunity states after WPV or OPV infections. However, it is possible to estimate how much waning immunity affects transmission if the right data from the right situations can be fit to models. With such estimates, the models can be used to estimate how much transmission might be occurring in the absence of paralytic polio cases.

Transmission model analyses have recently shown that the polio eradication achieved in high transmission settings like India and Egypt is a tenuous eradication (Mayer, Eisenberg et al. 2013). It is tenuous because waning immunity acquired from WPV infection before OPV vaccination campaigns with eliminated WPV will progressively increase the potential for WPV circulation over time. Since waning immunity mostly affects age groups not getting OPV directly but rather through secondary transmissions,

the increase in WPV transmission potential in the absence of paralytic polio could be large.

WPV transmission has been detected in the absence of paralytic polio in Israel (WHO 2013). While the waning of inactivated vaccine induced immunity, rather than WPV or OPV immunity, caused the situation in Israel, the theoretical demonstration of the waning effects of WPV and OPV in high transmission countries (Mayer, Eisenberg et al. 2013) makes the Israeli experience more important for two reasons. First, few countries have the type of WPV surveillance used in Israel that could detect asymptomatic infection circulation. The World Health Organization (WHO) is addressing this issue by increasing sewage surveillance. Second, the Israeli situation presents a unique opportunity to estimate waning immunity parameters by fitting models to the available data. Such parameter estimation would increase the validity of modeling estimates to determine where WPV has the best chance to circulate in the absence of paralytic cases. These are the areas where surveillance needs to be set up for non-paralytic poliovirus infections.

At the time this chapter is being written, three endemic countries, Nigeria, Pakistan, and Afghanistan, have never stopped polio circulation. Polio transmission in Nigeria has set off outbreaks widely across Africa but is now coming under control (GPEI 2013). Some of the outbreaks caused by viruses from Nigeria have taken over a year to control (GPEI 2013). Pakistan has also set off several significant outbreaks (GPEI 2013) and appears to be the source of cases detected in Israel as well as paralytic cases in Syria (GPEI 2013). The intensive and ongoing eradication efforts in these countries bring hope for final eradication in the near future, but waning immunity could be making adults from endemic transmission areas more capable of transmitting infections to new areas. For example, a virus in Chad appears to be the source of cases in Cameroon over two years after the last paralytic case detected in Chad (GPEI 2013). Moreover, waning of WPV and OPV induced immunity could be making many areas more capable of sustaining WPV transmission when cases arrive from endemic areas. Accordingly, WHO declared an emergency situation in May 2014 urging that all people, adults and children, traveling out of endemic areas provide proof that they have been recently vaccinated.

This emergency situation calls out for a better understanding of waning immunity, of whose waning immunity is likely to be boosted by getting an OPV infection from a vaccinated child, and of the conditions that allow WPV circulation with few or no paralytic cases. Applying transmission models to surveillance data will be essential to generate this needed understanding. Models will be needed to estimate key parameters

from the data, after which models can use these parameters to project where silent poliovirus transmission is most likely.

Using transmission models to estimate unknown parameters and unobserved variables

Models have variables and parameters. A variable changes value over time as a result of system influences. Parameters are fixed theoretical relationships in models that govern how the values of variables change over time. The polio example can be used to illustrate how models are used to estimate both unmeasured variables and unknown parameter values.

First, let us consider an example of estimating an unmeasured variable. Current surveillance systems only record paralytic poliomyelitis cases; they do not measure the frequency of non-paralytic infection. The AFP surveillance system has been very successful at detecting these cases because it incorporates good methods for evaluating the completeness of paralytic polio surveillance (WHO 2013). The circulation of WPV in the absence of paralytic poliomyelitis in Israel and the theoretical risk of waning creates a need for surveillance systems that also detect non-paralytic WPV infections. Since surveillance to detect non-paralytic polio can be very expensive, such surveillance needs to target the situations in which a high ratio of non-paralytic to paralytic cases can be expected.

An important step toward effective surveillance of non-paralytic polio infections is to describe the joint distribution of paralytic and non-paralytic infections using transmission models that are sufficiently detailed and realistic and that are informed by sufficiently detailed data on diverse aspects of the real world. Since direct surveillance of non-paralytic WPV infection rates is very expensive, surveillance must involve estimating those rates using models informed by other surveillance data. To date, model based inferences made about non-paralytic WPV rates are still crude (Duintjer Tebbens, Pallansch et al. 2013; Duintjer Tebbens, Pallansch et al. 2013; Thompson 2013; Thompson, Pallansch et al. 2013; Thompson, Pallansch et al. 2013), but the new methods for fitting models to data to be discussed later in this chapter should improve that.

Next, let us consider a parameter example. Essential parameters in recent polio models establish the patterns over time by which immunity wanes (Duintjer Tebbens, Pallansch et al. 2013; Duintjer Tebbens, Pallansch et al. 2013; Mayer, Eisenberg et al. 2013; Thompson 2013; Thompson, Pallansch et al. 2013; Thompson, Pallansch et al. 2013). No longitudinal data are available about the state of immunity of individuals and how that affects transmission potential that would allow one to infer parameters describing how fast immunity wanes. Nonetheless, waning parameters can be found that are consistent with available observations on different aspects of polio from different parts

of the world (Duintjer Tebbens, Pallansch et al. 2013). The methods used so far, however, have not taken advantage of recent advances in methods for estimating parameters of transmission models discussed in the next section.

Let us put this discussion of variables and parameters back into the context of traditional versus transmission model analyses in epidemiology. The variables used in standard risk factor epidemiology or data mining analyses are determined by what is in the data. The variables in transmission models, in contrast, are determined by causal theories defining what is needed to predict system behavior. When direct data on some variables are not available, transmission models can make inferences about those variables if enough good theory and data on other aspects of the transmission system are available.

The parameters in standard risk factor epidemiology or data mining models describe relationships between variables rather than causal system mechanisms. Thus, they do not allow for projection of future infection transmission levels. When using transmission models to project effects of policy choices, limitations on what is known about parameter values make policy choice projections less precise and less reliable. In order for surveillance systems to better inform policy choices, they should use transmission models to both project the consequences of policy choices and learn more from their data about unknown variable and parameter values.

New methods for estimating parameters from transmission models

One fits a model to surveillance data that characterizes patterns of infection over time by finding parameter values that reproduce these patterns in the surveillance data. Statistical analysis of time series data like those collected by surveillance systems traditionally focused on models with linear relationships between observations (Box and Jenkins 1970). Recent algorithmic advances for nonlinear models have made possible the formal statistical analyses that used to be available only for linear models, including confidence intervals for unknown parameters, model selection tests, and the computation of Bayesian posterior distributions. Furthermore, several recent methods have the convenient plug-and-play property that implementing the methodology requires the scientist to specify the dynamic model only via computer code to simulate trajectories (Breto, He et al. 2009; He, Ionides et al. 2010). Plug-and-play statistical methodologies for imperfectly measured dynamic systems include iterated filtering (Ionides, Breto et al. 2006), particle Markov chain Monte Carlo (Andrieu, Doucet et al. 2010), synthetic likelihood (Wood 2010), approximate Bayesian computation (Toni, Welch et al. 2009), and nonlinear forecasting (Kendall, Ellner et al. 2005). Both maximum likelihood inference and Bayesian inference involve the likelihood of the data given the model. Therefore, it may be counter-intuitive that inferences of this kind can be obtained when direct evaluation of the likelihood is unavailable. Nevertheless,

theoretical results underpinning iterated filtering (for maximum likelihood inference) and particle Markov chain Monte Carlo (for Bayesian inference) show that this is indeed possible.

All of the plug-and-play methods mentioned above are freely available in the open source R package POMP, which deals with inference for partially observed Markov process models (King, Ionides et al. 2009). Examples involving the use of POMP for epidemiological investigations include studies of malaria (Laneri, Bhadra et al. 2010; Roy, Bouma et al. 2013), cholera (King, Ionides et al. 2008), pertussis (Blackwood, Cummings et al. 2013), and pneumonia (Shrestha, Foxman et al. 2013). Introductions to statistical inference for nonlinear mechanistic models in the context of the pomp package are provided by the pomp package vignettes.

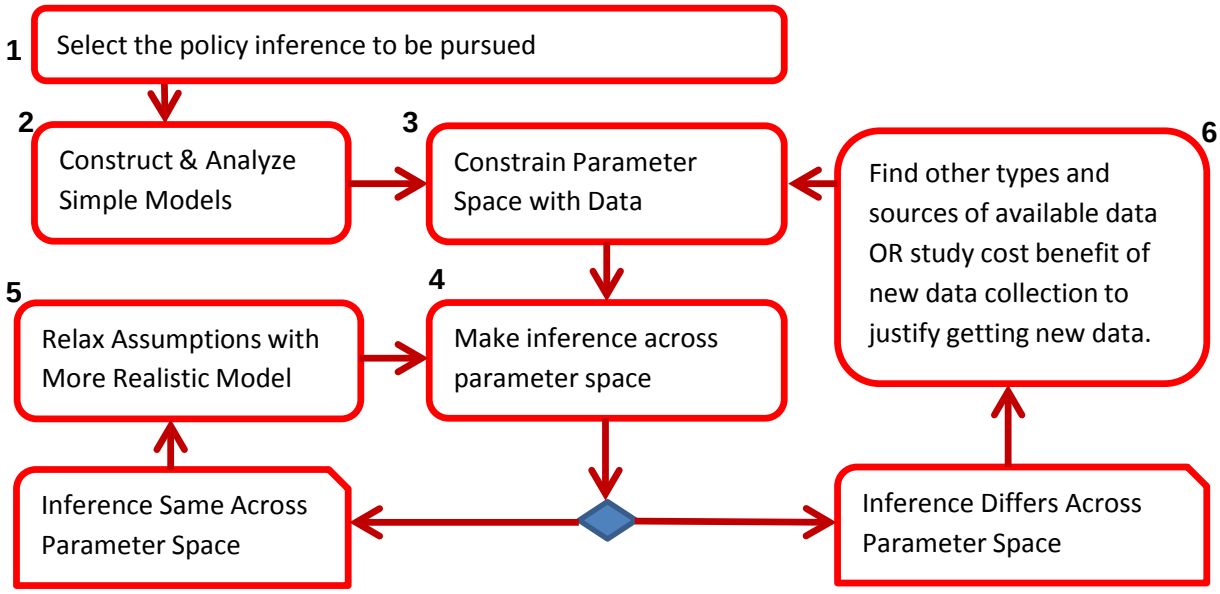
We propose that these methods promise to provide useful estimates of non-paralytic poliovirus infection rates in areas where good data on vaccination program activities and paralytic cases are available. As discussed later with regard to identifiability analyses, data on sanitation conditions and on genetic sequence patterns of isolated polioviruses may also be needed. Surveillance team members other than statisticians will not need to understand the technical aspects of the listed methods, but all team members can and should have an understanding of the general scientific approach.

Because these new methods are being developed in academia and will need modification to meet specific public health practice needs, and because they require a new way of thinking about what one can get from data and how one analyzes data by analyzing systems, collaboration between academics and field epidemiologists is essential in order for analyses of dynamic causal system models to become an important part of surveillance activities. Furthermore, since most academics do not appreciate the needs, flexibilities, and rigidities of a well-functioning surveillance system, the collaboration between service entities and academics must be established in a context where the goals of academics are unified with those of service agencies. After elaborating our polio example to incorporate model fitting for making policy decisions, we will then propose a framework for unifying academic and surveillance system goals for modeling. First, however, we will present a theory-based discussion about the validation of transmission model analyses that lead to policy choices.

Model choice, model validation, and the policy decision process

In this section, a particular approach to model choice and model validation will be presented. There is no universally valid model for making any possible inference—each policy question requires a model form adapted to the inference addressed. A model is validated with regard to its ability to inform inferences. When pure science is pursued the inference may be what theory is correct, but here we focus on policy choices.

Figure 2
Steps to Making Valid and Robust Policy Inferences Using Dynamic System Models



Just finding that a model fits available data does not validate a model for making any policy decision for two reasons. First, different models that lead to different policy decisions could fit the same data. Second, any model that fits the data makes a series of simplifying assumptions about what is important for a decision in the real world—that is the nature of models. In some cases, realistic relaxation of those simplifying assumptions may not change the fit to data dramatically, but it might change the decision chosen. For these reasons, model validation for specific inferences needs to follow the steps in Figure 2, which enumerates all action steps. Step 4 leads to a decision criterion for proceeding to an inference robustness assessment by proceeding to step 5 or to an identifiability analysis by proceeding to step 6. In many cases it will make sense to pursue both inference robustness assessments and identifiability analyses simultaneously.

Inference Robustness Assessment

Two questions that should be answered when modeling a transmission system to inform policy include 1) what aspects of a system and what details about processes and feedbacks in that system need to be included in a model in order for transmission models to generate good control decisions? and 2) how can a particular model form and a particular set of parameter values in that model be validated with regard to informing policy choices? The answer to these questions should be sought using a set of iterative steps that involve “inference robustness assessment (IRA)” (Koopman 2004; Koopman

2005) and “identifiability analyses” (Jacquez and Greif 1985; Jacquez and Perry 1990; Audoly, Bellu et al. 2001; Hengl, Kreutz et al. 2007; Meshkat, Eisenberg et al. 2009; Raue, Kreutz et al. 2009; Komorowski, Costa et al. 2011). These steps are presented in Figure 2.

The flow chart in Figure 2 has an initial process to reach the decision point after step 4. The decision is to proceed with either further IRA or further identifiability analyses. The figure then has two infinite loops coming through the decision point; the one going through step 5 is the inference robustness loop, and the one going through step 6 is the identifiability loop. These two loops represent the processes by which science continually develops deeper levels of understanding and increasingly verified theories. Policy decisions cannot wait for infinite loops to be completed—decisions must be made wherever one is within these loops. The processes in Figure 2 ensure, however, that the best model currently available for a particular policy decision is being used to make that policy decision.

The IRA process involves finding a simple model that is adequate for informing a control decision but is not too simple in the sense that its unrealistic simplifying assumptions cause the wrong control decision to be made. To ensure that a model is not too simple, one must verify that realistic relaxation of simplifying assumptions is unlikely to change a policy inference. This verification is done in Figure 2 by following step 5 whenever step 4 leads to a single policy choice. Skill in identifying assumptions, finding ways to relax assumptions, and choosing the most important assumptions to pursue are gained mainly by experience and are helped by a good theoretical foundation in both modeling and the relevant scientific, social, or professional disciplines. To identify hidden assumptions, it is helpful to have a diverse and multidisciplinary team involved.

Identifiability analyses

An identifiability analysis focuses on what data are needed to make a control decision using a causal system model. A policy choice is “identifiable” by a set of data if those data are consistent with only parameter values that lead to a single policy choice. Whenever that is the case, an IRA is the next step to help validate the model as appropriate for making the policy choice. When a policy choice is not identifiable using the current set of data, more data is needed. What is the best type of new data to pursue is determined by an identifiability analysis. In Figure 2, identifiability analyses involve looping through steps 6 then 3 then 4.

Types of data that can inform models

A surveillance system might gather data routinely on some things and might conduct surveys or special studies to gather data on other things. Demographic data are always

needed when modeling populations and may be collected by a health agency or others. Sanitation, transportation, economic, or service use data might also increase the identifiability of policy choices. The total data available might cover infection or disease incidence and prevalence, individual risk factors, population structure, patterns of contact between individuals, contacts with environmental reservoirs, control actions, laboratory results affecting the course of infection or transmissibility of individuals, and genetic sequences of pathogens. These diverse sorts of data deserve both standard descriptive analyses and integration into transmission model based analyses. When the data provide direct information on the parameters of a model, then the transmission model analysis need only run the model to interpret the significance of the surveillance data. The more complete model based analysis will use all of the data together to help estimate all otherwise unknown parameter values.

An important type of data for analyzing surveillance data across many years includes data on factors that might affect the completeness and accuracy of surveillance data, such as surveillance personnel activities and outbreak investigations. Surveillance personnel have many responsibilities and as different situations arise, they must decrease the time they spend on getting routine surveillance data. This can affect reporting completeness. A model based inference might not be robust to realistic relaxation of the assumption that surveillance is constant over many years. In other words, adding a term to a model that allows reporting completeness to vary over time could change a control inference made from analyzing the model. If so, in a model with variable reporting rates, the inference sought might not be identifiable. That is to say the inference could depend upon unobserved variability in the reporting rates. However, if reporting rates can be informed by factors affecting reporting completeness, identifiability might be recovered.

Making control decisions involving policy choices

The processes in Figure 2 are advisable whenever a model is used to inform policy. These processes represent the general steps of scientific progress that pursue deeper understanding. There is no endpoint that definitively says no more IRAs or identifiability analyses are needed; science should always seek deeper and wider understanding. Policy choices, however, must be made even when some threats to inference robustness have been identified and when inferences are not identifiable with available data. If policy makers were involved in the initial choice of policy inferences to be pursued, and if the modelers have used the models developed to help the policy makers understand the mechanisms generating infection control outcomes, then the team of surveillance personnel and modelers are in a position to inform policy makers so that they can make decisions in the face of residual uncertainties.

After recently announcing a WHO polio transmission emergency, WHO decided to require vaccination of travelers from polio endemic regions. (WHO 2014) This was the first time WHO has indicated that adults could be important in polio transmission. The resulting consternation and resistance in the affected countries might have been mitigated had there been a solid model based analysis supported by inference robustness and identifiability analyses. The threat to global eradication probably justifies this decision despite not being able to back it up with model analyses incorporating inference robustness and identifiability analyses. If appropriate model based analyses incorporating inference robustness and identifiability analyses were pursued earlier, however, then it is possible that more of the sequence data, population movement data, or sanitation data might have been integrated into the analysis to make the choice of this decision identifiable and thus improve the public support for it.

For the policy maker to be comfortable with how model analyses are informing their decisions, step one in Figure 2 is key. Policy makers must be involved in defining the inferences pursued using transmission models, but they cannot dictate those inferences because they are unlikely to fully understand the factors affecting the utility of different choices. The choice must involve an interactive process between the modeler team and the policy makers. One reason for this interaction is that “systems thinking” is required to choose policy options when dealing with infection control. While being adept at envisioning the feedback processes affecting policies is a characteristic of good policy makers, they may not be trained in envisioning the feedback processes involved in infectious disease control. Moreover, they may have little insight into the ability of models and data to inform policy choices. Therefore, a formal meeting to select the precise wording of policy choices to be pursued is advisable.

In such a meeting, policy makers should begin by presenting how they see their policy options, what their objectives are (e.g. minimize infections, deaths, days in hospital, disparities, etc.), what their constraints are (e.g. personnel or other resources), and what would lead them to choose different options. Then, modelers should discuss those options in terms of their possible effects on the behavior of transmission systems. This discussion should modify what the policy makers see as their options and lead to the selection of inferences to pursue. If this crucial first step is not pursued adequately and the goal of the modeling is poorly defined, then the modeling is more likely to wander in the complexity of reality and available data than it is to influence policy. We illustrate the steps of this process and the paths that this process can take with our polio example.

Validating transmission model based polio eradication policy choices

Identifying and selecting inferences to be validated

Beginning with step one in Figure 2, the relevant policy makers must be identified. WHO and GPEI officials aggregate and analyze global surveillance data and make policy decisions that could benefit from a transmission model analysis of their surveillance data. One modeling group worked with the United States Centers for Disease Control and Prevention and, through them, with WHO and GPEI. One thrust of this group's recent work emphasizes the need for a change from surveillance to detect paralytic polio cases to surveillance to detect poliovirus infections even in the absence of paralysis (Duintjer Tebbens, Pallansch et al. 2013; Duintjer Tebbens, Pallansch et al. 2013; Thompson 2013; Thompson, Pallansch et al. 2013; Thompson, Pallansch et al. 2013).

For our example, we can consider India, which has been declared polio free on the basis of no paralytic polio cases being detected for two years by a well-functioning AFP surveillance system. The road to eradication in India was difficult. After a seemingly intensive vaccination program knocked paralytic cases to a very low level, there was a big rebound in transmission and extremely intensive revaccination with different OPV formulations once again reduced paralytic cases to a low level. During that time, surveillance was set up in large cities by testing samples from the sewage system for WPV. Some cities without paralytic cases found WPV in their sewage, but the areas where paralytic cases appeared were almost all in regions lacking large sewage systems; in these areas, people defecate in open fields and there are few latrines. Elimination in these areas required very intensive vaccination as well as careful identification of migrant populations that might be missed by vaccination campaigns. Sanitation improvements were not investigated as a policy to improve polio eradication. If such improvements were pursued, the results of the crude system analysis indicate that eradication could be made less fragile (Mayer, Eisenberg et al. 2013).

Fitting models to data from endemic periods when not much is changing often fails to elucidate transmission dynamics in the populations modeled because endemic data cannot identify model parameters. Identifiability is lost because highly diverse models can give the same endemic incidence at parameter values that generate very different patterns during periods of changing vaccination. When the data come from periods when the system was markedly knocked off equilibrium and since bounced back, just as described for India, the data are much more likely to identify model parameters from available data. Thus, India, with its large population and intensive control and surveillance efforts, could provide estimates for immunity waning parameters. Models incorporating these parameter estimates could then contribute to choosing between

whatever policy options are the focus of analysis. Examples are presented in the following sections.

Inferring large non-paralytic polio outbreak potential

While most health officials believe it is unlikely that polio infections could be persisting in India without paralytic cases, the theoretical case for that belief is weak. Of particular concern is the potential for new occult introductions from Pakistan or Africa; while immunity may be strong in young children, it may have waned in adults since WPV circulation was stopped. Because the places in India where polio persisted the longest have very high transmission potential, it might be easier in those places to surpass the "reinfection threshold" (Gomes, White et al. 2005). The reinfection threshold determines when WPV transmission can be sustained by individuals who have previously acquired immunity from WPV or OPV infection. On the other hand, more OPV circulates in these areas after vaccination campaigns. Thus, repeated OPV infections transmitted from vaccinated children might keep waning of immunity from causing these areas to pass the reinfection threshold. It could be that the biggest risk of WPV circulation in the absence of paralysis is in areas with good vaccination levels but intermediate potential to transmit OPV. Transmission potential that is too low would not only fail to spread OPV but also fail to spread WPV. What populations are most likely to sustain WPV circulation as a function of vaccination levels is the kind of question where modeling can improve both intuitions and policy decisions. Indeed, relevant modeling insights have recently been published (Mayer, Eisenberg et al. 2013).

To improve intuitions on this issue, simple models could be used where model behavior is easier to explain. Then, one would observe and explain infection patterns as the values of parameters and the initial settings of variables are varied in the model. If a complex model is used where such explanations are difficult to verify, then neither the model system under investigation nor the real world are understood. Once the behavior of a simple model is explained, it is easier to explain the behavior of a model that adds complexity to that simple model. A simple model might have a homogeneous population where all individuals mix evenly with all others and all individuals of all ages have the same risk of dying and the same response to infection. The question we are discussing has to do with first infections versus subsequent infections, because paralysis only arises from first infections. Thus, the model must distinguish first from subsequent infections.

Even in the simplest transmission models, it can be difficult to predict how model behavior will change as parameters and variables change. When a prediction is made and then, upon running the model, the prediction is wrong, one can gain new understanding. This understanding might come from a process of hypothesizing what explains model behavior and testing those hypotheses by setting up special conditions

in the model. Or it might be gained by examining model behavior in fine detail to discover what leads to the observed behavior. Modelers should sharpen their intuitions by examining simpler models in this way before pursuing answers about the very complex real world.

In the case of polio, the modeler might run simple models that introduce vaccination programs to eventually eradicate transmission. Then WPV could be introduced once again into the population to examine the ratio of first WPV infections to reinfections. Using the methodology in the last paragraph, insight would be gained into what might cause a high ratio of infections in previously immune individuals in comparison to infections in individuals who have never had an OPV or WPV infection.

Simple models that help develop intuitions may behave quite differently compared to the far more complex real world. The next step in pursuing models that can inform policy is to think of all of the aspects of the real world that would have some chance of changing transmission patterns from those in the simple model. Each of those changes should be explored by using models that add them one at a time and retain them only if they do make a difference. This gets us back to the crucial step one in the Figure 2 flow chart.

Settling on inferences to be made through modeling

Suppose that officials in India or GPEI want to decide whether to set up a surveillance system for poliovirus infection that goes beyond sewage system testing. They might be a little skeptical about the value of this step compared to other investments of time and public health resources. Furthermore, suppose that modelers familiar with poliovirus transmission modeling are available to collaborate with these officials to determine what surveillance methods are worthwhile to pursue. Given this scenario, the first step is to set up meetings to decide on specific inferences about specific control options that will be pursued. This initial meeting should include a broad discussion about how policy makers and modelers view this issue in addition to focusing on the control options and inference statements that will influence the choice of those control actions.

To help clarify the cultural dynamics that are likely to dominate meetings on objectives between policy makers and modelers, we now turn to possible policy maker perspectives and modeler perspectives on what needs to be modeled. We go into considerable detail as to how these will affect the process of choosing inferences to be pursued with modeling because the ability of models to serve public health is so dependent upon this dialogue that leads to the choice of inferences.

Policy maker perspectives

There are several options policymakers may choose for polio surveillance. One option is an active guidance system that continuously updates how non-paralytic infection

surveillance is focused as new paralytic cases are diagnosed and non-paralytic infections are detected. This option follows the long tradition of the polio eradication initiative of focusing control on wherever problems are detected.. Another option is to focus on where rarer but more severe transmission problems might arise. WPV transmission in areas with better sanitation and hygiene might be less likely to experience outbreaks. If immunity has waned significantly in adults in these areas, however, the resulting outbreaks may be larger. Direction of surveillance efforts under this option is dependent upon model based output that can specify the chances of large outbreaks. Recall that an AB model is required for such inferences. Another option policy makers might choose is not to institute new surveillance of non-paralytic infection until it is observed that apparent eradication based on paralytic polio surveillance led to a false determination of eradication. In this case, modelers might bring up the chances that not adding new non-paralytic case surveillance systems might lead to such widespread infection before an outbreak is detected and control of that outbreak might be exceedingly expensive. The step 1 choice might then be to seek inferences about the risks to ultimately successful polio eradication intrinsic to proceeding with only a paralytic poliomyelitis surveillance system.

Another possible policy maker decision might be that any surveillance beyond sewage testing should focus on populations where the last paralytic cases occurred. In this case, modelers might bring up dynamics issues about OPV transmission and boosting that could alter second infection transmission potential. Policy makers might then be more interested in determining how past frequency of paralytic cases is related to the potential for undetected circulation of WPV after initial elimination of WPV transmission.

A third possibility is that testing diarrhea cases in young children is the surveillance that would be most reasonable, as it would have other benefits to the patient in addition to polio eradication benefits. In this case, modelers might bring up the characteristics of symptomatic patients who are good sentinels for occult polio transmission. That might lead to the pursuit of inferences about whether older individuals with greater chances of waned immunity should be the focus of surveillance.

Whatever policy makers decide, these possibilities need to be discussed when meeting with modelers and addressed in the inferences the modelers pursue in order to ensure that modeling affects policy. The different classes of inferences suggested here would require very different modeling approaches. If the approach chosen doesn't address policy maker defined issues determined by their concepts, they are more likely to dismiss the model based inferences as irrelevant.

Modeler perspectives

We can also look at possible views of non-paralytic infection surveillance from the modeler's perspective. Modelers are likely to be academics who want to discover broad general scientific principles that advance the development of new methods and new theories. They might be interested in whether new theories and description of B cell dynamics (Tarlinton and Good-Jacobson 2013) can help predict waning patterns after infection. Thus, they might be particularly focused on estimating waning parameter values through the modeling they pursue. In particular, they might want to test whether the assumptions behind waning patterns in recent polio models are correct (Duintjer Tebbens, Pallansch et al. 2013; Duintjer Tebbens, Pallansch et al. 2013; Mayer, Eisenberg et al. 2013; Thompson 2013; Thompson, Pallansch et al. 2013; Thompson, Pallansch et al. 2013). One assumption in those models is that maximal immunity is achieved after each live virus polio infection, whether a first or a subsequent infection or whether an OPV or a WPV infection. Violation of that assumption might affect whether vaccinations to control outbreaks in the end stage of polio eradication, especially non-paralytic outbreaks, should be directed to age groups other than those targeted by traditional special immunization activities. Pursuing these questions might be a more natural part of pursuing policy maker questions related to the risks from not instituting any new non-paralytic poliovirus surveillance.

The modelers might also have done previous work on how the synchrony of infections across geographic areas offers opportunities to elucidate fundamental parameters of transmission. This approach has been particularly productive for pertussis (Rohani, Zhong et al. 2010). For polio, examining synchrony across areas that eliminated poliomyelitis early and those that only did so at the end could greatly increase the power to fit parameter values. To further advance the methodology they have developed, the modelers may be more strongly drawn to addressing questions related to what geographic areas should be targeted for non-paralytic infection detection. If, in contrast, the modelers have been primarily interested in the how the natural history of infection affects transmission dynamics, they might be more strongly drawn to the question of what class of patients should be the target of surveillance.

Rather than engaging in a tug of war between policy makers' and modelers' interests, the modelers must accommodate the policy makers' interests. The choice of inference to be pursued must be the choice that will make the most difference to the populations on which the policy makers focus. There will be plenty of reason for the modelers to pursue their own special interests as they go through inference robustness or identifiability loops in Figure 2.

Pursuing inference robustness and identifiability loops

Modeling can be pursued to determine whether any non-paralytic polio surveillance beyond sewage testing is indicated. For simplicity of exposition, we dichotomize our outcome to say that current surveillance is either sufficient or it is not. Current surveillance consists of AFP surveillance and WPV detection in sewage systems. Suppose step 1 in Figure 2 settles on the following criterion; note that this criterion requires the use of an AB model. If a model generates only outbreaks that are detected and controlled before a total of 2,000 WPV infections occur in 99.5% of runs, then the decision is that current surveillance is sufficient. To answer this question, a model must have a variety of built-in control options that can be instituted given different levels of paralytic and non-paralytic infections in areas that correspond to the populations on which the policy makers focus. Also note that the key policy makers must be involved in setting such a criterion.

For step 2 in Figure 2, building even the simplest possible model in either a DE or an AB framework will entail considerable work, but since this question focuses on the chances of a particularly bad outcome, only an AB model will work. However, to find out what model aspects do or do not need to be included, the initial inference robustness and identifiability loops should be conducted using DE models. For these initial DE explorations, a different criterion will have to be used; the DE model can use the size criterion, but it cannot use the frequency (99.5%) criterion.

Let's say that the first pass at examining this question uses the DE model published recently by Duintjer-Tebbens et al (Duintjer Tebbens, Pallansch et al. 2013; Duintjer Tebbens, Pallansch et al. 2013) with modifications that allow for introduced outbreaks and outbreak control measures. This model is shown in Figure 3. It adds many dimensions to the compartmental flows seen in Figure 1. It divides the natural history of infection and immunity into categories related in oropharyngeal infection and intestinal infection. It models the reversion of OPV back towards WPV and thus can address the emergence of circulating vaccine derived polioviruses (cVDPV). One reason for doing this is the persistent problem of type 2 cVDPV in Nigeria. These model elaborations are captured in flow diagrams (Duintjer Tebbens, Pallansch et al. 2013) as seen in Figure 3.

These extensive model elaborations add further realism to the model. They enable it to address issues like cVDPV dynamics that could not be addressed with simpler models. However, they have details that might not be needed so we might begin by dropping out model elements we think might not be needed. We can add them back during inference robustness assessment analyses. Even in their complex form, however, they leave the model with many highly unrealistic simplifying assumptions that would deserve evaluation through an inference robustness assessment if the model were directed

toward answering any of the three classes of specific policy inferences discussed earlier. In particular, the assumption that the population is homogeneous with regard to exposure to people or contaminated environments is both highly unrealistic and is likely to affect the inferences sought. If a concern arises that special risk populations may be those most capable of circulating non-paralytic WPV, the elaboration of risk or geographic groups would be needed for IRA and for addressing basic policy inferences like where to focus non-paralytic WPV surveillance.

In step 3 of Figure 2 the model space is constrained by the same data used in the original publication (Duintjer Tebbens, Pallansch et al. 2013), which are very general with overall vaccination and infection rates across broad populations. Suppose that constraining the parameter space so the model outcomes fit with this observed data leads to a model where no large, uncontrollable outbreaks occur anywhere in this parameter space. The decision process coming out of step 3 in this case would lead to 'the inference is the same across parameter space'—current surveillance is sufficient to avoid catastrophic eradication failure. For this example we suppose that it is not the case that uncertainty in immune waning parameters leads to different inferences in different parts of feasible parameter space.

One should still question the robustness of this inference from this 'simple' model because the model unrealistically assumes no variation in transmission risk between individuals and all individuals mix homogeneously. Geographic and socioeconomic variation in sanitation and hygiene conditions is inconsistent with this assumption. The potential for large outbreaks in this model could be less than in a model where sanitation varies by block or district. Before feeling confident in the inference that the current surveillance system is sufficient, modelers should relax the unrealistic simplifying assumptions that sanitation and mixing are homogeneous.

Relaxing simplifying assumptions is best pursued using DE models, and there are two reasons why a DE framework for this IRA should be used before proceeding to the AB framework. One is the time and effort involved. The other is the potential to gain insights into the mechanisms by which a complex model generates different outcomes. To do so, modelers would add realistic details to the model little by little while exploring how those details generate effects on infection patterns. By exploring explanatory hypotheses of why their model generates different results and by examining in detail the dynamics that generate the observed results, modelers can come to understand what model characteristics explain different model behaviors.

In the inference robustness step 5 from Figure 2, the modelers might add sanitation and contact pattern variation by geography and socioeconomic level. The parameter space

for such variation might originally be quite broad. There is a high chance that in some of this parameter space catastrophic epidemics that threaten eradication after reintroduction of WPV are observed, meaning that special non-paralytic WPV surveillance systems are needed. In other words, the inference of low risk made using the simplest model would have been found to not be robust to realistically relaxing the unrealistic homogeneity assumptions. It also means that this latest iteration of step 4 in Figure 2 leads to the need for a new identifiability analysis loop—step 6 in Figure 2.

That lack of robustness on its own might lead to the decision to institute new non-paralytic WPV surveillance. However, it might not lead to such a policy if policy makers believe that the parameter space that leads to catastrophic outcomes is unlikely to exist in reality. In that case the lack of inference robustness could just lead to an identifiability analysis. One possible identifiability analysis would examine the effects of fitting model parameters to new data on geographical sanitation variation by district and to the original Indian data (Duintjer Tebbens, Pallansch et al. 2013). If it is expensive or politically difficult to get these data, a formal identifiability analysis would show the value of getting them and that the data could make a big difference to the inference in a cost-effective manner. That would lead to data collection and then to data fitting in a new step 3 of our iterative process.

If, in this new step 3, the parameter space is constrained to a region where the current surveillance system results in large outbreaks, then there would be strong reason to implement a new surveillance system for non-paralytic infections. Even if part of the parameter space does not produce large outbreaks, new insights from the modelers into transmission dynamics might convince policy makers that they should pursue new surveillance approaches. Performing an AB model analysis would help in this evaluation.

But, even with the new sanitation data, there would still be uncertainty, and non-paralytic infection detection surveillance could be quite expensive. Additional types of data might be collected to resolve this challenge. One particularly powerful type of data is genetic sequence data available from all WPV isolated in India for several years before elimination was achieved. Newly developed phylodynamic methods (Volz 2012; Volz, Ionides et al. 2013) could constrain parameter space enough to make the inference about the need for non-paralytic infection surveillance identifiable; these methods can use DE models.

Figure 3 - (Figure 1 from (Duintjer Tebbens, Pallansch et al. 2013))

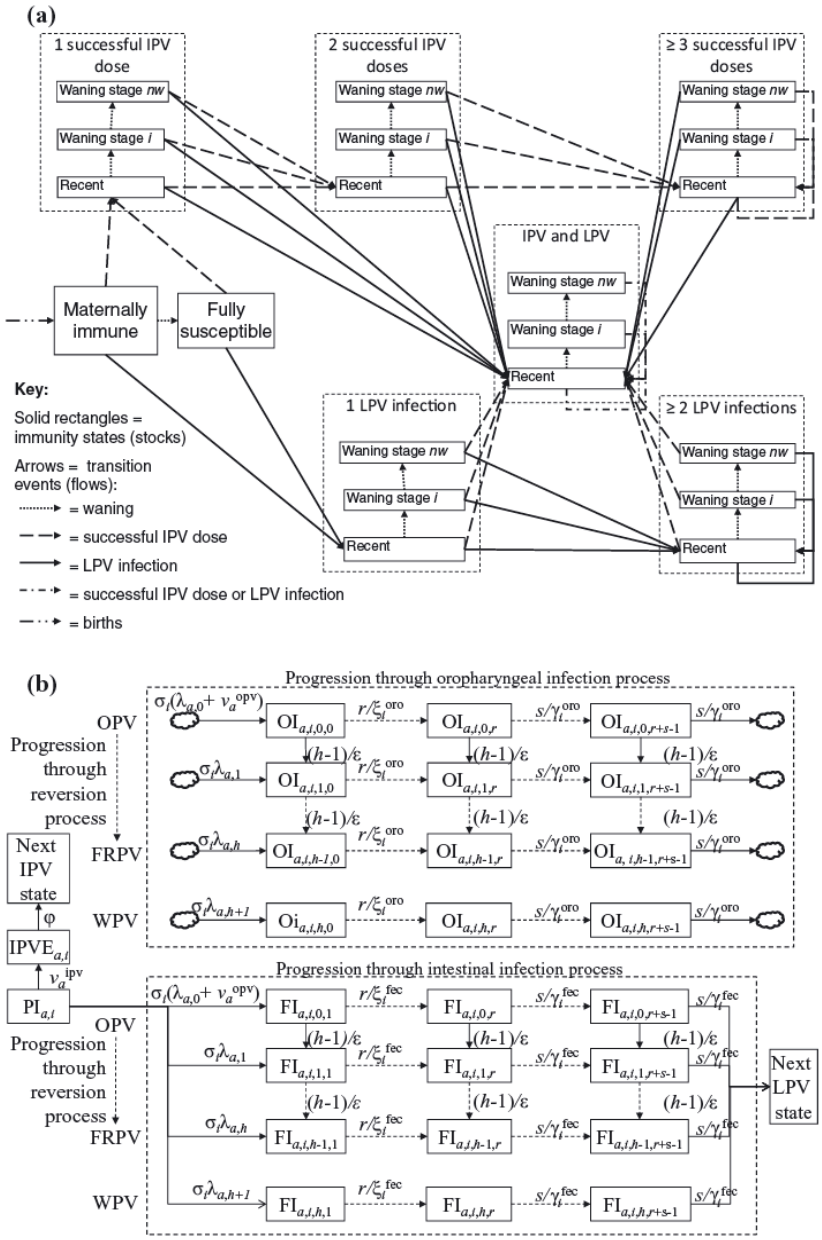


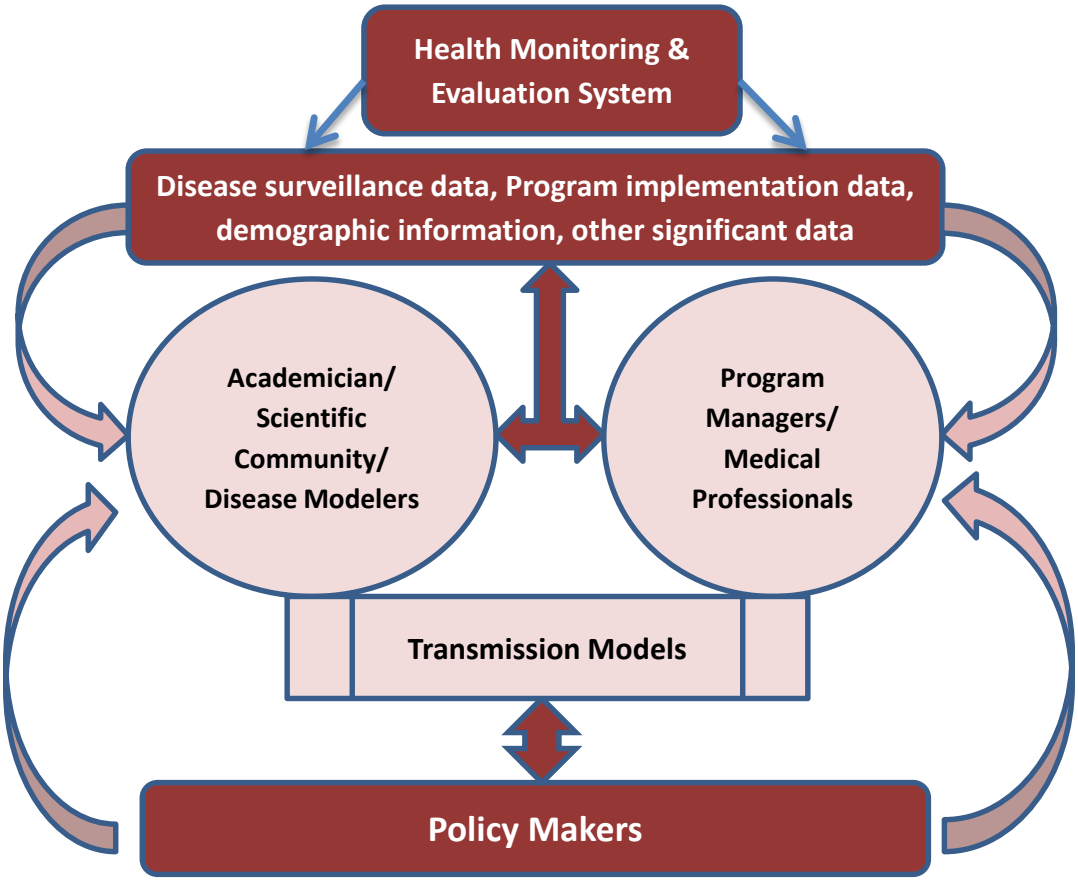
Fig. 1. Overview of the model structure.
(a) Flows between immunity states as a result of epidemiological events.
(b) Infection and reversion processes.
Acronyms: FRPV = fully-reverted poliovirus; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; WPV = wild poliovirus
Symbols:
$PI_{a,i}$ = partially infectible in age group a and immunity state i
$IPVE_{a,i}$ = IPV-exposed individual from immunity state i and age group a.
$FI_{a,i,j,k}$ ($OI_{a,i,j,k}$) = individual in age group a from immunity state i, infected with virus strain j and in fecal (oropharyngeal) infection stage k
$\lambda_{a,j}$ = force-of–infection to age group a for virus strain j
ν_a^{ipv} (ν_a^{opv}) = force-of-IPV(OPV)-vaccination to age group a as a result of routine and supplementary immunization
σ_i = relative susceptibility for immunity state i
ξ_i^{fec} (ξ_i^{oro}) = average duration of the fecal (oropharyngeal) latent period for immunity state i
γ_i^{fec} (γ_i^{oro}) = average duration of the fecal (oropharyngeal) infectious period for immunity state i
φ = IPV immunity delay
h = number of reversion stages
r = number of latent stages
s = number of infectious stages

Relationships between surveillance workers, policymakers, and modelers

One reason for describing this analytic path as elaborately as we have is to emphasize how important it is to specify the inference that will influence policy. If all of this work had been done but it turns out that policy makers would have always felt some pressure to set up surveillance for the detection of non-paralytic infection, the control decisions would not be much advanced by all this analysis. In that situation, the most influential and effective analysis would have been to specify in what populations or in what type of patients surveillance should take place. It would probably take an equal amount of modeling work to build the models needed for this inference as for the more general

inference, and proceeding directly to this inference could have saved a lot of time and effort.

Figure 4 -- Personnel relationships for integrating transmission modeling into surveillance systems



Another reason for presenting the example in detail was to provide background about how important the structure of relationships between different classes of individuals is for achieving the goal of making surveillance inform effective prevention efforts. In Figure 4 we revisit concepts regarding such relationships presented elsewhere in this book. The relationships between the groups in the central ellipses are central to integrating transmission models into surveillance systems, but the base of relationships that make such a system serve public health is supported and balanced by the inputs from policy makers. Policy makers can tip the system in one direction or the other. Without their input and collaboration, the system fails to serve public health. Policymakers must heavily influence the dialogue that determines what directions the system tips toward, and both modelers and others involved with public health surveillance must continually seek direction from policy makers.

Epilogue

We have presented an idealized vision of how a team of public health professionals and modelers can incorporate causal system modeling into disease control. From a science point of view, this vision is simply a scientific process that pushes theory about the way the real world is closer and closer to the complexity that characterizes the biology, ecology, and sociology that determine the health of populations. From a public health point of view, it is a path for continuous quality improvement in using public health data to guide disease prevention and control activities. From either perspective, the key to success is teamwork and good communication between individuals who might have different visions and goals.

Of course, the real world will not be so idealized. But there is no need to abandon this vision because an academic does not see public health practice as part of his or her research agenda or because a public health administrator sees this process as too difficult and theoretical to achieve within the bureaucratic agency structure. Practical progress may well involve initial pursuit of separate academic and public health practice goals while edging slowly towards a fuller integration of public health science and practice.

Job functions for an infection transmission modeler

1. Work with policy makers to identify reasonable policy options to investigate and inferences about potential program effects that could inform the choice of policies.
2. Identify the simplest model that presents a reasonable starting point for pursuing the inferences in function 1.
3. Implement model analyses or simulations that characterize infection transmission in a manner that achieves the policy inferences pursued.
4. Find available data or design systems that generate new data that can constrain parameter ranges in models intended to inform policy or that describe system behavior to which model parameters can be fit.
5. Use recently developed filtering or other fitting approaches to estimate the range of model parameters consistent with available data.
6. Analyze model behavior across the range of parameters consistent with available data to see which policy related inferences would be made in different regions of the parameter space that is consistent with available data.
7. Perform identifiability analyses and value of information analyses that indicate how much could be gained by fitting models to new sources of data.
8. Identify simplifying assumptions for the model in function 2 which if realistically relaxed could invalidate the inferences pursued.

9. Keep policy makers continuously informed with regard to how the analyses the modeler has performed might influence current policies or new policies that have been discussed.

Competencies for an infection transmission modeler performing policy analyses

1. Ability to formulate deterministic differential equation models and stochastic agent based models or combined models with both deterministic and stochastic behaviors that generate outcomes of importance to public health.
2. Ability to organize available data into formats that allow for determining the parameter sets in models that are consistent with available data.
3. Ability to relate model formulations and outputs to policy analysis objectives.
4. Ability to communicate with policy makers in a manner that leads to agreement on inferences about policy options that can be informed by model analyses and model fitting to data.
5. Ability to perform identifiability analyses and/or value of information analyses for determining what new data would be most useful for making specific policy decisions.

Job functions for Program Managers related to Infection Transmission Modelling

1. Coordinate discussions between and inputs from modelers, epidemiologists, and policy makers to establish goals for the modeling that will impact disease control.
2. Identify issues and challenges that could be addressed by modeling by analyzing population patterns in surveillance data.
3. Ensure the availability and quality of data required for constructing and analyzing models.
4. Ensure that the modeling activities adequately protect personal information privacy.
5. Discuss modelling inferences with policy makers and get their input regarding what analyses would further inform their policy decisions.
6. Ensure that modelers and policy makers have sufficient conceptual clarity regarding the inferences to be pursued through model analyses so that miscommunications can be avoided.

Work Competencies for Program Managers related to Infection Transmission Modelling

1. Knowledge and experience related to disease epidemiology and the effects of physical, social, economic, political, and cultural factors influencing epidemiologic patterns of disease.
2. Written and oral communication skills related to epidemiological sciences within the context of public health.

3. Knowledge of public health programs and current surveillance system at different levels.
4. Ability to Manage Information Systems related to disease surveillance.
5. Ability to interpret statistics tables and graphs generated by model analyses.

Key chapter points

1. Transmission models are built on a base of causal theory about how infection is transmitted and who transmits to whom and specifies needed variables like the number of individuals in different exposure or disease categories and needed parameters like the probability of transmission given contact between individuals or exposure to a source of pathogen.
2. Differential equation (DE) models use continuous population segments. They are deterministic and easier to analyze by non-experts using modern software.
3. Agent-based (AB) models are stochastic in that they parameterize the chances of different events occurring. They can relax unrealistic assumptions of large population sizes and about contact patterns that are intrinsic to DE models. Unlike DE models, they can be analyzed to determine the chances of different outcomes given a disease control decision.
4. Transmission modeling differs from data mining or traditional epidemiology analyses: mechanistic causal theory defines the variables used; analysis begins by examining model behavior to understand how variables and parameters generate model behavior; a formal process is used to determine what essential knowledge affects a decision; and causal inferences can be validated by inference robustness assessment.
5. Transmission models increase policy makers' understanding of what processes generate transmission levels and how policies affect those processes. Models also use surveillance data to estimate parameter values and infer what control actions are favored, and they estimate the values of variables.
6. Inferences about control actions can be validated by determining whether an inference is robust to realistic relaxation of simplifying model assumptions.
7. The key step in using transmission models to inform public health decisions is to get policy makers, surveillance personnel, and modelers to agree on what inferences should be pursued using the models.

Discussion Questions:

1. Compare and contrast DE and AB models.
2. Describe what would influence the choice of either a DE model or an AB model for making a final determination of the costs and benefits of establishing a non-paralytic poliovirus infection surveillance system that tests specific patients receiving care for illnesses.

3. What makes DE models a good choice for initial analyses to make inferences about infection control decisions? What would lead to using an AB model? When would an AB model not be necessary and when would it be essential?
4. How can transmission models improve our knowledge and understanding of disease transmission?
5. What are the processes through which transmission modeling could change the focus of surveillance for polio eradication from paralytic infections to non-paralytic infections?
6. Why do we want transmission models to be as simple as possible but no simpler? Explain the criteria to determine how simple a model is, what it means to be as simple as possible, and why a simpler model can have a greater effect on public health actions.
7. What is the advantage of having a routine process for analyzing measles surveillance data with a transmission model every time a new summary of results from the surveillance system is prepared? What knowledge could be generated by such an analysis that would not be generated by routine descriptions of surveillance data? How could this knowledge inform policy?
8. What are advantages and difficulties of having policy makers run some analyses? What type of model analyses would be most important for policy makers to perform?
9. How would the analyses performed by surveillance personnel differ from analyses performed by academic modelers?
10. Describe a process to get policy makers, surveillance system personnel, and academic modelers to collaborate to make surveillance data maximally inform policy decisions. Be specific about who should take the lead on what kind of activities and what it would take for those activities to best inform policy choices.

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