Epidemics 10 (2015) 11–15

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Seven challenges in modeling vaccine preventable diseases

C.J.E. Metcalf[a,*], V. Andreasen[b], O.N. Bjørnstad[c], K. Eames[d], W.J. Edmunds[d], S. Funk[d], T.D. Hollingsworth[e,f,g], J. Lessler[h], C. Viboud[i], B.T. Grenfell[a,i]

[a] Department of Ecology and Evolutionary Biology and the Woodrow Wilson School, Princeton University, Princeton, NJ, USA
[b] Department of Science, Systems and Models, Universitetsvej 1, 27.1, DK-4000 Roskilde, Denmark
[c] Centre for Infectious Disease Dynamics, the Pennsylvania State University, State College, PA, USA
[d] Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK
[e] Warwick Mathematics Institute, University of Warwick, Coventry CV4 7AL, UK
[f] School of Life Sciences, University of Warwick, Coventry CV4 7AL, UK
[g] Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK
[h] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[i] Division of Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 19 June 2014
Accepted 18 August 2014
Available online 27 August 2014

Keywords:
Vaccination
Modeling
Coverage
Immunity
Elimination

ABSTRACT

Vaccination has been one of the most successful public health measures since the introduction of basic sanitation. Substantial mortality and morbidity reductions have been achieved via vaccination against many infections, and the list of diseases that are potentially controllable by vaccines is growing steadily. We introduce key challenges for modeling in shaping our understanding and guiding policy decisions related to vaccine preventable diseases.

Introduction

Mathematical modeling has made key contributions to vaccination program design, from introducing the concept of herd immunity thresholds to predicting changes in post-vaccination epidemiology (such as increasing age at infection (Knox, 1980) and increasing inter-epidemic intervals). Nonlinearities in transmission dynamics mean that intuition may miss important aspects of the impact of vaccination programs that mechanistic models can reveal. Models also allow investigation of the potential impact of uncertainties in our understanding of contact processes, vaccine protection and future uptake. Consequently, models are becoming embedded in the decision-making process for global vaccine use.

Many key insights have been derived from simple models, particularly for those disease and vaccines that generate life-long sterilizing immunity (e.g., measles). However, these infections represent one end of a long spectrum. Most disease systems are much more complex, with vaccines being imperfectly effective in a variety of ways (Halloran et al., 2010). The same basic sets of questions pertain to these infections (e.g., quantifying spatial and social heterogeneity in susceptibility); and corresponding modeling challenges arise. Further, the development of new vaccines for infections with more complex dynamics and less complete immune action, combined with increasingly detailed policy questions regarding the implementation and effectiveness of vaccination programs, raises a number of new challenges in deploying dynamic models to support program design and evaluation. Here, we first outline challenges emerging at the population level (vaccine distribution and logistics, Challenges 1–3) and then detail some of the challenges that emerge in better describing the underlying biology of vaccination (Challenges 4–7).

1. Quantifying spatial and social heterogeneity in natural and vaccine-induced immunity

Immunological heterogeneity within a population is a major public health challenge, leaving pockets of people 'silently' unprotected, and hampering elimination efforts. Heterogeneity may result from differential uptake of vaccination, or from differences

* Corresponding author. Tel.: +1 609 258 3845.
E-mail addresses: cmetcalf@princeton.edu, charlotte.metcalf@zoo.ox.ac.uk (C.J.E. Metcalf).

http://dx.doi.org/10.1016/j.epidem.2014.08.004

in prior history of infection, or in underlying immunocompetence. Under-immunized groups may be vulnerable to outbreaks, even if they are part of a population in which, on average, vaccination coverage is high. The most commonly used coverage estimate, the number of doses delivered divided by target population size (Burton et al., 2009), can mask worrying levels of local heterogeneity.

Heterogeneity leading to low uptake can be a result of poor access to healthcare, recent migration and/or displaced populations, as well as cultural or religious attitudes about vaccination. Developing models that use existing data sources to quantify spatial and social heterogeneity in vaccine coverage, and hence immunity, is a major challenge. It is important to understand both the size (Lessler et al., 2011) and the identity of poorly served groups, and to understand why and where pockets of unvaccinated individuals arise dynamically. Models that can predict changes in vaccine demand over time, especially those linked to the spread of either complacency toward the need for vaccination, or suspicions of vaccine side-effects (Funk et al., 2010) will have immediate applications for public health policy (e.g. measles in Europe).

A related challenge is developing models that quantify the importance and dynamical consequences of social vs. spatial heterogeneity. For example, if vaccine refusers (i.e., individuals who actively reject vaccination when offered, with motivations ranging from complacency to conviction of the harmful effects of vaccination for their children; see also Funk et al., 2014) are clustered in space, the consequences for transmission and control are different than if they are spatially dispersed but socially connected. There is a further distinction between socially connected people who regularly meet (e.g., in schools) and those who do not (e.g. are connected through social media, etc. (Eames, 2009)). These distinctions will affect the best strategy for increasing vaccine uptake (e.g., local campaigns within communities vs. social-network driven campaigns). There is also a need to understand under what conditions such clusters become at risk for epidemic spread, and the risk they pose to surrounding groups where vaccine coverage may be high. As the degree of social and spatial heterogeneities increases, differential equation model-based approaches become increasingly unwieldy, and alternative methods may be a fruitful direction for research. While there has been much development recently in models that explicitly take population heterogeneities into account (Danon et al., 2011), it remains unclear how these relate to issues of vaccine coverage and resulting outbreak patterns. A related set of challenges concerns development of methods that can leverage the vast quantities of digital data relating to social media, and engage with all the associated limitations of these types of data (Salathé and Khandelwal, 2011).

Increasingly, serology is recognized as an important element of the public health evaluation of outbreaks and vaccination coverage (Wu, 2011; Van Kerkhove, 2010). Availability of serological data sources may enable improved mapping of susceptibility, but since an individual may be seropositive either as a result of having been vaccinated, or from having been infected (so seropositivity could be a marker of success or failure of a vaccination program) models will be needed to interpret these surveys. Serological markers also vary in their interpretability across diseases. Enhanced modeling of such data would improve both 'nowcasting' and 'forecasting' of immunity in the population. Dynamical models could also explore how to optimize reactive vaccination strategies triggered by such serological information.

2. Logistics and economics of vaccine delivery

High penetration of vaccination throughout a country is a major public health challenge, and is essential to an effective vaccination program, particularly if elimination is the goal (see also Klepac et al., in preparation). Models of targeted program delivery, the delivery system itself, the economics of, and behavioral responses to vaccination (Funk et al., 2014; Brito et al., 1991) have the potential to identify bottle necks and solutions. When resources are limited, a vaccination program must not only be effective, but also carried out economically.

Emergency situations are one key context where models can support vaccination delivery programs. For example, effective deployment of vaccines in emergency contexts characterized by limited vaccine supply (e.g., cholera) may rest on the relative merits of reactive vaccination vs. mass vaccination of "hotspots". Models may contribute to distinguishing between these two strategies. Since data in fast moving outbreak situations may be available with a lag of several days while the logistics of vaccination deployment may require weeks; models must both rise to the challenge of rapidly responding to the (often partial) data available, and taking into account explicit time-scales of delivery. Even where vaccine supplies are not limiting (i.e., measles, or meningococcal disease rather than cholera), the relative time-scales of delivery and spread of an outbreak through an under-vaccinated group (for measles, see Challenge 1) may mean that the outbreak is likely to extinguish itself before the intervention can take effect. Alternatively, the cost of running the intervention may not be justified given its likely impact. Finally, there is the question of when vaccination efforts can be halted in an outbreak situation (which hinges on the dynamic consequences of vaccination). Models may contribute to evaluating all of these outcomes.

The success of many of the models rests on the availability and quality of data used for parametrization – which in turn, often rests on obtaining the confidence and support of vaccine program managers, or other policy makers. To ensure that decisions are made on the best available data, recommendations need to be communicated and acted upon promptly; furthermore, to retain confidence in the usefulness of the modeling approach in the face of changing outcomes, a key challenge is that of communicating model methodologies and conclusions effectively (see Metcalf et al., in preparation). Even with the full support of key players, data (on both incidence and vaccination coverage) is often incomplete and fraught with uncertainty. The development of models that can address these issues is a very general challenge that emerges across all of the major challenges mentioned here.

A related set of questions that modeling could inform is the design of supply chains and the infrastructure of delivery and decision making (Lee et al., 2012). Models are currently used to *inform* decisions made on cost-effectiveness grounds. Models should also be used to *evaluate* such decisions: how reliable have estimates been? How good are the data – on delivery costs and coverage – that have gone into modeling; can uncertainty be reduced to make models more straightforward to interpret? How can existing programs best collaborate to optimize outcome – e.g. by delivering multiple vaccines at a single visit or enhancing the healthcare infrastructure? These issues are especially pertinent in the context of complexities of transboundary issues and complex funding of international vaccination efforts (Klepac et al., 2011).

3. Quantifying the dynamics at vaccination levels near the critical vaccination threshold

Early modeling work on vaccine-preventable infections was based in contexts where infection was endemic and in which every individual was likely to be exposed to infection. This research generated a detailed understanding of the dynamic interplay between susceptible recruitment, infection and immunity (e.g., Fine and Clarkson, 1986; Grenfell et al., 2001; Bolker and Grenfell, 1995).