Seven challenges in Modelling Vaccine Preventable Diseases

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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 modelling in shaping our understanding and guiding policy decisions related to vaccine preventable diseases.

Introduction
Mathematical modelling 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 [1] and increasing inter-epidemic intervals). Nonlinearities in transmission dynamics mean that intuition may miss important aspects of the impact of vaccination programmes 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 [2]. The same basic sets of questions pertain to these infections (e.g., quantifying spatial and social heterogeneity in susceptibility); and corresponding modelling 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 programmes, 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).

Challenge 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 in prior history of infection, or in underlying immunocompetence. Under-immunised 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 [3], 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 [4] 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 towards the need for vaccination, or suspicions of vaccine side-effects [5] 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 [6]) 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. [7]). 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 [8], 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 [9].

Increasingly, serology is recognized as an important element of the public health evaluation of outbreaks and vaccination coverage [10, 11]. 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 programme) 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.

Challenge 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 [12]). Models of targeted program delivery, the delivery system itself, the economics of, and behavioural responses to vaccination [6, 13] 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 programme 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 modelling approach in the face of changing outcomes, a key challenge is that of communicating model methodologies and conclusions effectively (see [14]). 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 modelling could inform is the design of supply chains and the infrastructure of delivery and decision making [15]. 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 modelling; can uncertainty be reduced to make models more straightforward to interpret? How can existing programmes best collaborate to optimise 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 [16].

Challenge 3: Quantifying the dynamics at vaccination levels near the critical vaccination threshold

Early modelling 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., [17-19]). However, as vaccine coverage reaches higher levels, for an increasing number of infections, key assumptions underlying these models no longer hold.

As vaccination levels approach the critical vaccination threshold (the point at which the effective reproduction number, R_E, falls below one), large parts of the population will not have encountered the infection, and patterns of immunity will be almost entirely determined by past and present vaccination programme. As dynamic patterns change from endemicity to outbreaks of varying size [20], infection shifts into (i) older age groups and (ii) susceptible pockets in hard-to-reach populations (those with poor access to health care, displaced populations,

migrants, areas where vaccinators may be at risk), and populations who chose to be hard to reach (refusers; see challenge 2). This opens the challenge of developing models that take into account changes in contact patterns of those infected. It has been shown that children have more contacts than adults do [21]. As the burden of infection moves into older age groups, does this mean that herd immunity is easier to achieve? Since infection will be focused in particular clusters of susceptibles, should we reconsider the scale at which we must measure vaccination coverage: from a country to a city, borough, or social group? The relevant patterns of contact may change from mixing between age groups to interactions between specific social groups in different locations. If susceptible clusters are connected on the scale of a country or continent, can infection persist in these clusters even if overall levels of vaccination are above the critical vaccination threshold? The appropriate modelling approach may no longer be the familiar spatially-homogeneous mass-action model, but a spatially-extended metapopulation with each patch representing a particular under-vaccinated community [22]. Answering these questions may require careful reconsideration of concepts such as that of Critical Community Size [23].

As natural disease circulation ends, any immune boosting due to natural exposure is likely to end. For many vaccines it is unclear if vaccine induced immunity will be maintained for the same length of time when disease does not circulate as when it does. If we can fully understand the immunodynamics (see Challenge 4), models can play a critical role in predicting how population immunity will change once disease circulation stops, and if changes in vaccination policy, for example additional booster doses at older age, may be needed to prevent re-emergence or protect newly vulnerable populations (e.g., the elderly). How to best address the resulting problem of scale (e.g. linking within-host immune processes with population effects such as herd immunity) remains an open and important question.

Challenge 4: Model immunodynamics – when are protective vaccines possible, and how can we measure protection?

Vaccines can be imperfect in a variety of ways - they may work in some people and not others (referred to as vaccine 'take'), they may reduce susceptibility by some amount in all individuals ('degree') and protection may wane over time ('duration') [24]. The success of vaccines at an individual level is determined by the detailed dynamics of the immune system and the kinetics underlying maintenance of immune memory. During the last decade, experimental immunology has provided an enormous richness of detail of the cell biology and proteomics responsible for the cascade of events associated with clearance of infection (e.g. [25, 26]). A key future challenge is to develop models that can address wildly different time scales associated with such clearance (cytokines are up-down regulated in minutes or hours while immune memory is lifelong or decays over decades) and capture redundancies within the immune system (e.g. [27]). Intermediate models may be part of the solution, clarifying the relative roles of cell-mediated versus humoral responses, and explaining the emergent

simplicity of pathogen persistence or clearance in the face of the bewildering underlying biological complexity.

The duration of protection is related to the population dynamics and homeostatic regulation of memory B and T cells. Mathematical theory has contributed importantly to this area, clarifying the kinetics of memory cell proliferation, their antigen-dependence versus –independence of maintenance and the overall longevity of memory (for a review see [28]). However, many obvious questions remain, both at the scale of the 'autecology' of specific memory lineages, and the 'community ecology' of the whole memory assemblage. Developing models of the subtleties of these dynamics is important for the success of the next generation of vaccines that propose to use, say, adeno- or herpes virus vectors to produce T cell vaccines [29].

Carefully calibrated immunodynamic models will ultimately touch on a large number of critical immune- and vaccine-related questions such as: what are the causes of and the role of persistent pathogen circulation in the maintenance of herd immunity (e.g. [30])? Can we distinguish fast waning and natural boosting, from slow waning and no boosting? Do such different scenarios produce qualitatively different dynamics and/or serology profiles? What are the immunodynamics responsible for protecting against infection, against disease, and against onward transmission? Designing models of a scale appropriate to answer these questions is a big theoretical challenge.

Challenge 5: Investigate when vaccines are evolution proof and when they are not

From an evolutionary perspective, the existence of pathogens for which immunity (natural or vaccinal) is life-long are surprising, since selection pressures favouring escape mutants will be vast (see [31]). Modeling infectious disease systems characterized by continuous immune escape from natural, and vaccine derived, immunity (e.g., influenza, Marek's disease [32]) may provide insights into "evolution proofing" medical interventions. Some initial work points to interesting long-term consequences of even partially effective vaccines against such pathogens, including reduction of transmission rates, improvement of herd immunity, and potentially slowing down of antigenic drift [33]. Conversely, in systems where between-strain competition is important, models indicate that vaccines with broad targets may not always be better than more specific ones [34]. A large part of the challenge is identifying where modeling could supply insight – for example, two pathways seem possible for influenza: T-cell immunity, or antibodies to conserved regions on the stalk protein. How should this be modeled? An interesting direction might be the development of a framework similar to the pharmaco-kinetic / pharmaco-dynamic model used for drugs; and then extending this to encompass selection pressures, and some of the detail of underlying mechanism. Further extending this to assess the role of population level processes such as age-structure [35] provides additional challenges.

We currently have no tools to evaluate signatures that might reflect vaccine escape, inform us about how soon we might expect to see vaccine escape, what age groups might be affected, and how vaccine escape might be distinguished from inefficacious vaccines. In the simplest analysis, vaccine escape might be thought of as a gradual process, occurring at a rate proportional to the cumulative number of cases, and therefore likely to make its effects known later in any given outbreak. However, effects of stochasticity and heterogeneity are likely to make such a distinction difficult to observe in practice, and models will be required to guide surveillance.

Challenge 6: Determine the implications of radically new vaccine technologies

Recent technological advances have led to the development of vaccines whose effects do not mimic natural immunity, and where modelling might make considerable contributions to anticipating public health outcomes. These include vaccines against bacterial pathogens involving multiple serotypes associated with complex carriage and disease states, such as meningococcal and pneumococcal vaccines (see challenge 7), and broad-based viral vaccines; universal influenza vaccines; multivalent dengue and human papilloma virus (HPV) vaccines. A proposed hepatitis C vaccine may not necessarily prevent the initial infection, but may prevent the chronic stages of the disease that eventually leads to cirrhosis or potentially death [36]. This is uncharted territory, as the population-level benefits of such vaccines are unclear, and the population dynamics and acquisition of immunity are typically more complex than in other more traditional vaccine-preventable disease systems.

The poster child for the issue of immune enhancement is dengue. Primary infection with one serotype may predispose for a more severe infection with another serotype (hemorrhagic fever). This has hampered the development of safe dengue vaccines for the last few decades. How immune enhancement may affect the long-term prospects of tetravalent dengue vaccines currently in clinical trials has only begun to be addressed by the modelling community [37-39]. Key challenges remain, including modelling local heterogeneities in serotype distributions and their transmissibility, mostly as a result of paucity of epidemiological and virological data, especially in settings where the epidemiology of dengue is rapidly changing such as South America. In addition, models have to account for the complex and still debated biological mechanisms responsible for immune enhancement, and the lower efficacy of existing vaccines to a subset of serotypes [39].

Challenge 7: Account for the microbial community ecology of vaccination

Increasingly, vaccines are being developed for systems where the community context of focal pathogens is complex. Predicting outcomes in these novel contexts is of clear public health importance and comes with its own set of modelling challenges.

There are two ways in which complex interactions can occur. First, vaccines may induce differential selection pressure on particular strains of the pathogen, thus indirectly affecting pathogen evolution. Vaccine escape strains of pertussis and Marek's disease offer striking examples, but the introduction of multivalent vaccines (that protect against a targeted subset of the strains in a pathogen complex) all have this potential, and can lead to vaccine-induced strain replacement. While the pneumococcal vaccine now includes up to 13 serotypes historically associated with severe infections, it does not fully cover the population of circulating serotypes (estimated at ~100). While invasive pneumococcal disease rates have declined in countries using the vaccine, serotype replacement has occurred in a number of developed countries, with non-vaccine serotypes accounting for an ever larger proportion of carriage and disease [40]. It is challenging to model the long-term benefits of such programs with little information on what makes a serotype pathogenic, especially in developing country settings. Further modelling challenges are to accurately represent the multi-strain dynamics of circulating pathogens and duration of vaccine-induced immunity, while predicting the pathogenic potential of non-vaccine serotypes that may emerge or become more predominant over time. The outcome of pathogen evolution will depend on the exact nature of the interaction between the strains, and may in fact also depend on host population structure. We need models that can tell us how strain replacement depends on the nature of the strain interactions. Host population structure may also affect the potential for strain replacement, since the removal of a superior competitor may release less fit strains into the vacated niche.

Second, vaccines against one organism may have indirect effects on others. For example, bacterial pneumonia is a known cause of mortality following influenza infections, but we have not yet understood how this will be affected by new influenza and bacterial vaccinations. Further, the morbidity associated with commensal pathogens, and in particular meningitis, which only cause disease under specific circumstances is not well understood within the context of disease transmission dynamics. Human challenge studies show that bacteria that share a niche are characterized by colonies of different strains and species expanding and contracting dynamically. We do not yet know the impact of vaccinating against one species on the dynamics of the others. Modelling will play an essential role in interpreting new experimental and surveillance studies of these issues.

Conclusions

The overwhelming public health success of vaccines to date is largely attributable to vaccines that provide long-lived immunity. With a few exceptions (e.g., rubella), what modelling had to offer in these cases was mostly a matter of refinement, as distributing more vaccine always led to less disease. The situation is more complex in the modern vaccine era. The focus for tried and true vaccines has shifted from individual protection, to elimination and maintaining immunity (and enthusiasm for vaccination) in the absence of disease circulation. New vaccine products lead us to confront more complex disease systems (dengue, HPV) where vaccination may carry its own risks or cause ecological disruptions with unknown consequences. In this new era, we need more sophisticated

modelling methodologies that capture the complexities of these systems and can account for geographic and social heterogeneity in risk and vaccine use. There is also the opportunity for mechanistic models to play new roles beyond predicting vaccine effectiveness. The models of the future may be used to confront logistical constraints, help translate data into measurements of program (or vaccine) performance, and even guide the biological development of vaccine products.

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References

1. Knox, E.G., *Strategy for rubella vaccination.* International Journal of Epidemiology, 1980. **9**: p. 13–23.
2. Halloran, M.E., et al., *Design and analysis of vaccine studies*. 2010: Springer.
3. Burton, A., et al., *WHO and UNICEF estimates of national infant immunization coverage: methods and processes.* Bulletin of the World Health Organization, 2009. **87**: p. 535-541.
4. Lessler, J., et al., *Measuring the performance of vaccination programs using cross-sectional surveys.* PloS Medicine, 2011. **8**: p. e1001110.
5. Funk, S., M. Salathé, and V.A. Jansen, *Modelling the influence of human behaviour on the spread of infectious diseases: a review.* Journal of the Royal Society Interface, 2010. **7**(50): p. 1247-1256.
6. Funk, S., et al., *Challenges in modelling the dynamics of behaviours towards infectious diseases.* Epidemics.
7. Eames, K.T., *Networks of influence and infection: parental choices and childhood disease.* Journal of The Royal Society Interface, 2009. **6**(38): p. 811-814.
8. Danon, L., et al., *Networks and the epidemiology of infectious disease.* Interdisciplinary perspectives on infectious diseases, 2011. **2011**.
9. Salathé, M. and S. Khandelwal, *Assessing vaccination sentiments with online social media: implications for infectious disease dynamics and control.* PLoS computational biology, 2011. **7**(10): p. e1002199.
10. Wu, J.T., et al., *Estimating infection attack rates and severity in real time during an influenza pandemic: analysis of serial cross-sectional serologic surveillance data.* PLoS medicine, 2011. **8**(10): p. e1001103.
11. Van Kerkhove, M.D., et al., *Studies needed to address public health challenges of the 2009 H1N1 influenza pandemic: insights from modeling.* PLoS medicine, 2010. **7**(6): p. e1000275.
12. Klepac, P., et al., *Six challenges in the eradiction of infectious diseases.* Epidemics, in prep.
13. Brito, D.L., E. Sheshinski, and M.D. Intriligator, *Externalities and compulsary vaccinations.* Journal of Public Economics, 1991. **45**(1): p. 69-90.
14. Metcalf, C.J.E., J. Lessler, and W.J. Edmunds, *Six challenges in public health and modeling* Epidemics, in prep.
15. Lee, B.Y., et al., *The impact of making vaccines thermostable in Niger's vaccine supply chain.* Vaccine, 2012. **30**(38): p. 5637-5643.
16. Klepac, P., R. Laxminarayan, and B.T. Grenfell, *Synthesizing epidemiological and economic optima for control of immunizing infections.* Proceedings of the National Academy of Sciences, 2011. **108**(34): p. 14366-14370.
17. Fine, P.E.M. and J.A. Clarkson, *Seasonal Influences on Pertussis.* International Journal of Epidemiology, 1986. **15**: p. 237-247.
18. Grenfell, B.T., O.N. Bjørnstad, and J. Kappey, *Travelling waves and spatial hierarchies in measles epidemics.* Nature, 2001. **414**: p. 716-723.

19. Bolker, B. and B. Grenfell, *Space, persistence and dynamics of measles epidemics.* Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 1995. **348**(1325): p. 309-320.
20. Jansen, V.A., et al., *Measles outbreaks in a population with declining vaccine uptake.* Science, 2003. **301**(5634): p. 804-804.
21. Mossong, J., et al., *Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases.* PloS Medicine, 2008. **5**: p. e74.
22. Keeling, M.J., O.N. Bjornstad, and B.T. Grenfell, *Metapopulation dynamics of infectious diseases*, in *Ecology, Genetics and Evolution of Metapopulations*, I.A. Hanski and O.E. Gaggiotti, Editors. 2004, Elsevier. p. 415-445.
23. Bartlett, M.S., *Measles Periodicity and Community Size.* Journal of the Royal Statistical Society. Series A (General), 1957. **121**: p. 48-70.
24. McLean, A.R. and S.M. Blower, *Modelling HIV vaccination.* Trends in microbiology, 1995. **3**(12): p. 458-463.
25. Pilyugin, S.S. and R. Antia, *Modeling immune responses with handling time.* Bulletin of mathematical biology, 2000. **62**(5): p. 869-890.
26. Thakar, J., et al., *Constraint-based network model of pathogen–immune system interactions.* Journal of The Royal Society Interface, 2009. **6**(36): p. 599-612.
27. Bergstrom, C.T. and R. Antia, *How do adaptive immune systems control pathogens while avoiding autoimmunity?* Trends in ecology & evolution, 2006. **21**(1): p. 22-28.
28. Antia, R., V.V. Ganusov, and R. Ahmed, *The role of models in understanding CD8+ T-cell memory.* Nature Reviews Immunology, 2005. **5**(2): p. 101-111.
29. Arinaminpathy, N., J.S. Lavine, and B.T. Grenfell, *Self-boosting vaccines and their implications for herd immunity.* Proceedings of the National Academy of Sciences, 2012. **109**(49): p. 20154-20159.
30. Lavine, J.S., A.A. King, and O.N. Bjørnstad, *Natural immune boosting in pertussis dynamics and the potential for long-term vaccine failure.* Proceedings of the National Academy of Sciences, 2011. **108**(17): p. 7259-7264.
31. Metcalf, C.J.E., et al., *Five challenges in evolution and infectious disease.* Epidemics.
32. Atkins, K.E., et al., *Vaccination and Reduced Cohort Duration Can Drive Virulence Evolution: Marek'S Disease Virus and Industrialized Agriculture.* Evolution, 2013. **67**(3): p. 851-860.
33. Arinaminpathy, N., et al., *Impact of cross-protective vaccines on epidemiological and evolutionary dynamics of influenza.* Proceedings of the National Academy of Sciences, 2012. **109**(8): p. 3173-3177.
34. Flasche, S., et al., *The impact of specific and non-specific immunity on the ecology of Streptococcus pneumoniae and the implications for vaccination.* Proceedings of the Royal Society B: Biological Sciences, 2013. **280**(1771): p. 20131939.
35. Lange, A. and N.M. Ferguson, *Antigenic diversity, transmission mechanisms, and the evolution of pathogens.* PLoS Computational Biology, 2009. **5**(10): p. e1000536.
36. Plotkin S.A., Orenstein W.A., and O. PA., *Vaccines*. 6th ed. 2013: Saunders.
37. Chao, D.L., et al., *Controlling dengue with vaccines in Thailand.* PLoS neglected tropical diseases, 2012. **6**(10): p. e1876.

38. Coudeville, L. and G.P. Garnett, *Transmission dynamics of the four dengue serotypes in southern Vietnam and the potential impact of vaccination.* PloS one, 2012. **7**(12): p. e51244.
39. Rodriguez-Barraquer, I., et al., *Potential opportunities and perils of imperfect dengue vaccines.* Vaccine, 2014. **32**(4): p. 514-520.
40. Weinberger, D.M., R. Malley, and M. Lipsitch, *Serotype replacement in disease after pneumococcal vaccination.* The Lancet, 2011. **378**(9807): p. 1962-1973.