Emerging, evolving, and established infectious diseases and interventions

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Planning, implementing, and evaluating interventions against infectious diseases depend on the nature of the infectious disease; the availability of intervention measures; and logistical, economic, and political constraints. Infectious diseases and vaccine- or drug-based interventions can be loosely categorized by the degree to which the infectious disease and the intervention are well established. Pertussis, polio, and measles are three examples of long-known infectious diseases for which global vaccination has dramatically reduced the public health burden. Pertussis vaccination was introduced in the 1940s, polio vaccination in the 1950s, and measles vaccination in the 1960s, nearly eliminating these diseases in many places.

Many known infectious diseases tend to be epidemic, but exactly when and where these epidemics will occur is uncertain. For such sporadic infectious diseases, it may be most efficient to implement a reactive vaccination campaign once an outbreak has begun. Planning for reactive vaccination requires keeping a mobile vaccine stockpile available that can be quickly moved for emergency vaccination. This strategy could be used for epidemic cholera, such as occurs in parts of Africa (1). When cholera was introduced into Haiti in 2010, such a stockpile did not exist. Limited supplies of cholera vaccine were scattered in different locations, and a decision was made not to vaccinate the local population, even though mathematical models showed that with limited quantities of vaccine, concentrating vaccination in high-risk areas would be most efficient (2). Now that such a stockpile of 2 million doses of oral cholera vaccine exists (3), it can be used for future cholera epidemics. Mobile stockpiles, such as the oral cholera vaccine, often have a finite shelf life, and their use can be valuably reassigned in endemic locations, such as Bangladesh, that experience annual cycles of high incidence.

For long-term intervention strategies, sustainability is an issue, and strategies can change as the economic constraints change or as new products become available. For example, a new product against meningococcal A meningitis was developed that overtook the reactive vaccination strategy in the meningitis belt of sub-Saharan Africa. An international commitment working through the Meningitis Vaccine Project developed an inexpensive vaccine against meningitis A (4) that can be used in proactive vaccination. Initial introduction has been carried out or is planned in 26 African countries, with mass vaccination of people up to the age of 29 years to be followed by routine vaccination of young children.

Emerging infectious diseases sometimes lend themselves to effective vaccination. In light of the ongoing human cases of avian influenza A (H7N9) in China, the United States is preparing to stockpile vaccines for human cases of H7N9. When the pandemic influenza A (H1N1) emerged suddenly in 2009, influenza vaccine manufacturers turned their production lines to developing and producing appropriate vaccines for immediate administration. Yet for other emerging diseases like HIV/AIDS, which was discovered more than 30 years ago, no effective vaccine has successfully been developed for human use. For several newly emerging infectious diseases, it is questionable when or if vaccines or drugs can be developed at all. One example is Middle East respiratory syndrome (MERS), a viral respiratory illness caused by a coronavirus first reported in Saudi Arabia in 2012. Another example is the arbovirus chikungunya, which is spreading explosively in the Americas, with 650,468 confirmed and suspected cases reported by the Pan American Health Organization as of 29 August 2014. Although antivirals, vaccines, and monoclonal antibodies are under early development, Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, wrote that “in the meantime, we can only keep our fingers crossed” (5) that the epidemic in the Americas will decline on its own before becoming more widespread. According to (5), even if a vaccine were available, chikungunya outbreaks spread too rapidly for reactive vaccination to be effective. In the current Ebola outbreak in West Africa, there is no pharmaceutical intervention. For these newly emerging infectious diseases, surveillance and containment, education, and avoidance are the main responses available until vaccines or drugs may be developed.

Interventions in infectious diseases can have more than just direct protective effects in the...
individuals receiving the intervention (6). An intervention strategy can also have indirect protective effects in associated unvaccinated individuals. Accounting for both the direct and indirect effects will give a more accurate measure of the cost-effectiveness of a program; hence, the combined direct and indirect effects need to be assessed. Dynamic mathematical transmission models offer valuable tools for planning infectious disease strategies, particularly for taking potential indirect effects into account. Especially when vaccines confer modest direct protection, the indirect and overall effects of widespread vaccination may affect the cost-effectiveness of vaccination. An example is the cholera vaccine, for which indirect effects play an especially large role in the cost-effectiveness of large-scale vaccination programs. A dynamic mathematical model of cholera vaccination showed that the percentage of cases expected to be averted by vaccinating different proportions of the population is much higher when both indirect and direct effects, as opposed to only direct effects, are taken into account (Fig. 1). When taking only direct protection into account, the same model showed that the cost per disability-adjusted life years (DALYs) averted is barely cost-effective at all levels of coverage. But when taking both indirect and direct protection into account, a vaccination program is much more cost-effective (Fig. 2).

However, reliable mathematical models depend on good epidemiological data. Often the data required to inform the models are not collected in field trials. For example, in most vaccine field trials, cases are ascertained based on clinical symptoms, then the specific infectious agent is confirmed by a laboratory test, so efficacy against clinical disease is determined. But much more information about how vaccination affects transmission is needed for the mathematical models. For example, data are needed on the effect of vaccination on asymptomatic infection and the degree to which infectiousness is reduced in breakthrough infections. Whether the vaccine protects some people completely and others not at all, or whether it reduces the probability of becoming infected in everyone equally, has important population-level consequences. The time of infection, the onset and end of infectiousness and its temporal variability, and contact patterns are seldom measured but greatly influence the outcomes of simulated interventions. Uncertainty regarding these important inputs results in uncertainty of the potential epidemiological effects and cost-effectiveness of a vaccination program. Policy-makers are increasingly asking for mathematical models to aid in decision-making. Moving forward, vaccine studies need to include plans to measure as many of these inputs as possible for well-informed mathematical modeling, as pointed out 20 years ago (7).

As vaccines against dengue (8) and malaria (9) become available, models can help us understand how these emerging vaccines might be used most effectively. In a phase III trial, a dengue vaccine has been shown to be effective against clinical dengue and has proven twice as effective in individuals with preexposure to natural dengue (8), providing an important input for modeling vaccination in populations with different levels of dengue exposure. However, the trial does not provide information on whether the vaccine protects against infection or just disease, or whether it reduces the infectiousness of infected individuals for mosquitoes. The exact nature of the interaction of vaccine-induced immunity with preexisting immunity and exposure to infection is also not well understood and can affect the interpretation of vaccine efficacy and effectiveness (10). All of these inputs are necessary to model the potential population-level effects and cost-effectiveness of dengue vaccination programs in different populations.

**Evaluation**

In addition to modeling indirect and overall effects of vaccination, such effects of widespread vaccination can be assessed by appropriate field studies and surveillance. Either randomized or observational studies can provide assessment of indirect and overall effects of intervention programs. For example, studies of cholera (11) and typhoid (12) vaccination, both of which confer only modest direct protection, have been conducted to evaluate the indirect effects of widespread vaccination. Plans for evaluation should be an integral part of implementing a vaccination strategy. For example, before introducing the meningitis A vaccine in Africa, the capacity to evaluate the indirect and overall effects of the strategy on nasopharyngeal carriage was established in several countries by the MenAfriCan (the African Meningococcal Carriage Consortium) project. But studies can also be undertaken after introducing vaccination. A study analyzing insurance data to evaluate direct, indirect, total, and overall effectiveness of rotavirus vaccines in the United States compared the prevaccination baseline years with the years after vaccination (13). This study revealed important indirect effects that need to be taken into account when estimating the sustained impact of the vaccination program. Delivery of a new dengue vaccine would offer the opportunity for a well-planned phased introduction to
evaluate not only the direct effect of vaccination, but also the indirect and overall effects. In all instances, good field epidemiology and surveillance are required.

**Changing fronts**

Even when a good intervention is available, problems can arise, requiring ongoing careful epidemiological assessment of apparently excellent interventions. Interventions can put selective evolutionary pressure on pathogens, resulting in drug resistance and immune escape. The emergence of drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant tuberculosis, as well as drug-resistant malaria parasites, is the result of evolutionary pressure. The United States is experiencing a resurgence of pertussis cases, despite high coverage and booster vaccination of teenagers. The reasons are poorly understood, but it is possible that the current acellular pertussis vaccines do not produce long-lasting immunity (16). In addition, pertussis strains that lack one of the important vaccine antigens have evolved because of immune escape and have spread in recent years (16). Careful epidemiological assessment of the changing pertussis situation is required to guide development of new vaccines and intervention strategies (16).

Influenza viruses evolve antigenically over time, escaping both natural and vaccine-induced immunity. Challenges arise from producing an influenza vaccine each year, and constant monitoring of the influenza viruses is needed. Global influenza virological surveillance has been conducted through the World Health Organization’s (WHO) Global Influenza Surveillance and Response System for more than half a century. Twice a year—one for the Northern Hemisphere and once for the Southern Hemisphere—the WHO advisory panel decides what viruses will be incorporated in the next seasonal influenza vaccine (17).

Although global vaccination has eliminated polio in many parts of the world, choosing between live-attenuated oral polio vaccine (OPV) and inactivated polio vaccine (IPV) is a crucial policy decision once elimination has been achieved. OPV is less expensive and easy to administer; can be transmitted to close contacts and in the environment, helping to spread vaccination; and induces more natural immunity in the gut, preventing onward transmission. However, OPV can revert, causing very occasional cases of polio. IPV is more expensive, but it induces the production of antibodies that can prevent paralytic disease. IPV does not induce gut immunity and thus does not prevent onward transmission, but it also does not raise the same safety concerns as OPV. When polio has been essentially eliminated and the vaccine is affordable, then the switch to IPV from OPV is a sensible policy decision. However, this choice can also be fraught with difficulties. Israel switched to IPV for 9 years, but through intense environmental surveillance discovered circulation of type 1 wild poliovirus and thus reintroduced OPV (18, 19). This excellent environmental surveillance facilitated the rapid response to the changing situation.

The shifting landscape of infectious diseases and interventions poses challenges. Focused field epidemiology and surveillance are needed to provide the information required to make informed policy decisions about interventions to further global public health.
Editor's Summary

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