Vaccines in the public eye

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Preventive vaccines are widely acknowledged as the best hope for protection against infectious pathogens such as avian flu, HIV and SARS. As a result, they have received much recent attention in the media that has exposed some of the challenges involved in optimally using vaccine technology.

The infectious diseases introduced by Europeans killed 95% of the pre-Columbian Native American population[1] and the 1918 Spanish flu pandemic caused 50 million deaths after infecting 1 billion people, nearly half the world's population of 1918[2]. In our era, SARS (severe acute respiratory syndrome) quickly encircled the globe to infect 8,400 people[3] with a rapidity dramatized by a 78-year-old woman carrying the infection from Hong Kong to Toronto and precipitating a chain reaction causing 44 Toronto deaths[4]. Concerns that an avian flu pandemic could cause 4 million deaths have followed the wake-up call of SARS[5].

How do we as a global society safeguard against an increasing number of new pathogens[6]? Preventive vaccines are widely acknowledged as our best and most cost-effective protection[6–8]. By inducing adaptive immunity, vaccines protect where innate immunity, which evolves slowly and regionally, cannot. The recent media attention directed at vaccines has exposed several challenges underlying the development and administration of vaccines. Here, we consider those challenges related to bioethics, policy and finance.

Vaccine bioethics

Universal immunization programs have been credited with the elimination of smallpox, near eradication of polio, and reductions in incidence and burden of disease from diphtheria, whooping cough and measles[9]. These successes are often interpreted as reflecting the principle of herd immunity, the assumption that vaccine benefits are better realized when more people within a community are immunized. In following the guiding principles of herd immunity, an entire population need not be vaccinated. However, some critical proportion must be, with the exact percentage dependent on several factors, including how infectious the pathogen is and whether geographically proximal clusters of unvaccinated individuals exist.

Herd immunity presents bioethical challenges because individuals do not just benefit from their own vaccination but also from the vaccination of others. Thus, individuals who refuse vaccinations can benefit from the vaccinations others undergo. But refusal to be vaccinated can also endanger others, including those who have been vaccinated.

These bioethical challenges must be confronted because, despite successes, persuading a majority of the population to accept vaccination has, at times, been difficult. Some minorities consistently reject vaccination, perhaps because of difficulties believing that vaccines are based on sound science and manufacturing principles. Certainly, as with other pharmaceuticals, the possible adverse side effects of vaccines must be acceptable or the likelihood of side effects must be low enough that risks are acceptable. But whereas most pharmaceuticals treat active illnesses, healthy people must accept a foreign (vaccine) agent in their bodies, often without tangible experience of illness or risk. Vaccine acceptance has been a particular challenge when the prevalence of the disease protected against is low, as it is impossible to prove there is no risk in vaccination, especially with respect to adverse events that may occur in a distant future[10].

Vaccine rejection actually emerged coincidentally with universal immunization. Soon after the mandatory vaccination acts of 1853 and 1867 in the UK led to smallpox vaccination for 90% of infants (in England and Wales), the London Society for the Abolition of Compulsory Vaccination was founded[11]. Its activity led to a Royal Commission review of mandatory vaccination and to the Act of 1898, which recognized conscientious objection to compulsory immunization. The exemption of conscientious objectors was an important factor in the subsequent reduction of vaccination rates[11]. Another contributing cause was that after 20 years of near-universal vaccination, smallpox, the key illness targeted by the vaccination acts, had been virtually eliminated[12]. It seems the near eradication of smallpox had made vaccination a less compelling imperative.

How much do people decide to accept or reject vaccination based on their perceptions of risk? We addressed this assumption in a series of randomized, population-based surveys in Canada, the US and France, using questions drawn from extensive literature review[13–26] that probed attitudes about vaccine risk and safety, vaccine efficacy, anxiety about vaccines, philosophical oppositions and perceptions of knowledge about how vaccines work. In our analyses, we used the questions on attitudes and knowledge to predict the self-reported acceptance of the current flu vaccine, as well as of hypothetical vaccines for HIV/AIDS and

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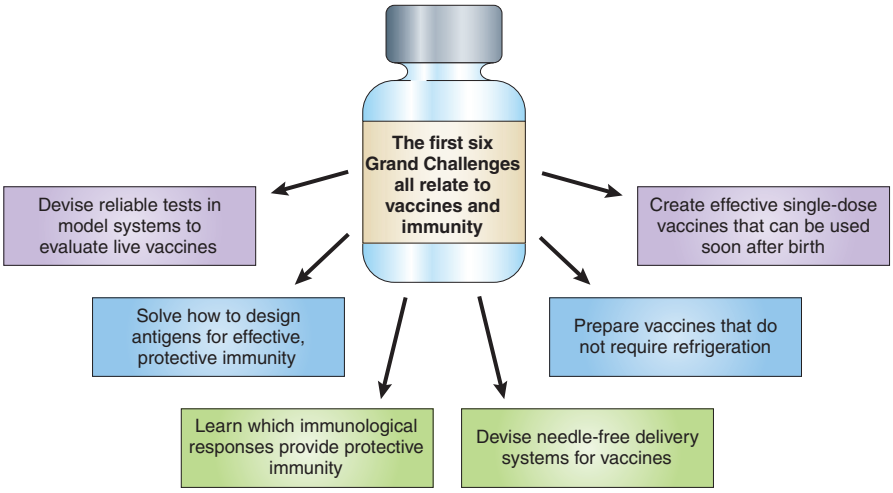

Figure 1 The Grand Challenges in Global Health related to vaccine improvements.

hepatitis C. We found the most statistically significant (P = 0.000–0.029) predictor of acceptance was vaccine effectiveness, with vaccine safety and knowledge also significant (P = 0.000–0.039) predictors. As these results were similar across vaccines, it would seem that people first consider the effectiveness of a vaccine before assessing the risks involved, and then consider how much they think they know in coming to conclusions about both[27].

Given that people who reject vaccinations may compromise the health of the population, bioethical questions center on whether the actions of those who reject vaccination introduce unfair detriments to the population and, conversely, whether the rights of those who reject vaccination are overridden by universal vaccination programs. Our literature review of immunization bioethics (L. Keifer, K. Wilson, P. Ritvo & R. Upshur, unpublished data) identified four themes to guide us through these complex issues: (i) autonomy—immunization programs must not unduly restrict individual or community freedom; (ii) beneficence—immunization programs must, nonetheless, be effective; (iii) nonmaleficence—immunization programs must not cause avertable harms; and (iv) justice—immunization programs must involve equitable sharings of risks and benefits by all community members. These themes are both conflictual and complementary. For example, individual rights can be violated if individuals are forced to accept vaccinations (a violation of autonomy), but they are also violated if vaccination refusals result in a decrease of vaccine effectiveness that hampers protection against vaccine-preventable diseases (beneficence and justice). Furthermore, the nonmaleficence of immunization programs must be ensured by the same precautions taken to ensure vaccine safety. Such precautions are similarly central in the concepts of beneficence and justice.

Strict government systems regulate the pharmaceutical industry and are used to ascertain whether drug products are sufficiently safe and efficacious to be marketed[28], and vaccines present a special case, as they are aimed at virtually 100% of the population. Even though most vaccines are safe, with 100% exposures, risks below 1% may result in sizeable numbers of adverse events when large populations are exposed[29]. Although more stringent criteria than those regularly used in testing and manufacturing drugs may be relevant for vaccines, the question is how stringent should they be?

The difficulty in answering this question was illustrated in a recent controversy surrounding the question of whether hepatitis B vaccination increases the risks of subsequent multiple sclerosis. A 2004 study on the use of recombinant hepatitis B vaccine and the risk of multiple sclerosis included 163 cases of multiple sclerosis and 1,604 controls[30]. By accessing the UK's General Practice Research Database, investigators identified individuals with a first multiple sclerosis diagnosis between 1993 and 2000 and matched each of the 163 identified multiple sclerosis cases (for age, sex, and date of joining the practice) with up to 10 randomly selected controls[30]. Compared with unvaccinated individuals, vaccinated individuals had 3 times the likelihood of developing multiple sclerosis (95% confidence interval; odds ratio 1.5–6.3). The study results directly conflicted with a 2002 US Institute of Medicine (IOM) review that endorsed the safety of the hepatitis B vaccine and rejected a causal relationship between multiple sclerosis incidence and relapse in adult recipients of hepatitis B vaccine[31].

The IOM review drew on extensive prior evidence that markedly differed from the recent findings. First, it referred to the prelicensure clinical vaccine trials that documented no significant associations with nervous system disorders. Second, it referred to the hundreds of millions of people worldwide who had received hepatitis B vaccinations and had not developed multiple sclerosis. Furthermore, several prior studies were cited, using a variety of research designs, that indicated safety[32–35]. For example, a study using the Centers for Disease Control and Prevention's Vaccine Safety Datalink project assessed associations between hepatitis B vaccine and demyelinating diseases in US managed-care organizations (MCO)[32]. In a sample of 422 cases of demyelinating disease and 921 matched controls (people of similar age, gender and MCO status who had no demyelinating disease), no association was found between vaccination against hepatitis B and onset of demyelinating disease[32]. In a similarly designed study, 192 women with multiple sclerosis and 645 controls were evaluated. The researchers found no elevations of risks associated with hepatitis B vaccination at any time before onset of multiple sclerosis and within 2 years of onset, findings also interpreted as indicating no association between hepatitis B vaccination and multiple sclerosis. Other study designs yielded similar results[33], including a European study that assessed whether multiple sclerosis relapses were associated with vaccination against hepatitis B. In this study of 643 individuals diagnosed with relapsing multiple sclerosis, findings indicated no association between relapse (during the 2-month period after vaccination) and hepatitis B vaccination[34]. Finally, the incidence of multiple sclerosis in 578,308 adolescents in British Columbia was investigated before and after hepatitis B vaccination and no evidence was found of any links between vaccination, multiple sclerosis or other demyelinating diseases[35]. The important point of all these studies is the repetitive conclusions that provide much evidential counterweight to recent findings.

Important criticisms of the 2004 study have also been articulated by the Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO)[36]. The Committee noted that of the original 713 cases of multiple sclerosis, 163 were selected, and eventually only 11 vaccinated individuals were used in deriving the hazard data. Such a selection process is fraught with risks of inadvertent bias. Moreover, because the practice of vaccination against hepatitis B in the UK at the time of the study was targeted toward high-risk individuals, the sample did not represent the general population and was skewed in a way that may have introduced bias.

Policy

The interpretations of these data are complex but crucial for the 168 countries that currently follow or plan to follow WHO recommendations to include the hepatitis B vaccine in national programs. To contrast the range of current policy we can consider Ontario, Canada, where a universal hepatitis B vaccination policy, largely revolving around a school-based program, proceeds smoothly, and France, where a school-based hepatitis B immunization program was suspended in 1998. Why is there a contrast in policy in these two jurisdictions?

The evolution of hepatitis B vaccine policy in France can be traced back to a 1994 decision to include the vaccine in the infant immunization schedule and to implement it in a high-risk group vaccination strategy. The third component of the policy adopted then was to conduct annual vaccination campaigns in schools, targeting preadolescents in the first year of secondary school, between the ages of 10 and 12 years[37]. Implementation of these strategies (between 1994 and 1997) yielded a substantial coverage of preteenagers (75–80%)[37] and the adult population (*e.g.*, coverage in the 25–34-year-old group was estimated at 30% by 1998). However, between 1994 and 1998, there was an apparent increase in the adverse-event notifications received by the French Medicines Agency (Agence Francaise de Securite Sanitaire des Produits de Sante, AFSSAPS), primarily involving central demyelination episodes after hepatitis B vaccination (D. Levy-Bruhl, personal communication). Although a temporal association could be assumed between frequent exposure, such as hepatitis B vaccination, and the onset of a certain number of multiple sclerosis cases, these data were difficult to interpret because there was suspected to be an undernotification of multiple sclerosis cases (D. Levy-Bruhl, personal communication). In a subsequent 1998 meeting of the AFSSAPS, several studies were reviewed to reassess associations between episodes of central demyelination and the hepatitis B vaccine. These included a French pilot study[38], a larger French multicenter study[39] and a study that utilized the same General Practice Research Database later used in the Harvard study reviewed above[40]. In the three studies reviewed, the odds ratios were all elevated above 1.0 (OR: 1.8, 0.5–6.0 (ref. 38); OR: 1.4, 0.4–4.5 (ref. 39); OR: 1.4, 0.8–2.4 (ref. 40)), possibly suggesting slightly higher risks for development of multiple sclerosis in those vaccinated with hepatitis B compared with those who were not vaccinated. But none of the statistical analyses reached conventional significance ($P = 0.05$) levels, and as such, it was difficult to confirm or discount a small increase of risk (D. Levy-Bruhl, personal communication).

These studies were further supplemented by a risk-benefit modeling study of hepatitis B vaccination in France for a fictitious cohort of 800,000 preteenagers, followed to 35 years of age[37]. The modeling suggested the risk of multiple sclerosis onset attributable to hepatitis B vaccination over the time period modeled would result, in the worst-case scenario, in 2 or fewer cases of multiple sclerosis compared to the benefits of preventing between 3 and 29 cases of acute fulminant hepatitis and between 12 and 147 cases of cirrhosis. This modeling study is provocative, as it indicates that the eventual policy decision (to suspend the school-based vaccination program) might ultimately prevent multiple sclerosis onset in just two individuals, while simultaneously foreclosing on the opportunity of preventing severe complications of hepatitis B disease in a considerably larger number (somewhere between 15 and 176 individuals).

The elimination of school-based hepatitis B vaccination, justified on the basis of the need to "better take into account the individual benefits and risks" of the vaccine (D. Levy-Bruhl, personal communication), has probably been a contributing factor to a continuing pattern of decreased hepatitis B vaccination activities and hepatitis B vaccine sales in France. The policy is also probably associated with the currently modest coverage of hepatitis B vaccination in infants and preadolescents, as coverage at 24 months in 2003 was about 28%, whereas school health surveys suggested 30% coverage in 10–11-year-olds (2000), compared to the 75–80% coverage achieved by 1997 (D. Levy-Bruhl, personal communication). A statistical comparison of data from 1997 and 2000 was not reported. The Technical Committee on immunization has regularly reviewed relevant data since 1997, and as of their last assessment (September 2004) the Committee has decided not to modify the current vaccination strategy that continues the suspension of the school-based strategy (D. Levy-Bruhl, personal communication).

Responding to vaccine rejection

The optimal response to vaccine rejection is a universal question, as relevant in France and the UK (hepatitis B and measles-mumps-rubella (MMR) vaccines), as in the Nigerian state of Kano[41] and the Indian state of Bihar[42] (both recently reported episodes of polio-vaccine rejection were linked to perceptions the vaccine could cause infertility). Not surprisingly, the level of confidence in the public authorities who are promoting a vaccine seems to be an important factor in vaccine acceptance and rejection. In view of the factors affecting vaccine acceptance discussed earlier, trust in authorities might be expected to be highly correlated with perceptions of vaccine knowledge, as the information most people receive about vaccines comes from 'authorities.' Thus, it is not surprising that loss of confidence in public authorities resulting from poor management of other risks might cause a 'risk amplification' effect amidst perceptions that public risks are not well managed[43,44]. This can be followed by 'risk contamination'[43], a case of reduced acceptance of the management of another risk. These phenomena, risk amplification and contamination, may help explain why people have been less willing to accept the risk of adverse events from the MMR vaccine (currently 80% of children have received MMR vaccinations by their second birthday in England, compared to 82% in 2002–2003 and well below the peak coverage of 92% in 1995–1996)[45].

The movement against the MMR vaccine was largely triggered by a controversial case series published in the *Lancet* hypothesizing that the vaccine was temporally associated with development of a variant form of autism[46]. Despite the existence of several other epidemiological studies refuting the existence of such a link and the partial retraction of the *Lancet* study because of conflict-of-interest concerns, UK policy makers have had difficulty reassuring the public about the safety of the MMR vaccine[47]. An important contributing factor to this phenomenon might have been the public's loss of confidence in government authorities following the perceived failure of adequate protection from bovine spongiform encephalopathy risks[48]. Consequently, the publication of a case series, generally viewed as a low level of evidence, could trigger a reaction amongst a population sensitized to distrust public health officials. The consequences of this loss in trust are important, as declining vaccination rates for MMR have been observed in association with outbreaks of measles[49].

Bioethics and policy across nations

Although there are bioethical and policy challenges in administering vaccines within countries, we face greater challenges when focusing beyond national boundaries. This is evident in the Grand Challenges in Global Health project announced by the Bill and Melinda Gates Foundation in 2003, as 6 of the 14 challenges involve vaccine technology (**Fig. 1**).

Although the project should result in important advances in vaccine technology, few advocate relying on philanthropy to finance the development of new vaccines. Instead, there is a search for a new approach to multigovernment and multiagency funding. One important motivation is that efficacious vaccines are highly cost effective[7,50]. When compared to

other pharmaceutical products, the number of lives saved per invested dollar is substantial. But the very effectiveness of vaccines ironically reduces their perceived profitability for the private sector. Whereas most profitable pharmaceuticals entail long-term use (*e.g.*, anticholesterol medications), one or several administrations of vaccines often result in long-term or lifelong protection. The 'market' for a preventive vaccine is eliminated as the vaccine is 'marketed,' although this effect is mitigated, to some degree, by the fact that new potential vaccine recipients are continually being born. A further problem is that effective vaccines can be so crucial in reducing mortality (*e.g.*, malaria, HIV/AIDS) that bioethical imperatives necessitate worldwide dissemination, regardless of ability to pay. Thus, free-market logic is difficult to apply.

Jeffrey Sachs and Andrew Kremer, noted macroeconomists, believe the solution lies in a variant of the 'push-pull' logic proposed to speed lifesaving vaccine development[7,51]. Whereas 'push' refers to government subsidization of research and development, the 'pull' advocated by Sachs and Kremer refers to the governmental insurance of profitable markets for vaccines, after proof of effectiveness. Their view is that financial incentives will motivate private-sector scientists to speed vaccine development. Currently only 2% of the vast worldwide pharmaceutical market actually involves vaccines[52]. Thus, there is reason to search for new ways to subsidize the market and generate more effective pharmaceutical industry activity.

Sachs and Kremer's argument is that the cost-effectiveness and health value of several life-saving vaccines, internationally, is irrefutable (*e.g.*, HIV/AIDS, malaria, tuberculosis)[52]. Thus, multiple nations should make an advanced commitment to buy these vaccines. After they are proven to be effective, the virtual commitment transforms into a real purchase. In macroeconomic terms, a very high return could be achieved with a moderate amount of funds from each G-7 country, if all coordinated to create this virtual 'purchase fund'[52]. A key point of this future 'virtual' commitment plan is that it need not compete with the funding of other health interventions[7]. In other words, an agreement to pay 'on delivery' of effective products need not detract from the financing of current programs such as antiretroviral treatment for HIV/AIDS or distribution of effective mosquito netting to prevent malaria.

Is there the 'political will' to enact such a plan? International debate continues over whether the support of health and reduced mortality should take precedence over other forms of aid to developing nations. As an example, Carol Bellamy, UNICEF's executive director, was recently criticized for being overly focused on a "rights-based approach to the future of children that ignores the fact that children have no opportunity unless they survive"[53]. It is unreasonable to expect that vaccines for HIV/AIDS and malaria will reach the top of an international funding agenda unless global reductions in mass mortality are first firmly established as a top priority.

Problems inherent to Sachs and Kremer's plan[52] must also be considered. For example, several nations must overcome prior legislation that establishes legal restraints on committing to a budget item over several years and the right international 'contract' law mechanisms must ensure that the purchase agreements are binding. Additional reservations revolve around shifting too much emphasis to 'pull' while maintaining too little on the 'push,' or initial subsidization of research activity. Will the public support financing a strong enough 'pull' and agree to the transfer of a large enough sum of money upon delivery of a vaccine to truly motivate pharmaceutical firms? There are also questions about whether the time dimensions (*e.g.*, for an HIV/AIDS vaccine) are too long for companies and researchers.

Still, the multiple forms of 'pull' funding, as well as the concept, itself, are attractive. Besides the 'high-profile signing of intent' (virtual money on the table linked to binding agreements), the 'pull' incentive could take the form of 'transferable patent extensions' in which companies developing the target vaccines are entitled to one or more years of patent extension on any product in their portfolio (potentially amounting to billions of dollars in increased revenue). Or 'pull' could involve tax breaks given to the successful company, over several years, ensuring a more profitable, longer-term business. The important point in the 'pull' logic is that it is not a problem of finding enough financial resource, it is a matter of agreement on a financial plan and the will to carry it out now rather than later[52]. Alternatives to the purchase fund concept include a proposal, recently made by French President Jacques Chirac, to levy an international tax on financial transactions, or fuel for air and sea transport, or airline tickets that could generate ten billion dollars per year for the global fight against AIDS[54]. The common point, however, with the purchase fund is the generation of a large enough resources to pursue the optimal combination of treatment and prevention strategies (including vaccines).

Final comments: the shared bloodstream

On 27 January 2005, the first person-to-person transmission of avian influenza was reported[55]. With this new evidence, its pandemic potential increased. From the avian flu situation and the other challenges addressed in this commentary, we can see that we are quite a distance from the time when immunocompetence was an intimate and local matter. People (and animals) who lived in close quarters developed immunocompetence related to the pathogens shared—through food, water, air and imperfect sanitation. In their exchanges, they, in effect, shared a common bloodstream. This shared bloodstream now extends across the globe and across multiple cultures and socioeconomic strata. Whether we are affected by SARS, AIDS or avian influenza, our biology bonds us in common vulnerabilities. To the extent that we acknowledge these vulnerabilities, vaccine technology addresses our needs for personal security and compassionate response.

Two recent developments provide encouragement. In an intermediate trial involving child subjects in Mozambique, a new vaccine reduced the morbidity risk of malaria by 30% and the risk of contracting severe malaria by 58%[56]. This first clear success suggests a malaria vaccine could dramatically reduce mortality in sub-Saharan Africa. Another recent breakthrough was a highly effective human papillomavirus vaccine. Human papillomavirus is the cause of most cases of cervical cancer and the second-leading cause of cancer-related deaths of females in the world[57]. An effective vaccine, properly disseminated, could significantly reduce mortality. These two examples illustrate how vaccine development can make the world healthier and safer. This is not just vision. This is science harnessed effectively.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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