Vaccines: Very Successful, Strangely Controversial**

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Summary

Vaccines prevent disease before individuals can become infected and thus, along with economic development, represent the greatest hope to alleviate the burden of infectious diseases and save lives worldwide. Many vaccines also offer the advantage of primarily targeting the young, hence not only saving lives in general, but particularly preserving the prime years of life. Development of vaccines requires a partnership among academia, industry, and government. However, there are multiple hurdles to maximizing the use of vaccines globally. While there are a host of scientific issues that are beyond the scope of this discussion, in this paper I specifically address some of the issues for which the intersection of policy makers, academics, and industry plays a vital role: combating the anti-vaccine movement, improving influenza vaccines, and strengthening the ability of regulatory agencies to efficiently evaluate vaccines.

Current realities

Not only do vaccines save millions of lives every year, they also prevent the cruelly disabling effects of infectious diseases.[1] The use of vaccines, primarily starting in the 20th century, has greatly ameliorated the historically widespread infectious disease burden. Perhaps the most stunning success was the global elimination of smallpox. Childhood diseases that once crippled and killed millions, such as polio, measles, mumps, rubella, and tetanus, have also been greatly reduced worldwide.[2] Recently, immunization efforts have also reduced the rate of diarrheal disease (through the rotavirus vaccine) and childhood meningitis (through the *Haemophilus* influenza type b vaccine). Some vaccines also protect against cancers caused by infectious diseases. For example, introduction of a hepatitis B vaccine in 1981 has prevented liver failure and liver cancer, thus becoming the first "anti-cancer" vaccine. Unfortunately, the World Health Organization (WHO) estimates that 1.7 million children will die annually from vaccine-preventable diseases. Obstacles, including social and economic barriers, still hinder the maximal use of effective vaccines in both poor and rich countries.

In spite of the remarkable efficacy and safety of vaccines, an anti-vaccine movement has arisen in the United States and Europe, paradoxically led by people who are well connected (such as celebrities) and/or well educated. This campaign originally centered on the unfounded fear that the measles, mumps, and rubella (MMR) vaccine causes autism — a link put forward by Dr. Andrew Wakefield in a 1998 *Lancet* paper that was recently discredited due to flawed scientific methods and financial conflicts of interest (*The Lancet*, 2010). The anti-vaccine movement is also comprised of individuals who believe that the purpose of vaccines is to develop "herd immunity" and who are unwilling to have their children be vaccinated for the common good. This idea puts the public, especially unvaccinated children, at risk. Of note, due to concerns surrounding the safety of the MMR vaccine, parents began to withhold vaccination from their children, coinciding with a number of large measles outbreaks (Jansen *et al*., 2003).

[1] When the great vaccinologist Dr. Maurice Hilleman died in 2005, Dr. Anthony Fauci, head of the National Institutes of Allergy and Infectious Diseases, and Dr. Paul Offit, chief of Infectious Diseases at the Children's Hospital in Philadelphia, noted in a New York Times article that he had likely saved more human lives than any other scientist in the 20th century.

[2] WHO estimates that immunization currently averts 2.5 million deaths every year in all age groups from diphtheria, tetanus, pertussis (whooping cough), and measles. The WHO also estimates that "more than 5 million people who would otherwise have been paralyzed are walking today because they have been immunized since the [polio eradication] initiative began in 1988," let alone the lives saved and paralysis averted since polio vaccines became widely available in the 1950s.

Influenza, which causes extensive morbidity and mortality and is a target of annual vaccination campaigns, presents a somewhat unique challenge.[3] Because of the variable nature of the influenza virus, a new vaccine — the composition of which is determined by educated guess — must be administered annually. Not only is seasonal influenza a major public health concern, but so too is the possibility of a pandemic that would evolve from a new or re-emerging type of virus. The 1918 influenza pandemic killed approximately 20 million people. Such a pandemic would again have the potential to kill many millions of people, despite our advanced technology, and undoubtedly overwhelm the health care system. The current technology used to produce influenza vaccines involves the use of eggs, thus growing the virus in an antiquated system. Modern genetic ways to generate influenza vaccines are now available but, due to regulatory hurdles, have not yet been put into place in the U.S. and are only beginning to make headway in Europe. These new recombinant DNA and cell-culture techniques could help us to respond in a more nimble fashion to annual changes in the makeup of influenza viruses. The Food and Drug Administration (FDA) and its European counterpart (European Medicines Agency) play active roles in assessing and approving new vaccine technologies. Unfortunately, the FDA is markedly underfunded and can be bureaucratic, thus slowing progress considerably. In addition, the need to protect industry secrets can make the decision-making process less than transparent. The agency is also in the unenviable position of being criticized for moving ahead too slowly, while at the same time being criticized by others for being less than careful.

Scientific opportunities and challenges

A major challenge facing scientists (in both academia and industry) and policy makers is how to overcome the current anti-vaccine sentiment in the U.S. and Europe. Vaccine manufacturers will need to continue to closely monitor vaccine safety both in preclinical trials and after vaccine implementation. Ongoing safety surveillance by the FDA and manufacturers already takes place (e.g., removing thimerosal from vaccines in 2001). However, there is often a disconnect between the data and the anti-vaccine advocates that no amount of research can overcome (e.g., many individuals continue to believe that thimerosal is linked to autism even though its removal had no effect on autism rates in subsequent years). While the science is presently clear that vaccines generally are safe, the court of public opinion and the corresponding realm of public policy are where the current challenges to the effective use of existing vaccines lie.

While the influenza vaccine has been reasonably successful (approximately 50% efficacy), a number of key scientific and policy challenges have emerged. These challenges also raise significant opportunities for improvement in influenza vaccination. First, as previously noted, influenza vaccine virus strains classically have been grown in eggs. However, recent advances allow production of these viruses in a more controlled, modern environment that permits more effective vaccine production. Specifically, genetic engineering now allows scientists to make different types of influenza virus in the laboratory using animal cells. Because this is being done using recombinant DNA methodology (cloning), the viruses can be more readily and rapidly made to reflect the makeup of the influenza viruses that are circulating in a given year. These types of technologies would also be particularly useful when applied to rapidly emerging epidemic strains of virus such as H5N1 or H1N1 influenza. The primary hurdle is assuring safety and swift implementation of these methods through regulatory mechanisms. The ultimate key to success in fighting influenza is the development of a vaccine that is effective against almost all strains of influenza, yet the development of a "universal vaccine" remains a major scientific challenge.

[3] The WHO estimates that influenza causes 3 million to 5 million cases of severe disease and 250,000 to 500,000 deaths every year.

Another issue that affects all vaccines is the current lack of clinically useful and available adjuvants, which are substances that potentiate the immune response to a given virus or bacteria that is being vaccinated against. Developing adjuvants is a major scientific challenge and also a regulatory one, as safety must be clearly delineated. Improvement in adjuvants has the potential to benefit the development of all vaccines.

Policy issues

- To not lose the battle to the vaccine deniers, policy makers must initiate a vigorous campaign to encourage vaccine uptake and combat vaccine misinformation. A vigorous public campaign that includes well-known political figures and celebrity volunteers (and their children) receiving vaccines is in order. Public health officials should appear on radio and TV "talk shows" to promote vaccine usage.

- Policy makers should support improved efforts to develop vaccines by funding university and industry partnerships, since substantial industry involvement is imperative. Industry is now finding that vaccines can be profitable in addition to their remarkable public health benefits. As in all other vaccine endeavors, public/industry cooperation is needed to ensure original thinking and translation of interesting ideas into clinical utility.

- The FDA must be empowered to improve its performance by being given a mandate that is compatible with progress, as well as substantially more funding from taxpayer and industry dollars. This would also improve the ability to attract more talented individuals to the FDA and similar agencies in other countries. Unfortunately, the present FDA budget, which already is insufficient, is facing a US$200 million cut by Congress. If we want both efficient progress and attention to safety, we must be willing to pay for it.

- In view of their life-saving potential, vaccine regulatory decisions should be made on a "fast-track" system. This would also apply to new methods of making vaccines, such as molecular technology for making new influenza vaccines.

- The focus of much influenza vaccine research should be the development of a universal influenza vaccine and better adjuvants.

- Governments should invest heavily in vaccination campaigns and should actively seek support and cooperation from nongovernmental organizations to implement the use of vaccines, many of which are available at a reduced price for use in poor countries.

References

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The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. David Markovitz (see above). Dr. Markovitz initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Markovitz. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Markovitz, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Vaccines save lives from infectious diseases. Yet, an anti-vaccine movement has emerged that has increased vaccination refusal among the public. The issues associated with accurately communicating the benefits and risks of vaccines must be more vigorously addressed jointly by scientists and policy makers.

- Since successful public messaging campaigns are critical to improving vaccine uptake, scientists and policy makers must improve their communication skills (e.g., via training programs). Novel approaches to conveying such reliable information must be considered (e.g., employing celebrities or other public figures to act as appropriate spokespersons).

- Because vaccine research and development is greatly dependent on perceived profitability within the pharmaceutical industry, public-private partnerships are a useful mechanism for stimulating vaccine innovation. New public-private partnerships must be created and existing partnerships among government, academia, and the private sector must be strengthened.

- Fostering a culture where all sectors view public-private partnerships as collaborative and mutually beneficial will bolster these collective efforts to improve research and development and, thereby, improve the appropriate use of vaccines. Incentives to pharmaceutical companies for establishing public-private partnerships (e.g., tax breaks, first-in-line privileges, and guaranteed number of buy-ins) are needed to encourage participation. Problems associated with the short-term (generally annual) government budgets and longer-term interests of the private sector's research efforts also need to be reconciled.

- The pace of regulatory decisions concerning vaccines should be accelerated without lowering safety standards. However, caution must be exercised in how a faster regulatory process is explained to the public to prevent such changes from being viewed as unsafe or risky. Entrenched attitudes within the regulatory agencies responsible for vaccine review are a barrier to transforming regulatory processes. It is critical that misplaced confidence in oversight and issues of self-interest within regulatory agencies be avoided by enhancing the professional experience and standing of their employees (e.g., by increasing the number of staff, creating more stimulating roles for talented scientific regulators, and providing new opportunities for scientific education and advancement).

Current realities

There was general consensus throughout the discussion that vaccines have been remarkably effective tools for saving many lives worldwide from infectious diseases. However, it was also agreed that, despite the demonstrated efficacy of vaccines, vocal and popular critics have instigated an effective anti-vaccine movement that has exaggerated the risks associated with vaccines. The anti-vaccine movement has been successful in increasing vaccination refusal among the public, despite the fact that there is still widespread acceptance within the public health community that vaccines offer a favorable benefit/risk profile. This disparity between the views of health care professionals devoted to examining the scientifically credible information and a small but vocal part of the public underscores the gap between scientific understanding and public acceptance. This topic became a central issue throughout the debate.

Vaccine research and development is largely dependent on perceived profitability within the pharmaceutical industry. While it was acknowledged that vaccines do not have the same profit margins as drugs for chronic health issues, public initiatives and funding have helped create public-private partnerships that have offset industry's economic concerns and have encouraged increased vaccine innovation. Additionally, it was noted that the public likely does not fully understand how vaccine research and development is supported. Issues regarding vaccine uptake among the public were also raised. The example of the significant amount of government financial support for an influenza vaccine and the public reluctance to use the vaccine was noted.

During the discussion of the effectiveness of market forces as catalysts for vaccine development and distribution, it was suggested that the concept of trickle-down economics has influenced the increased dissemination of some vaccines. This influence has been especially effective when vaccines were created in wealthier countries to address not only infectious diseases domestically, but also major needs in less-wealthy regions of the world. Although it was recognized that trickle-down economics can provide benefits in promoting both vaccine research and dissemination, there was substantial disagreement regarding the policy role that trickle-down economics should play in disease control. In particular, concern was voiced that wholesale reliance on market forces is not sufficient to ensure access to the quantity of life-saving vaccines needed to address worldwide needs.

The procedures and funding for the United States Food and Drug Administration (FDA) were identified as major sources of delay in the approval process for vaccines. As an example, the FDA vaccine review group does not currently have enough employees to conduct internal research both thoroughly and quickly. As a result, the timeline required for vaccine market approval remains far too long. A similar situation exists in Europe. Many regulators within the FDA and its European counterpart, the European Medicines Agency (EMA), may be comfortable with the status quo related to vaccine review because they benefit from the security associated with the current detailed and cumbersome process.

The liability and litigation procedures relating to vaccines approvals have historically also been major barriers to innovation and progress. The promotion of serious tort reform was identified as a critical step to improving the approval process while protecting public rights.

Scientific opportunities and challenges

It was widely agreed that confirming the scientific validity of evaluations of vaccine safety and efficacy, as well as communicating the benefit/risk information to the public, are ongoing challenges for both the scientific and governmental communities. Scientists must first be able to

validate the safety and value of a particular vaccine and then, in turn, to effectively convey this information to public health officials. While it was agreed that the scientific community is generally capable of confirming vaccine safety, it was argued that its members are less skilled in providing clear and informative messages to policy makers. These scientific and policy groups must jointly take responsibility for conveying the resultant understanding to the public in a fashion that reassures the lay person and encourages appropriate vaccine uptake. There was strong support that these communication skills must be significantly improved in both the scientific and policy communities that deal with infectious diseases and the use of vaccines.

There was general consensus that the anti-vaccine movement is a serious barrier to the appropriate use of vaccines and requires more attention from the scientific and policy communities. Discussion centered on the need for more effective public messaging campaigns to appropriately counter the influence of those who question the value and safety of vaccines. Some advocated for the scientific community to take the lead in carrying out the message against the anti-vaccine movement and that, to do so effectively, scientific leaders must develop better communication skills.

Although public-private partnerships for vaccines do exist among government, academia, and the private sector, there was consensus that such partnerships need to be strengthened. Embracing opportunities to enhance such partnerships through both financial and regulatory avenues was strongly endorsed. In addition, the importance of fostering a culture where all sectors view the process as collaborative and mutually beneficial was emphasized.

Vaccine research and development is a protracted process that requires substantial investment over long periods of time. It was widely noted this has been a continued challenge for public-private partnerships between government and the pharmaceutical industry due to the misalignment of short-term (generally annual) government budgets and the longer-term interests of industry's research efforts.

It was emphasized that the current FDA organizational structure related to vaccine approval needs to be altered to accelerate the pace of regulatory decisions. Within this, it was noted that regulators and manufacturers have adapted to the current process and, therefore, may resist any substantive changes. There was also consensus that any regulatory improvement should not lower safety standards, and that the public perception that the process is being unduly accelerated should be avoided. Currently, user fees (i.e., fees paid by industry to the FDA at the time of product review) play a significant funding role for FDA review activities, and any structural funding changes must consider the size and use of these fees.

There was general agreement that the creation of a universal influenza vaccine would provide a significant opportunity to improve human health globally. However, the issue of whether this type of vaccine can in reality be created was raised. Consensus was reached that the concept of a universal influenza vaccine must be evaluated in a multidisciplinary review. In addition, there was agreement that other new ideas should also be reviewed from the outset to avoid the repetition of past missteps (i.e., attempts to implement initiatives that were never properly reviewed and later deemed scientifically unsound).

Policy issues

It is critical that a realistic mechanism be found that provides formal communication training for those scientific and policy leaders who are increasingly responsible for effectively communicating the risks and benefits of vaccines to the public. Public understanding and confidence in the safety and efficacy of vaccines remain an essential step for increasing vaccine uptake. The public and scientists would also benefit from a better understanding of how the

government works to establish the safety and efficacy of vaccines. Several different fellowship programs were discussed for scientists, which provide an opportunity to work in government offices on a short-term (e.g., two weeks) or longer-term (e.g., one or more years) basis. It was noted, however, that there is no one optimal track for all scientific leaders.

It was strongly recommended that tactics to combat the anti-vaccine movement center on providing messages to the public that are credible, clear, and appropriate for a lay audience. It was further proposed that celebrities and/or other public figures be engaged in the process to present the information through the media.

There was agreement that the wide variety of stakeholders associated with vaccine research, development, and delivery must be involved in any public-private partnership. Government, academia, and the private sector all have significant roles to fulfill. It was also noted that some less-traditional areas of government should be included in these partnerships. For example, it was suggested that the U.S. Department of Defense (DoD) be included since it has been successful in integrating the views of stakeholders from academia, government, and the private sector.

Incentives to establish public-private partnerships are important to facilitating cooperative efforts. Incentives from government to industry could include direct financial support through contracts and grants, tax breaks, regulatory consultations during the research and development process, first-in-line privileges, and guaranteed number of buy-ins. Incentives from government to academia could include new grant funding targeting vaccine research and technology and employment opportunities for qualified graduates trained in vaccine research and development.

In addition, the regulatory process related to vaccine development and approval needs to improve. While only regulatory agencies are positioned to implement such changes, discussions with the private sector are needed to facilitate reasonable outcomes. Entrenched attitudes and wholesale acceptance of the status quo were consequently deemed counterproductive to the improvement of regulatory practices. As part of these efforts, increased staffing within the FDA was endorsed. It was proposed that, in addition to funding for supplementary positions, attracting talented scientific regulators is imperative. Expanding opportunities for FDA employees to be engaged in more creative activities (e.g., promoting grant opportunities and encouraging research/publication) was cited as a valuable tactic that should be considered to improve the culture of the FDA working environment and attract new scientific talent.

It was repeatedly mentioned that the existing regulatory bottlenecks for vaccine approval must be removed. This issue was considered of particular importance in the event that efficacious vaccines are developed for high-burden diseases, such as HIV/AIDS. While it was suggested that the establishment of regulatory reciprocity networks might decrease vaccine approval delays by pooling resources and reducing duplication of efforts, it was agreed that such an approach required further study on its viability and efficiency.

There was general agreement that vaccine approval acceleration should be pursued, but it was asserted that caution must be exercised in how a quicker process is marketed to prevent the public from viewing these changes as unsafe or risky. For example, it was proposed that such acceleration should not be characterized as fast track.

From a policy perspective, vaccines can be viewed as victims of their own success. As the prevalence of a disease controlled by a vaccine diminishes, political interest in the disease wanes and the public develops a skewed view of the benefit/risk profile. Lessened public and political interest in existing vaccines can narrow the market for a particular vaccine, which can reduce manufacturer interest in producing it. When this occurs, supplies often diminish, access

may be negatively impacted, and support/funding for research into new vaccines is frequently impaired.

The comparative value of high-impact, low-cost public health measures (e.g., clean water) versus vaccines was discussed. While it was questioned whether funds would be better spent on improving general public health, no complete agreement was reached on this point. It was argued, however, that even with rising, global economic pressures, it should not be necessary to choose between basic public health measures and vaccines. In part, this is because their funding sources often differ. Public health measures are generally funded through governments and international organizations. Conversely, vaccine development is substantially funded by for-profit companies in affluent countries, potentially benefiting all world sectors. While it was agreed that these investments should be carefully scrutinized, it was also noted that investment in both areas are fundamentally important for infectious disease prevention worldwide.