Would You Ever Recommend Driving a Motorbike Without a Helmet?

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Summary

Vaccines prevent infections by mimicking them and eliciting memory of this event so that our bodies will eradicate the microorganisms once they show up, even decades after vaccination. The eradication and control of diseases such as smallpox are examples of the effectiveness of vaccination. Not only are vaccines effective, but they have proven to be a cost-effective method of disease management and should be further explored in the fight against infectious diseases. The advent and continued development of synthetic biology have contributed significant new avenues to vaccine development and production. These new paths will allow for the quicker, increased, and cheaper production of vaccines — which in turn allow for the wider use of vaccines, especially in resource-poor countries. Recent anti-vaccine movements have threatened the uptake of vaccines across the world, especially in developed countries, and have led many parents to refuse to vaccinate their children. This negative outcome has contributed to the resurgence of diseases that were previously conquered in these countries, such as measles and mumps. Vaccines are an important resource in the toolbox for the prevention of infectious diseases. However, by inadequately championing the development and use of vaccines, policy makers still do not fully take advantage of the disease-prevention opportunities that they provide. In this paper, we discuss two issues relating to vaccines: 1) the use of existing vaccines, and 2) research activities to discover new vaccines. We will expand first on why we do not vaccinate every single person in the world with the available vaccines, and second why we do not increase public and private investment in synthetic biology research aimed at vaccines against all infectious diseases that impact human and animal health.

Current realities

Infectious microorganisms are the only living organisms on earth that have succeeded in exploiting man. Yet, vaccines effectively prevent infections by mimicking them and eliciting memory of this event, so that our body will eradicate the microorganisms once they show up, even decades after vaccination. The burden of infectious diseases has been enormously reduced through vaccination, leading to the eradication of some diseases (e.g., smallpox) and near eradication of others (e.g., polio). Diseases such as tetanus and diphtheria are very rare in the developed world, and others (e.g., meningitis due to pneumococcus) would virtually disappear if available vaccines were implemented to cover all pediatric populations. Although infections are mostly regarded as a problem of developing countries or of a small fraction of hospitalized patients in developed countries, it is noteworthy that infections are responsible for many life-threatening diseases and that chronic infections are associated with 10%–15% of all tumors (zur Hausen, 2009). Also of note, vaccines are among the best anti-cancer remedies because they can prevent some infections that cause tumors, such as hepatitis B (HBV) (responsible for liver tumors) and human papilloma virus (HPV) (responsible for cervical cancer).

Because vaccines prevent diseases by avoiding infection onset and disease development, they are the ideal remedy. Furthermore, vaccines are probably the most cost-effective tools we have to avoid infections. The cost-effectiveness of vaccines has been calculated by comparing the cost of a vaccine with the overall cost of therapy, hospitalization, and lost working days. For example, the Centers for Disease Control and Prevention (CDC) estimates that measles, mumps, rubella (MMR) vaccination saves US$16 for every US$1 spent for vaccines. This calculation does not take into account the value of avoiding the disease — the “intangible” value of being healthy. Vaccines have typically been viewed as low-tech medical remedies that should have low prices. Previously, the cost per vaccine dose was generally less than US$1. Since the introduction of the first recombinant vaccines, however, vaccine-development costs have been on par with cutting-edge, high-tech products. Yet, public health agencies have continued to ask for something that is impossible: high-tech *and* low-price products. The introduction of synthetic biology offers the opportunity to reduce development costs and therefore generate products that are high tech at moderate prices.

A reductive, though widely accepted, definition of synthetic biology is that it is a synthetic science that seeks to construct novel molecules and systems for useful (in our case, medical) purposes. Synthetic biology has already made some significant contributions to therapeutic medicine, such as artemisinin, the most-effective known anti-malarial drug. In preventive medicine, the introduction of genomic approaches to vaccine development has shown there is a gap between the development of technology and tools, and their applications. The difficulty of translating tools into applications is an obstacle for the growth of the vaccine field. So far, applications have focused on individual products rather than on developing a technology base to support many different products.

Although in the past some vaccines had poor safety profiles, mostly due to poor manufacturing, in the past 20 years, vaccine development and production have resulted in biological vaccines with optimal safety profiles. However, anti-vaccine movements (mainly in developed countries) consider vaccination an unnatural practice that can itself cause diseases in healthy individuals. Moreover, a few fraudulent publications have been used to give scientific dignity to the anti-vaccine movement. For example, the MMR (measles, mumps and rubella) vaccine has suffered a violent campaign against its use after an academic publication linked this vaccine to children's autism (Wakefield et al., 1998). This paper resulted in a dramatic decrease in MMR vaccination coverage, leading to the lethal spread of these diseases in countries, such as Canada and Switzerland. This paper was fully retracted in 2010, after it was demonstrated this research was carried out with dishonest and unethical conduct.

Scientific opportunities and challenges

The first key question is why do we not vaccinate every single person in the world with the vaccines that are presently available? The answer to this question is twofold, depending on the part of the world to which we refer (i.e., more-affluent or less-affluent countries). In more-affluent countries, the major obstacle to universal vaccine coverage is the anti-vaccine movement. This movement finds strong support among those who perceive recombinant DNA technology (call it molecular, system, or synthetic biology) as a sort of unnatural evil that puts vaccinated individuals at risk of terrible diseases in the future. In less-affluent countries, it is a matter of economic priorities of the governments, as well as of the type of help they receive from more-affluent countries. Not only is donor money needed for less-affluent countries, but proactive educational campaigns need to be promoted in those countries and logistical help needs to be provided for vaccine distribution.

The second key question is why do we not increase investment in research to develop vaccines against all infectious diseases that impact human and animal health? Synthetic biology provides, for the first time, the possibility to develop vaccines against the great majority of infectious diseases. This applies to even the most complex and difficult diseases, as was the case for the meningococcal B vaccine. Increased investment in research depends on the priorities of those making key decisions related to research programs in the public and private sectors. We should provide solid arguments showing how these investments can be rewarding from economic, social, and political perspectives. For example, infectious diseases can impact economies (including those of more-weathy countries), as recently shown by the economic impacts of severe acute respiratory syndrome (SARS) and pandemic influenza. Research has also found a possible relationship between a country's child death rates due to vaccine-preventable infections and their probability of engagement in armed conflict. Researchers suggest that vaccines, by preventing mortality, can "function as agents of conflict resolution" (Hotez, 2001). Among the challenges that synthetic biology could help to address in the vaccine field is the development of tools to generate more applications. Synthetic biology should help define approaches that promote the implementation of genomic technologies and tools that allow commercially viable scales and time frames for the development of multiple vaccines.

Policy issues

- In a time of budget cuts in research and prioritization of programs, a long-term investment in synthetic biology for new vaccines to prevent infectious diseases (that certainly will affect a sizeable fraction of our world) should be considered as an alternative to complex and expensive defense programs to prevent possible bioterrorist attacks (that most likely will never affect anybody). Moreover, synthetic biology could help spread in the private sector the impetus to invest in the development of tools to generate more applications.

- Government funding for infectious-disease research should be restructured to consider a less-expensive passive immunization strategy for microorganisms that have potential interests for bioterrorists (e.g., anthrax). This strategy should be based on zero research activity and the stockpiling of newly produced monoclonal antibodies. However, most of the public research investment should be targeted toward active immunization (i.e., vaccinations).

- Financial investments aimed at achieving full-vaccination coverage in developing countries should be considered a peacekeeping effort and instruments of foreign policy. This visionary use of vaccines should be rewarded by the funding of vaccine research from agencies dedicated to peacekeeping activities, such as the United Nations (UN).

- We should proactively campaign for scientific education that could avoid a society of charlatans denying scientific successes and asserting the danger of vaccines as anti-natural tools that are created only to generate profits at any cost. An appropriate media campaign should be launched by public-health agencies to educate the public on the safety of synthetic biology, the value of vaccines, and the concept of disease prevention rather than treatment

- Consider vaccines as the most solid helmet one can wear that will protect us from collision with infectious microorganisms throughout our fast lives. Finally, ask whether you would ever recommend driving a motorbike without a helmet.

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. Sergio Abrignani (see above). Dr. Abrignani 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. Abrignani. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Abrignani, 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 are a cost-effective method of disease prevention, yet children around the world still frequently die from vaccine-preventable diseases. Barriers to vaccine coverage are complex and, in general, are often different in less-wealthy regions (e.g., economic barriers to distribution and theories of conspiracy by the West) than in more-wealthy regions (e.g., anti-vaccine sentiments and low perceived risks of disease due to herd immunity).

- Strategies to promote vaccine uptake must be developed and improved. Such efforts should include messaging which strives to achieve a social consensus that all eligible individuals must be vaccinated. International sharing of best practices and lessons learned in the area of risk communication related to vaccines must also be encouraged. Efforts outside of the realm of messaging also need to be further researched and considered for implementation (e.g., penalties and mandates). Social scientists, such as communication experts, should be included in this work.

- Leadership is needed to develop a consistent, single statement of strong commitment for universal immunization — vaccinating all eligible individuals with all existing vaccines. To obtain a mutually supportive "one voice" for vaccine use, all the stakeholders, including scientists, physicians, academics, societal leaders, and governmental policy makers, must have access to detailed, credible information about logistics, feasibility, and benefits of a universal vaccine coverage effort.

- National and international leaders should consider the value of universal vaccination as an issue related directly to security and social stability. The use of vaccines may also have a role to play in foreign policy and national security.

- Synthetic biology, a relatively new area of biological research, is changing the way that vaccines are designed and manufactured, allowing for the more-rapid and lower-cost production of vaccines. For scientists and policy makers to accurately discuss credible options and to collectively create effective policies related to synthetic biology, the development of a clear and coherent definition of synthetic biology is necessary.

- Passive immunization using monoclonal antibodies, particularly after an outbreak, is not currently a viable alternative to active immunization due to considerable challenges including logistics, clinical trial problems, storage and shipping issues, and high cost. From a military perspective, ensuring a state of readiness for troops via active immunization is preferable to employing passive immunization after a bioterrorist event.

Current realities

There was consensus that vaccines can and do effectively prevent infections; they have saved many lives and have the potential to save many more. In addition to their high degree of efficacy, it was generally agreed that vaccines are a cost-effective method of disease prevention. However, children around the world still frequently die from vaccine-preventable diseases because the appropriate vaccines either are not available or not taken.

Although there was general agreement that the use of vaccines should be promoted, it was also recognized that immunizations are often thought of as a privilege and not a right. This distinction is not new and has been previously demonstrated in other social areas. Formal education, for example, used to be a privilege only available to a select few. Now, education is often viewed as a right. In some countries, not only is education mandatory, school nonattendance is a crime.

Individuals, regardless of their intelligence or educational status, often do not base their decisions on rational risk assessment. The reluctance to take available vaccines can often be attributed to an unconfirmed fear of the potential negative consequences. A “negativity bias” frequently causes people to focus on dangers rather than benefits. When individuals perceive a situation as out of their control, they often make decisions that may appear to be irrational, such as ignoring public health recommendations related to vaccination.

Synthetic biology was recognized as a relatively new area of biological research that is changing the way that vaccines are designed and manufactured by reshaping development and production factors such as speed of development, availability, and cost. For example, it was noted that synthetic biology has enabled scientists to create a wide range of new antigens. Synthetic biology has enabled more rapid production of vaccines at lower cost, which was generally perceived as a significant benefit, especially for resource-poor countries.

The differences between passive and active immunization were discussed. Passive immunization was explained as the administration of *in vitro* produced antibodies or *in vitro* primed immune cells. Both can recognize a specific antigen (i.e., a toxin or other foreign substance that induces an immune response) within the body of a non-immune individual. Passive immunization provides only temporary immunity, meaning it must be frequently repeated, but passive immunization is useful because protection is immediate. Active immunization was defined as the administration of antigens, which then causes the body to create its own antibodies. Because the body produces its own antibodies, protection against disease may last anywhere from several years to a lifetime. However, active immunization is not useful in all scenarios (e.g., bioterrorist attacks) because it may take several weeks for protection to take effect.

It was noted that mandates concerning the use of vaccines vary by country, as well as within countries (e.g., vaccine mandates in the United States are a state issue). Mandates have also changed over time in some countries (e.g., in Japan, vaccination is no longer compulsory) due to political and legal factors.

Scientific opportunities and challenges

The debate emphasized the significant and complex barriers to vaccine uptake by the public. The lack of a single global voice among scientists, physicians, policy makers, and other interested groups was cited as a key obstacle to the public's view of universal vaccination worldwide. It was also highlighted that barriers to vaccine uptake in less-wealthy regions are different than barriers in more-wealthy parts of the world. While it was suggested that economic factors comprise the principal barrier to vaccine coverage in less-wealthy areas, it was also proposed that non-economic issues can be equally problematic. For example, conspiracy theories, such as polio vaccines from wealthier countries purposely containing anti-fertility agents, have led to low polio vaccine uptake within certain countries during the past decade. In addition, attention was drawn to social, behavioral, and logistical factors as noneconomic barriers to influenza vaccine uptake in less-wealthy regions. In more-wealthy countries, the anti-vaccine movement, based on unconfirmed fears of acquiring secondary diseases, was identified as a major barrier to vaccine uptake. However, other issues were also identified. During the H1N1 influenza pandemic, for example, anti-vaccine groups played only a minor role in vaccine refusal. More influential factors, including risk perception and decision-making theory, were cited as determinants of noncompliance with H1N1 vaccination recommendations. It was also noted that many parents believe herd immunity will protect their children, even if they are unvaccinated.

Negative side effects from vaccination are generally infrequent (e.g., severe measles vaccine side effects are rare, but have been observed), yet the public's perceived risk of side effects was considered a significant barrier to vaccine uptake. When adverse effects do occur among a small group, it can quickly heighten public concern and escalate rates of vaccination refusal — thereby driving up disease incidence. It was suggested that scientists and policy makers must acknowledge that the decision to vaccinate children can be a difficult one for many parents. Overcoming parents' perceptions and concerns about their children's health will likely be a continuing challenge, but one that must be effectively addressed.

There was considerable discussion regarding the definition of synthetic biology. It was pointed out that a simple Google search reveals multiple definitions, and that even experts do not have a universally agreed-upon definition. Although there was no consensus, a proposed definition was, "the science that is producing life." It was further purported that the definition of synthetic biology varies depending on the context of the discussion, since it is comprised of multiple components. One component of synthetic biology, for example, is the manipulation of DNA (or genomes) to make new organisms; another is using biologic parts to perform specific functions. It was also noted that the term systems biology is sometimes used interchangeably with synthetic biology. It was contended that from a policy maker's perspective, it is important to have a clear and coherent definition based on well-defined scientific terms.

Scientists are beginning to achieve new successes in vaccine research due in part to advances made through synthetic biology. As technology has evolved, opportunities to develop vaccines that produce correlative, or sterilizing, immunity (i.e., completely prevent an infection in addition to preventing clinical disease) have expanded. Yet, this type of vaccine is still not possible for many diseases. For example, in recent years, research has focused on vaccines that produce sterilizing immunity for human immunodeficiency virus (HIV), but such research has not been successful. It was pointed out that some diseases do not, nor ever will, have a "helmet." Some will only have "brakes."

Some research has shown a statistical association between higher vaccine coverage and lower rates of armed conflict in a country. Such findings were used to justify support for promoting vaccines for the purpose of aiding peacekeeping efforts. However, significant questions were raised regarding whether the statistical relationship reflects a true association or is actually the result of other, confounding factors.

Policy issues

There was general consensus that a single statement of strong commitment for universal immunization (i.e., vaccinating all eligible individuals with all existing vaccines) is essential — one voice among scientists, physicians, academics, societal organizations, governments, and policy makers. Questions were raised about who would lead such an effort to speak in a single voice. Specifically, the UN was identified as a potential vehicle. However, it was pointed out that the UN may not be an appropriate organization to take the leadership role primarily because it does not conduct vaccine research.

To commit to the idea of one voice, it was argued that policy makers will need more detailed information, including how many vaccines are involved, the logistics of vaccine distribution, the feasibility of a universal coverage effort, and the benefit-risk profile of vaccines. It was urged that additional information and research in these areas be developed to provide policy makers with a clear, positive way forward.

Concern was expressed that public trust could be damaged if problems arose as a result of a universal vaccination promotion effort. It was concluded, however, that published data strongly indicate that the benefits of moving forward outweigh the risks. While some also asserted that a forceful, unified statement about universal vaccination should be made regardless of the availability of funds, others countered that conversations about logistical factors (e.g., how to pay for the effort) should be the first step in the process.

The possibility of using mandates and penalties to boost wider vaccine coverage was debated. It was suggested that instead of making vaccinations compulsory, penalties might be more effective (e.g., prohibiting unvaccinated children from attending public school). However, the feasibility of penalties was questioned and there was disagreement over the effectiveness of such approaches. It was argued that coercive strategies are often counterproductive.

The importance of messaging to promote vaccine uptake was widely expressed. It was agreed that current dialogues with the public about the importance of vaccination are frequently ineffective. There was consensus that messaging or marketing efforts should strive to achieve a social consensus that all eligible individuals must be vaccinated. Such messages need to be articulated in terms that are meaningful to the lay public.

It was generally agreed that the scientific community and policy makers should include social scientists (including communication experts) in efforts to promote the acceptability of vaccines. When moving from the basic science to implementation, the point was raised that researchers who understand the uptake of ideas, namely social scientists, are necessary.

It was suggested that there should be more international sharing of best practices and lessons learned in the area of risk communication related to vaccines. The importance of building on existing success stories was highlighted (e.g., how many lives were saved due to vaccination).

Recent influenza vaccine promotion exemplified a successful messaging effort. Due primarily to H1N1 messaging in the previous year, influenza season vaccination coverage of U.S. children reached its peak in 2010–2011. A suggestion was also made that communication should emphasize the return on investment of vaccines, since numbers often resonate with people. In terms of lessons, learning from failed public health efforts was endorsed. For example, it was purported that the repeal of the motorcycle helmet law in one Virginia county resulted from the framing of helmet use as a personal liberty instead of underscoring societal health implications (e.g., health care costs). It was argued that this scenario demonstrates the importance of exercising caution when developing vaccine and other public health messages.

The importance of communication was not disputed. However, it was argued that education alone may not be sufficient for increasing vaccine compliance. People are typically not good at making risk/benefit assessments, because of the tendency to focus on fear of the unknown and anything that is uncontrollable. It was therefore suggested that other strategies should also be developed.

It was advised that instead of likening the risk of not being vaccinated to riding a motorbike without a helmet, a more appropriate analogy would compare it to driving a Lamborghini without a seatbelt. While there is a small risk associated with wearing a seatbelt, it is still recommended that drivers and passengers wear them.

Based on research linking higher national vaccination rates to lower prevalence of armed conflict, it was recommended that vaccinations should be seen as a defense issue and part of a peacekeeping effort. While it was proposed that an international body (e.g., the UN or the Group of Eight [G-8]) should be convinced to view vaccines as an instrument of foreign policy, it was strongly counterargued that this proposal requires further substantiation based on experience.

There was consensus that vaccination should be viewed as a national priority by governments. Many also argued that vaccination should be considered a defense issue. The point was raised that the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), one of the most successful and well-funded programs, was only brought to action when HIV/AIDS was made a U.S. security issue. This sentiment, however, was not unanimous. In terms of implementation, there was an appeal for using non-security apparatuses (in contrast to national security forces) to achieve vaccination goals.

There was general consensus that universal immunization is important. However, this dominant viewpoint was disputed by an assertion that expanding other public health efforts (e.g., clean water and sanitation) may be a more effective strategy for preventing infectious diseases than increasing vaccination rates. It was argued that because vaccination campaigns have not always been completely successful (e.g., for polio), disease prevention may be better achieved and a greater return on investment maintained through the development of clean water and sanitation systems. This assertion was vigorously debated and much dissent was expressed. It was counterargued that clean water provision is not a fail-safe solution — in the 1950s, more-wealthy countries experienced high levels of morbidity and mortality from polio despite the presence of clean water. The prevailing view was that vaccines and other preventive public health measures are both essential, and therefore should not be considered mutually exclusive.

Because limited funds are available for vaccination efforts, resources must be prioritized. The relative merits of allocating funding for passive versus active immunization were extensively debated. It was proposed that governments should redirect spending to a passive immunization strategy. This view was based on the assertion that passive and active immunization could be equally effective, and for some diseases passive immunization may be more effective. It was further contended that diseases for bioterrorist attacks (e.g., anthrax) should be prevented via passive immunization because active immunization is generally ineffective post-exposure. However, there was no general agreement on this point. It was counter-argued that passive immunization using monoclonal antibodies, particularly after an outbreak, is not a viable alternative due to considerable challenges including logistics, clinical trial problems, storage and shipping issues, and high cost. Moreover, from a military perspective, it was argued that ensuring a state of readiness for troops via active immunization is preferable to employing passive immunization after a bioterrorist event.

There was disagreement regarding the efficacy of wealthier countries donating vaccines to less-wealthy countries versus helping less-wealthy countries set up the requisite technology for developing their own vaccines. It was pointed out that successful efforts currently exist to help less-wealthy countries develop their own vaccine production (e.g., by the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority [BARDA] and the World Health Organization [WHO]). Additionally, some less-wealthy countries, such as India, are already moving rapidly to produce their own vaccines. It was argued, however, that while sponsoring the building of production plants may be an appropriate strategy in countries such as India and China, technical and infrastructural difficulties may hinder similar efforts elsewhere.