

A REPORT FROM THE AMERICAN ACADEMY OF MICROBIOLOGY

VACCINE DEVELOPMENT:

CURRENT STATUS AND FUTURE NEEDS



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EXECUTIVE SUMMARY

The American Academy for Microbiology convened a colloquium March 4-6, 2005, in Baltimore, Maryland, to discuss vaccines, current infectious disease problems, the potential for new and better vaccines, vaccine safety, research issues surrounding vaccines, and education and training topics. Twenty one experts in vaccine research and development from academia, industry, and government deliberated and determined several recommendations for future progress in creating and applying vaccines.

The success of vaccines in controlling disease has been profound. Many diseases that formerly raged unchecked are now under control and others have been eliminated in parts of the world. Despite this success, many infectious diseases continue to seethe and strike, particularly in developing nations where vaccines are unavailable, unaffordable, or both. Other diseases are poised for upsurges in incidence, either by “natural” (i.e., non-human induced means) or at the hands of bioterrorists. Vaccines are available for some of the diseases that continue to plague humans, but not for others. Even when a licensed vaccine is available for a given disease, numerous barriers can block its use, including technical, economic, cultural, and legal obstacles.

The licensed vaccines currently available are powerful, but in many cases improved formulations are needed that offer better effectiveness, longer protection, or lower production costs. Of course, vaccines are also needed to provide protection from the infectious diseases that have not yet been targeted with a vaccine. Researchers and vaccine developers face a number of hurdles in devising these novel vaccines, including a lengthy sequence of required tests and validation steps.

The safety of vaccines is paramount and has increased enormously during the last two decades. Proven adverse events from the use of licensed vaccines are rare, and vaccines with known safety problems have been removed from the market. Anecdotal links between vaccines and a number of disorders have been discredited, but the controversy

over these alleged ties remains. Rational evaluations of vaccine safety need to account not only for the risks, but also the benefits vaccines offer the person vaccinated and his or her community.

Vaccine research can benefit from the use of many promising new approaches and methods. Scientific unknowns with respect to vaccines, including the details about how vaccines work to provide protection and how different types of immunity are induced, stand in the way of further progress and need to be addressed. Much basic research remains to be conducted on these fundamental issues.

Vaccines can enhance the health and well-being of people all over the globe—a fact that needs to be better communicated to the public if misperceptions about vaccine-associated risks are to be overcome. The popular media, educational programs, and government-sponsored campaigns should be put to use in accomplishing greater public awareness of vaccine benefits.



INTRODUCTION

Vaccines are relatively new and powerful weapons against infectious disease. Past experience with pandemic influenza and a looming threat from a new strain of the influenza virus serve to illustrate just how important vaccines have become in protecting human health.

In 1918, the Spanish flu infected about a fifth of the world's population. With a mortality rate of 2.5%, the pandemic killed an estimated 50 million people worldwide. At the time, humans had to rely largely on their naïve immune responses to stave off infection. Since then, advancements in hygiene, modern medicine, and antimicrobials have afforded us some additional protection, but the war against influenza continues as flu pandemics strike again and again every 10-30 years.

Today, the world faces a new strain of influenza that could be as devastating as the Spanish flu. The influenza virus H5N1, a form of avian flu, has touched off small outbreaks in Asia twice in the past eight years with a 52% mortality rate—a shocking statistic. If the avian flu were to spread to humans again and adapt itself to spread from person to person, the results could be disastrous.

Vaccines may be the best defense against avian flu. Unlike in 1918, it is now possible to design vaccines against influenza that can save millions of lives. Although it is far from clear which H5N1 strain to target in making an avian flu vaccine, let alone how to finance it, produce it, and ensure its safety, many scientists and public health authorities are optimistic that an H5N1 vaccine is within reach.

Ever since Edward Jenner's first experiments with cowpox and smallpox in 1796, humans have been using technology to enhance the immune system and combat the worst infectious diseases. Vaccines have controlled formerly widespread infections like pertussis, diphtheria and meningitis due to *Haemophilus influenzae* and nearly eliminated measles and polio. Although humans still fight disease every

day, vaccines have given us the upper hand against these and other major diseases.

FACTORS COMMON TO SUCCESSFUL VACCINES AND VACCINATION PROGRAMS

The most successful vaccines and vaccination programs share certain features that can be used as a roadmap for implementing new programs.

Successful vaccines are, first and foremost, highly effective. They bring about clear improvements in public health where they are applied and offer protection from disease for lengthy periods. Good correlates of protection (measures of vaccine effectiveness) are known for some successful vaccines.

Political and leadership factors also play roles in the success of vaccination programs. The political will and governmental support for improving public health must be in place to make vaccination work. Oftentimes, the participation of international bodies, like the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), or non-governmental organizations, like the Gates Foundation and Rotary International, are critical to success. Such organizations can provide important knowledge and credibility in addition to crucial financial support. The infrastructure to support disease surveillance and vaccine delivery is essential.

Practical matters critical to the success of vaccination include economic and supply considerations. Most often, successful vaccines are affordable vaccines, but all programs must, in the end, be supported by credible financing. Reliable vaccine supply is also critical for success.

In establishing an effective vaccination program, the public must be made aware of the benefits and risks associated with vaccines. The sense that vaccination is not only a personal decision, but also a public health measure, should be

instilled. The value of vaccines in preventing disease, thereby avoiding more costly and difficult treatment of disease, is also an important concept to convey. In these situations, educating leaders is a good first step in educating the public.

The relative importance of the various factors listed above can vary from one location to the next. The cost of a vaccine, for example, is more critical in poorer areas, and the participation of international bodies is needed only where sufficient governmental support for vaccination programs is not available.

DISEASES THAT HAVE BEEN CONTROLLED THROUGH VACCINATION

The success of vaccines has been profound; numerous diseases have been brought under control, particularly in developed nations. The best vaccination efforts have been able to either eradicate (wipe out worldwide) or eliminate (eradicate within national or regional boundaries) a given disease.

ERADICATED: SMALLPOX

The WHO officially declared smallpox eradicated in 1979—a feat that remains one of the greatest public health triumphs to date. As the only infectious disease that has been eradicated, the smallpox vaccination campaign was exceptional in many ways. The circumstances surrounding this disease and the vaccine were unique, and it should not be taken for granted that future vaccination programs will be able to duplicate this success.

The smallpox virus was an uncomplicated agent to manage with vaccines. It was represented by only a single strain, it lacked an environmental reservoir, and the symptoms of disease were easy to identify. Moreover, the smallpox vaccine was inexpensive, it was easy to administer, it could be manufactured in the field, and post-exposure prophylaxis was possible.

Today, safety concerns would make a program like the smallpox eradication effort much more complex. The reuse of bifurcated needles to deliver the smallpox vaccine, for example, would be dangerous today given the prevalence of bloodborne viruses, like HIV and hepatitis B. Strict attention to individual rights practiced today would prevent widespread application of a vaccine like vaccinia, the smallpox vaccine, which carries a number of health risks (even though smallpox itself is much more hazardous than the vaccine).

ELIMINATED DISEASES

Diseases widely regarded as “eliminated” from certain areas include measles and polio. Elimination of a disease from a specific region is not the same as eradication since the dis-

ease can return if the infectious agent is reintroduced into an area where vaccination coverage has been relaxed.

Vaccines have interrupted measles transmission in the western hemisphere, but outbreaks in Europe and Japan still occur from time to time, phenomena that reflect the comparatively low vaccine coverage in those regions that stem from anti-vaccine sentiments. On the other hand, low measles vaccine coverage and outbreaks in developing nations are products of spotty access to healthcare. Measles may never be eradicated without increased access to vaccines, enhanced surveillance, and a long-term financial commitment to the cause.

Polio has been eliminated from most countries, but it remains endemic in parts of Southeast Asia and Africa. In the mid-1980s, it was discovered that mass immunization programs are necessary to interrupt polio transmission—routine infant immunization was not effective. Polio was originally targeted for global eradication by the year 2000, but this goal has been postponed due to the failure in some regions to comply with universal vaccination.

CONSEQUENCES OF HALTING VACCINATION

Vaccination programs can end or fail for any number of reasons, including safety concerns, religious reasons, local supply failures, civil strife, financial problems, and others. Individuals can refuse vaccines for these same reasons. Halting a vaccination program can have serious consequences for public health, both locally and abroad.

Once a program is halted, or a large number of individuals refuse vaccination, the disease the program was designed to target inevitably returns. Examples of resurgence of a formerly managed disease abound; measles rebounded in parts of the U.S. and the United Kingdom, pertussis returned to Sweden, polio returned in Nigeria and other African countries, diphtheria returned to newly independent states after the break-up of the former Soviet Union, and the list goes on and on. After halting vaccination, it can be very difficult to return to the level of coverage achieved previously. In the absence of disease eradication, vaccination must continue.

CURRENT INFECTIOUS DISEASE PROBLEMS AND THREATS

Infectious diseases of concern to public health officials can be placed into two broad categories: problems and threats. Infectious disease problems include those conditions that have relatively high incidence rates, exhibit high morbidity or mortality, or have high economic impacts. Infectious disease threats include those diseases that are comparatively rare but have the potential to escalate in incidence in the near future. Vaccines are available for many of the diseases that pose problems and threats to public health, but a number of technical, economic, cultural, and legal barriers can impede the optimal use of licensed vaccines.

FOREMOST INFECTIOUS DISEASE PROBLEMS

Despite the best efforts of researchers, medical professionals, and public health officials, a number of infectious diseases continue to pose significant public health problems. There are two contrasting perspectives on what comprises a “significant” infectious disease problem—the view from developed nations and the view from developing nations. Diseases of concern in the developed world are strikingly different from diseases developing nations contend with, in part because of the success of vaccination efforts in richer nations. Also, some diseases are limited geographically for ecological reasons, like the need for a suitable vector or appropriate habitats. The agents listed in Table 1 are noteworthy for their high infection rates, for exhibiting high morbidity or mortality, or for their economic impacts in both developed and developing nations. Vaccines are available for some of these diseases, but not for others.

Currently, the most significant infectious disease problem worldwide is HIV. Spread by multiple modes of contact, the human immunodeficiency virus mutates readily, evading while simultaneously destroying host immune defenses and sidestepping antiviral therapies. To date, efforts to develop an effective HIV vaccine have been thwarted by enormous

technical challenges. Ongoing work looks promising, but a solution is still several years away. HIV, malaria, and tuberculosis are three of the world’s most significant infections, yet we do not have highly effective vaccines to prevent any of these diseases.

INFECTIOUS DISEASE THREATS

A number of infectious agents that are relatively rare today are poised for an upsurge in incidence by either “natural” (Table 2) or terrorism-related means (Table 3). The natural threats are led by the influenza strain H5N1, which, like many of the other natural threats, is a zoonotic organism, an infectious agent that crossed over from animals to humans. Originally found in poultry, the virus has sickened humans in Asia twice in the past decade. (See Box A for a discussion of this threat and the potential for developing H5N1 vaccines.) Zoonoses may quickly become serious problems for human health if the agents adapt to the human environment by mutation, recombination, reassortment, acquisition of new genes, plasmid or phage interchange of genetic material, or geographical advance of their vector.

Human pathogens that could be employed for terrorist purposes (Table 3) must be easily deliverable, but they need not be extremely virulent. Infectious diseases must only be severe enough to instill panic and disrupt civil life in order to be of use to a terrorist group. Many agents could be enhanced through engineering to either make the diseases they cause more severe or to enable the agent to escape vaccines or treatment.

BARRIERS TO OPTIMAL USE OF LICENSED VACCINES

The struggle to protect human health from an infectious disease hardly ever ends with development of a good

vaccine. A number of barriers lie in the way of employing licensed products, including technical, economic, cultural, and legal obstacles.

TECHNICAL OBSTACLES

Technical obstacles to optimal use of vaccines are led by a number of manufacturing issues. Oftentimes, a lack of sufficient manufacturers, vaccine or materials shortages, compliance issues, and problems with contamination can hinder widespread vaccine use. Recent experience in the United States has revealed the potentially disastrous effects of relying on too few manufacturers of a vaccine. The availability of influenza vaccine during the 2004-2005 flu season was severely hampered because of contamination in the product of one of the two flu vaccine manufacturers.

Vaccine incompatibility can also pose a problem. Combining vaccines reduces the number of injections necessary to protect an individual from infectious disease, and, therefore, usually increases the use of that vaccine (see Cultural Barriers, below), but certain vaccine formulations are incompatible. For example, the live oral cholera vaccine liquid formulation and live typhoid enteric coated capsule formulation are not compatible and must be delivered separately, diminishing the likelihood that each will be effectively distributed.

The expense and difficulty involved in replacing banned materials like calf serum (in vaccines for use in the European Union) and Thimerosal has resulted in abandonment of certain vaccine formulations. Thimerosal is the best vaccine preservative available, and its elimination has forced the industry to move away from multidose vials and toward single-use vials, products which are more expensive to manufacture and distribute.

Limitations on the method of delivery or the devices necessary for delivery can also limit the application of a licensed vaccine, as can the lack of uniformity in the vaccine administration schedules between different countries.

In addition to the universal barriers described above, the developing world faces several other technical challenges in deploying licensed vaccines. Oftentimes, vaccines cannot be manufactured in the developing world because of a lack of production facilities, technical expertise, or appropriate shipping and storage resources. Cold storage is required for most vaccines, but less developed nations cannot always accomplish this, leading to failures in vaccine quality. Infrastructure through which vaccine programs can be administered is often weak or nonexistent in the developing world, another factor that limits vaccine uptake. This deficiency can be found at all stages of program implementation, from a shortage of trained personnel at vaccination sites up to a shortage of qualified individuals in governmental agencies needed to design and administer vaccine programs. Finally, safety and liability concerns over

TABLE 1.

Infectious agents that pose significant human health problems in the U.S. or abroad

SEXUALLY-TRANSMITTED AGENTS	LICENSED VACCINE AVAILABLE?
HUMAN IMMUNODEFICIENCY VIRUS (HIV)	NO
HUMAN PAPILLOMA VIRUS (HPV)	NO
HERPES SIMPLEX VIRUS (HSV)	NO
CHLAMYDIA TRACHOMATIS	NO
NEISSERIA GONORRHOEAE	NO
TREPONEMA PALLIDUM	NO
RESPIRATORY AGENTS	
INFLUENZA VIRUS	YES
RESPIRATORY SYNCYTIAL VIRUS (RSV)	NO
PARAINFLUENZA VIRUS	NO
HUMAN METAPNEUMOVIRUS (HMPV)	NO
MYCOBACTERIUM TUBERCULOSIS	YES
HAEMOPHILUS INFLUENZAE TYPE B	YES
STREPTOCOCCUS PNEUMONIAE	YES
GROUP A STREPTOCOCCI	NO
CHLAMYDIA PNEUMONIAE	NO
MENINGOCOCCUS A, C, Y W-135	YES
MENINGOCOCCUS B	NO
ENTERIC AGENTS	
SALMONELLA SPECIES	NO
SALMONELLA TYPHI	YES
SHIGELLA SPECIES	NO
VIBRIO CHOLERAЕ	YES
ESCHERICHIA COLI (ETEC, EHEC, EPEC)	NO
HELICOBACTER PYLORI	NO
ROTAVIRUS	U.S. LICENSE APPLICATION SUBMITTED (LICENSED IN MEXICO)
NOROVIRUSES	NO
VECTORBORNE AGENTS	
PLASMODIUM FALCIPARUM	NO
DENGUE FEVER VIRUS	NO
JAPANESE ENCEPHALITIS (JE) VIRUS	YES
YELLOW FEVER (YF) VIRUS	YES
HANTAVIRUSES	NO
BORRELIA BURGDOFFERI	NO
SCHISTOSOMA SPECIES	NO
LEISHMANIA SPECIES	NO
HOOKWORM (MULTIPLE GENERA)	NO
NOSOCOMIAL AGENTS	
STAPHYLOCOCCUS AUREUS	NO
PSEUDOMONAS SPECIES	NO
ENTEROCOCCUS SPECIES	NO
GRAM NEGATIVE ENTERIC BACTERIA	NO
CANDIDA SPECIES	NO
OTHERS	
HEPATITIS A, B VIRUSES	YES
HEPATITIS C, E VIRUSES	NO
CYTOMEGALOVIRUS	NO
RABIES VIRUS	YES
GROUP B STREPTOCOCCUS	NO

the possible reuse of vaccination needles (either as a time- or cost-saving measure or for abuse of illicit drugs) in developing nations can prevent manufacturers and public health agencies from providing vaccines.

ECONOMIC OBSTACLES

In the United States, most barriers to the use of licensed vaccines are economic or cultural. Economic barriers include the current pricing structure, a system that often fails to adequately compensate the companies that develop vaccines in the early years following licensure. Governments and other purchasers must realize that the development and production of vaccines could be severely hampered if better recovery of costs is not realized. Additional costs associated with auto-disable needles in the developing world in order to improve injection safety increases the cost of dispensing vaccines, putting vaccines even further out of reach for these countries.

Vaccines have led to elimination of several diseases in developed nations, including polio, measles, and others, but many of these diseases remain endemic in developing countries where the poor lack access to vaccination. Investing in vaccination programs and other health and environmental initiatives in developing countries will help to abolish the health disparities between rich and poor nations. Programs like these should be established not only for humanitarian reasons but for international security as well.

CULTURAL OBSTACLES

The most significant cultural barrier to effective use of licensed vaccines may be the refusal of individuals to accept vaccines on religious or ethical grounds. Vaccines may also be refused because of mistaken perceptions of risk or because of a reluctance to accept personal risk in favor of benefits to the population at large. Refusal is a significant problem in the industrialized world, where a population that refuses vaccination can serve as a reservoir or entry port for a disease, although such individuals are generally protected by herd immunity stemming from widespread acceptance of the vaccine. However, vaccine refusal is a greater problem in developing nations, where fewer people are vaccinated and herd immunity is less influential, offering less protection to susceptible individuals.

The existence of different infant immunization schedules in different countries also poses a stumbling block. Assuring the safety and efficacy of a given vaccine requires extensive research that is specific to the timetable by which it is administered. Carrying out that research for many different schedules drives up the clinical costs of vaccine development, costs that inevitably make vaccines more expensive for the consumer and impede the use of that vaccine. Standardization of immunization schedules, particularly in European nations (which comprise a large, heterogeneous market for

TABLE 2.

Infectious agents that pose a significant human health threat due to non-manmade causes ("natural threats")

ZOONOTIC AGENTS

INFLUENZA VIRUS H5N1
SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS
HENDRA VIRUS
NIPAH VIRUS
SIMIAN HEMORRHAGIC FEVER VIRUS
EBOLA VIRUS

EMERGING AGENTS

SHIGELLA DYSENTERIAE 1
MULTI-ANTIBIOTIC RESISTANT (SALMONELLA TYPHI)
MULTIPLE-ANTIBIOTIC RESISTANT (MYCOBACTERIUM TUBERCULOSIS)
PRIONS
HERPES ZOSTER VIRUS
WEST NILE VIRUS
RIFT VALLEY FEVER VIRUS
H3N2 AND H1N1 VARIANT FLU VIRUSES
YERSINIA PESTIS

AGENTS SUSCEPTIBLE TO ACCIDENTAL RELEASE

INFLUENZA VIRUS H2N2
SARS

OTHER AGENTS

ANTIBIOTIC RESISTANT ORGANISMS
NEW ENTEROVIRUSES
NEW RETROVIRUSES

TABLE 3.

Infectious agents that pose significant human health threat from intentional release

AGENTS

SMALLPOX VIRUS
BACILLUS ANTHRACIS
BOTULINUM TOXIN (FROM CLOSTRIDIUM BOTULINUM)
SHIGELLA DYSENTERIAE 1
FRANCISELLA TULARENSIS
YERSINIA PESTIS
EBOLA VIRUS
VENEZUELAN EQUINE ENCEPHALITIS VIRUS
ENGINEERED INFLUENZA VIRUS
OTHER ENGINEERED ORGANISMS

vaccines), would help to keep costs down and make vaccines more available to those least able to afford them.

Another cultural barrier is the failure of consumers to recognize that a vaccine could save hours or days of productivity and spare the immunized the pain and suffering associated with an infectious disease. Consumers who do not appreciate these benefits are reluctant to pay high prices for vaccines. Paradoxically, in the developed world, consumers are often willing to pay high prices for pharmaceuticals that treat the effects of less severe, noninfectious disorders that have minimal tangible impacts when compared with infectious diseases. A common attitude is that drugs are only needed to treat illness, and, therefore, the concept of drugs

Intellectual property issues also pose a problem in the application of vaccines. Developing countries that cannot afford to buy vaccines from manufacturers in industrialized countries are prevented from manufacturing those vaccines themselves, at least in part, by the constraints of international law.

Combination vaccines are better accepted by parents than separate injections for the component vaccines (see Cultural Obstacles, above), and, therefore, offer better coverage for infectious disease among the populations to which they are made available. The licensure process for combination vaccines is very difficult and expensive, however, which drives up the cost of producing combination vaccines and inhibits their development. Intellectual property issues, where differ-

“[a] cultural barrier is the failure of consumers to recognize that a vaccine could save hours or days of productivity and spare the immunized the pain and suffering associated with an infectious disease”

used to prevent illness is often underappreciated. It is possible that the reluctance of consumers to pay what they perceive as high vaccine prices is tied to the common misperception that contracting an infectious disease strengthens the body and that vaccines prevent that opportunity for enhancement.

Another cultural bias preventing the full use of licensed vaccines is apprehension about genetically modified organisms. Recombinant technology is increasingly used in the manufacture of modern vaccines, but staunch opposition to these technologies exists in many parts of the world. Such resistance may prevent individuals or health organizations from applying high-quality vaccines that happen to be the product of recombinant techniques.

The number of injections required to immunize an infant or child also plays a role in the acceptance of vaccines by parents. The greater the number of injections a parent is told their child needs, the less likely that parent is to allow the child to be immunized.

LEGAL OBSTACLES

The biggest legal problem facing licensed vaccines is the litigation associated with vaccine side effects. This is a particular problem in the U.S., where litigation as reprisal for accidental injury is well-accepted, but it is less of a problem in other nations.

ent antigens were developed by different companies, may also hinder development of new combination vaccines.

PREGNANT WOMEN AND THE APPLICATION OF LICENSED VACCINES

Vaccines are rarely prescribed to pregnant women because of liability concerns by medical professionals and vaccine developers and a pervasive cultural reluctance to expose pregnant women and fetuses to the risks associated with vaccination, even in the absence of data documenting such risks. Additional research to determine the impact of vaccines on pregnant women and their children is required. A better system to compensate pregnant women who experience adverse effects from vaccination is also needed.

VACCINES REMOVED FROM THE MARKET

Vaccines are not fixed in the marketplace; formulations may be removed from the market for any of a number of reasons or combination of reasons (Table 4). For example, a vaccine may become obsolete; the smallpox vaccine was removed from use after that disease was eradicated. A vaccine may also lose market share to a newer, better formulation, as did the whole-cell pertussis vaccine, a relatively risky product, when the safer acellular formulation became available.

TABLE 4.**Vaccines removed from the market**

VACCINE	COMMENTS
SMALLPOX	SMALLPOX ERADICATED
ORAL POLIO (OPV)	POLIO REGIONALLY ELIMINATED A SAFER VERSION (INACTIVATED POLIO VACCINE) WAS AVAILABLE THAT REPLACED THE LIVE ATTENUATED ORAL VACCINE IN INDUSTRIALIZED COUNTRIES
ROTAVIRUS (ROTASHIELD®)	SAFETY CONCERNS (IMPLICATED AS A CAUSE OF INTUSSUSCEPTION IN INFANTS)
LYME DISEASE	SAFETY CONCERNS (REAL AND/OR PERCEIVED AUTOIMMUNE SIDE EFFECTS) ECONOMIC REASONS (ACTUAL MARKET PROVED MUCH SMALLER THAN ORIGINALLY ANTICIPATED, EXPENSIVE LITIGATION)
ADENOVIRUS	ECONOMIC REASONS (THE COSTS OF ADHERING TO NEW GOOD MANUFACTURING PRACTICE RULES WERE PROHIBITIVE FOR THE MANUFACTURER)
HEPATITIS B (PLASMA-DERIVED)	PERCEIVED SAFETY RISKS (HUMAN PLASMA WAS SEEN AS UNSAFE FOR VACCINE PRODUCTION IN THE WAKE OF THE DISCOVERY OF AIDS IN THE 1980S) REPLACED BY AN IMPROVED PRODUCT (RECOMBINANT HBV VACCINE)
HBV RECOMBINANT	SUSPENDED FROM USE IN SCHOOL-AGED CHILDREN IN FRANCE PERCEIVED SAFETY RISKS (UNSUBSTANTIATED LINKS TO MULTIPLE SCLEROSIS)
WHOLE CELL PERTUSSIS	REMOVED FROM THE MARKET IN SWEDEN BECAUSE OF SAFETY CONCERNS (REPLACED IN OTHER MARKETS WITH THE ACELLULAR PERTUSSIS VACCINE)
KILLED MEASLES	SAFETY CONCERNS (ATYPICAL MEASLES)
HIB POLYSACCHARIDE	REPLACED BY AN IMPROVED PRODUCT (HIB CONJUGATE VACCINE)
NEURAL TISSUE-DERIVED RABIES	REPLACED BY AN IMPROVED PRODUCT (CELL CULTURE-DERIVED VACCINE)
INTRANASAL INACTIVATED INFLUENZA (ADJUVANTED WITH WTLT)	SAFETY CONCERNS (BELL'S PALSY)

Safety concerns and unforeseen side effects, either real or perceived, can drive a vaccine maker to remove a product from the market. The rotavirus vaccine Rotashield® was pulled from use because of a link to intussusception (a type of bowel obstruction) in vaccinated children, discovered only after administration of the vaccine to more than one million children. In developing countries, the risk of fatal dehydrating diarrhea due to rotavirus is higher than the risk of intussusception. However, in industrialized countries, few infants die from rotavirus infection, thereby yielding an unfavorable risk-benefit ratio for this vaccine in such countries.

Economic concerns can also play a role. The vaccine for Lyme disease was discontinued when the market for that product proved to be much smaller than the manufacturer originally estimated. Manufacture of adenovirus vaccine was

discontinued due to the expense required to repair the production facilities. Because the U.S. is the single largest market for vaccines, insurance and Medicare vaccine reimbursement policies in the U.S. can define vaccine availability for the rest of the world. If the U.S. insurance industry or Medicare system choose to deny compensation for a given vaccine, the vaccine manufacturer will most likely cease production, notwithstanding the willingness of other nations to purchase the product.



NEW VACCINES

The development of vaccines ranks among the greatest achievements in medical history. The smallpox vaccine alone has saved the lives of countless millions around the world and prevented the suffering and disfigurement of millions more. Despite the proven power of these tools, vaccines are still unavailable for many of the infectious diseases that plague humankind, particularly those diseases that are most devastating in poorer nations and the less severe (but inevitably destructive) and less common infections that are endemic around the world. Vaccines have driven the most serious infectious diseases out of the developed world. Today, research and development must continue this progress and abolish the diseases that continue to strike unchecked, particularly those without suitable treatment options. Research also needs to attend to the continual improvement of existing vaccines to elicit fewer adverse effects and to devise formulations that can be made less costly and more widely available.

New or improved vaccines for the following agents are currently under development. In some cases no vaccine exists, but in other cases vaccine development is directed towards improving efficacy, lowering costs, or enhancing distribution to the target population.

SEXUALLY TRANSMITTED INFECTIONS

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The struggle to develop a vaccine for HIV has been ongoing since the virus was first discovered in 1982, and though a great deal of progress has been made, an effective and safe vaccine remains elusive. Over 70 prospective HIV vaccines have undergone Phase I trials, and several of these have gone on to Phase II trials. Today, only two experimental vaccines have made it to Phase III.

Nearly all vaccine designs and vectors have been tried in the effort to build an HIV vaccine. Some of the promising for-

mulations today include a prime-boost vaccine (so named because of the two-pronged strategy of administering a primer vaccine and following up later with a booster vaccine), that is being tested in Thailand, and a vaccine based on three recombinant adenovirus constructs, each expressing a different HIV gene.

Given the limits of the available technology and the current state of knowledge on HIV, in the short-term it appears unrealistic to expect an HIV vaccine to achieve “sterilizing immunity,” the eradication of the virus from the immunized system. Many new experimental vaccines induce T cell immunity that may reduce the viral load for extended periods. Such a vaccine, though not ideal, could slow the progress of the virus, offer an improved quality of life to those infected, and decrease or delay secondary transmission to other individuals. Even a less-than-ideal vaccine could have a substantial impact on the spread of the HIV pandemic.

The likelihood of developing an effective vaccine that prevents HIV acquisition in the near future is very low. Historically, most vaccines have worked by antibody blocking, or limiting, incoming infections so that they do not cause disease. Blocking antibody has proved difficult to elicit for HIV because of the high variability and heavily camouflaged nature of its exposed proteins. Understanding how to elicit broadly neutralizing antibodies that many believe will be needed to prevent infection will require further research. In addition to the variability of the virus, a lack of natural immunity in exposed individuals, the fact that the virus integrates into the host genome, and a lack of an animal model in which HIV causes disease all pose serious technical hurdles. Prior immunity to the vectors used in experimental HIV vaccines, like adenoviruses, may also pose a problem in HIV vaccine development. There is also lack of incentives for vaccine developers to tackle the technical, operational, and logistical obstacles involved in producing and testing a new product. Moreover, conducting vaccine trials in developing countries, where a vaccine

is needed most (given the current inaccessibility of antiviral drugs), is challenging because of difficulties in training qualified personnel and the stigma associated with contracting HIV. Regulatory hurdles, including a lack of expertise on local and national decision-making bodies (e.g., institutional review boards, regulatory agencies) also impede trials in the developing world. At least initially, a dose of an HIV vaccine will probably be very expensive

HUMAN PAPILLOMA VIRUS (HPV)

Two promising vaccines for HPV are undergoing advanced clinical trials, but questions about when to vaccinate and whether vaccination should be tailored differently for men and women have come up. Also, the appropriate serotype breadth of the vaccine, that is, whether it should cover two or four virus serotypes, is disputed. The duration of immunity offered by the experimental vaccines is not known, but it is thought that the antibodies for HPV last for a number of years. Unfortunately, an HPV vaccine is probably going to be prohibitively expensive for use in the developing world, where it is needed most.

HERPES SIMPLEX VIRUS (HSV)

A variety of experimental vaccines for HSV are in development. Glycoprotein HSV vaccines, one of which is in Phase III trials at present, have been shown to be moderately effective in preventing infection in women, but the duration of that protection is not known. Development has been slowed by a lack of understanding about natural immunity to the virus and unknowns about the size of the prospective market for a HSV vaccine.

CHLAMYDIA TRACHOMATIS

A few candidate vaccines for chlamydia are in the early stages of development, but the chronic nature of the disease, lack of understanding about protective immunity to the infection, problems with funding, and questions about the target market for a prospective vaccine continue to hamper development efforts.

NEISSERIA GONORRHOEAE

Given the characteristics of *Neisseria gonorrhoeae*, many different types of vaccines for gonorrhea may be feasible. Early studies on candidate vaccines have shown that these formulations can be effective in preventing infection, but a lack of appropriate in vitro systems and animal models has meant slow progress in this area.

TREPONEMA PALLIDUM

No vaccines for *Treponema pallidum*, the bacterium responsible for syphilis, are currently available.

ESCHERICHIA COLI (URINARY TRACT INFECTIONS)

Although urinary tract infections are extremely common, a vaccine for the *E. coli* strains commonly responsible for this condition has yet to be developed. Identifying a conserved

common antigen shared by all of the potential offending *E. coli* strains is a daunting prospect that few vaccine developers are willing to tackle, especially given the minor role these infections play in overall public health.

RESPIRATORY INFECTIONS

INFLUENZA VIRUS

Despite the annual development and distribution of attenuated and inactivated influenza vaccines tailored to the anticipated dominant strains of the season, influenza climbs to epidemic proportions in the U.S. and elsewhere every year. Clearly, production of the influenza vaccine and the vaccine itself are fraught with problems, and improvements are desperately needed. Pinpointing the flu strain that will be dominant in a given year often poses difficulties, as strain variation cannot always be anticipated. Development of an influenza vaccine that can reduce community spread or cover the drifted strains that appear in the midst of flu season would have a considerable impact. Influenza vaccine development has received increasing attention recently due to heightened fears of a global pandemic caused by avian influenza and resulting vaccine shortages.

Vaccine effectiveness is another problem area. The flu vaccine is less immunogenic and effective in the elderly and possibly in very young children. Also, vaccine coverage is consistently inadequate, even in members of high-risk groups to whom vaccination efforts are specifically targeted. A live intranasal vaccine may be a better form of vaccine for administering to children than injectable vaccines, given the greater likelihood of acceptance by parents, the ease of administration, and the superior mucosal immunity offered by intranasal formulations.

Production concerns have also come to the fore; a distinct lack of manufacturing ability has often left many willing consumers without vaccine. The most notorious case of undersupply was experienced during flu season 2004-2005 in the U.S., when the product from a single manufacturer was removed from the market because of sterility concerns and left hundreds of thousands without a dose. Moreover, instability of the market for flu vaccines poses a problem for manufacturers, who count on being able to sell their product in order to make a profit.

Given the human and economic costs of influenza, renewed effort must be poured into achieving better acceptance of the flu vaccine. Children should be more aggressively targeted for vaccination, as they are at high risk from flu complications and are known to pass on flu to the elderly, another vulnerable group. More universal vaccination of school-age children would afford the additional benefit of herd immunity to the non-vaccinated. The use of the popular media in this campaign should be explored.

RESPIRATORY SYNCYTIAL VIRUS (RSV)

Although urgently needed, a vaccine for RSV is not currently available. A live attenuated vaccine is undergoing clinical trials, but this formulation may carry excessive risks for infants. It is possible that once an RSV vaccine is licensed and available, the community will have to rely on herd immunity to protect very young children.

The single largest barrier to manufacturing an RSV vaccine is a lack of companies willing to make it. The legacy of failed RSV vaccines, one of which actually triggered enhanced respiratory disease, and ensuing litigation has made manufacturers reluctant to get involved.

Perceived links between RSV vaccines and sudden infant death syndrome have also stymied progress in vaccine development. Moreover, natural immunity to RSV is not strong, and our knowledge of protective immune responses to RSV is inadequate—both of which may complicate the technical aspects of RSV vaccine development.

PARAINFLUENZA VIRUS

A licensed vaccine for the parainfluenza virus is not available, but an experimental formulation is in the early stages of human trials. The need to develop a multivalent vaccine that is effective against the various serotypes of parainfluenza has posed an impediment to progress and is a daunting prospect for prospective manufacturers.

MYCOBACTERIUM TUBERCULOSIS

Despite efforts by vaccine developers over the years, only one vaccine for tuberculosis is available on the market today—the Bacillus Calmette-Guerin (BCG) vaccine. The BCG vaccine has proven effective, but it does not induce long-term immunity.

Several experimental vaccines are under development. Promising candidates include a modified *Mycobacterium bovis* strain that has been engineered to enhance its immunogenicity and various subunit vaccines with adjuvants. Designing trials of experimental tuberculosis vaccines will likely prove to be a stumbling block. In light of the effectiveness, albeit short-lived, of the BCG vaccine, the chances of success in developing a new, more effective vaccine are good, if research continues in this area.

HAEMOPHILUS INFLUENZAE TYPE B (HIB)

Superb conjugate vaccines (which link a polysaccharide to a protein) for *Haemophilus influenzae b* (Hib) are currently in use, including formulations that are combined with whole cell pertussis, diphtheria, and hepatitis B vaccines, formulations that are useful in delivering the necessary vaccines to residents of developing nations. Eligible countries can receive the Hib vaccine free for five years from the Global Alliance for Vaccines and Immunization (GAVI). Unfortunately, since most countries have not previously measured

the burden of invasive *H. influenzae* infection before implementation of the vaccine, the impacts of the vaccine are largely unknown.

STREPTOCOCCUS PNEUMONIAE

Effective vaccines for pneumococcal diseases (which are caused by *Streptococcus pneumoniae*, also known as pneumococcus) are in great demand for both industrialized and developing nations. *S. pneumoniae* is the most common bacterial cause of hospitalization for pneumonia, meningitis, and acute otitis media in the very young and the elderly in industrialized countries. In developing countries, this pathogen is a major cause of morbidity and mortality among infants and young children, largely due to pneumonia. The recent licensure of a 7-valent conjugate vaccine (in which the capsular polysaccharide has been linked to a protein carrier to enhance its immunogenicity) has been met with enthusiasm. Other formulations (9- and 11-valent) of conjugate vaccines are being evaluated, and recent results from large scale Phase III trials in South Africa and Gambia are encouraging. Unfortunately, the conjugate vaccine has serious limitations, including a high manufacturing cost, making them inaccessible in the developing countries where they are most needed to reduce child mortality, and a lack of effectiveness against some of the pneumococcal serotypes that most commonly strike adults. Other pneumococcal vaccines that do not rely on immunity based on the over 90 pneumococcal polysaccharide-based serotypes, but instead induce responses to proteins common to all or most pneumococci, are currently in development as well. It has proven to be very expensive to develop a pneumococcus vaccine, and prospective manufacturers face major financing, supply, and advocacy issues.

GROUP A STREPTOCOCCUS PYOGENES

Several interesting candidate vaccines for Group A *Streptococcus pyogenes* are undergoing clinical trials, but it has taken vaccine developers many years to get this far. Problems in developing Group A strep vaccines have ranged from providing adequate protection from each of the various Group A serotypes to preventing the inadvertent induction of rheumatic fever and rheumatic heart disease.

CHLAMYDIA PNEUMONIAE

Several candidate vaccines for *Chlamydia pneumoniae* are in the early stages of development and have yet to be tested in clinical trials. A vaccine for *C. pneumoniae* is needed, particularly if the tentative links between infections with this organism and coronary artery disease or atherosclerosis are substantiated. A lack of data on the role of protective immunity and insufficient understanding of the public health importance of *C. pneumoniae* stand in the way of faster progress in developing a good vaccine.

NEISSERIA MENINGITIDIS

There are a number of licensed monovalent and multivalent (active against one or many subtypes) polysaccharide and polysaccharide-protein conjugate vaccines for the A, C, Y, and W-135 serotypes of *Neisseria meningitidis*, the causative agent of meningococcal disease. The B serogroup has proven more problematic for vaccine developers, since its capsular structures are similar to certain structures found in the human central nervous system, arousing concern that vaccines that stimulate reactions against the B subtype may also stimulate reactions to the body's own tissues. Vaccines derived from B serogroup outer membrane proteins have worked well, but they are strain-specific and may not be effective in children. Meningococcal vaccines for infants need particular improvement.

Analysis of the *N. meningitidis* genome and the use of available correlates of protection have enabled identification of broadly immunizing proteins that circumvent the need for strain-specific meningococcal vaccines. Clinical trials with these proteins are ongoing. Alternative approaches to consider in developing a vaccine for *N. meningitidis* include improved OMV and lipo-oligosaccharide-based conjugate vaccines.

ENTERIC INFECTIONS

SALMONELLA TYPHI

Three licensed vaccines for typhoid are available, all of which are moderately effective, and other promising formulations are currently under development. The heavy reliance on non-vaccine typhoid control measures in the developing world (where typhoid is most prevalent) has sapped motivation to develop a vaccine. Finding a manufacturer for typhoid vaccines has been, and will likely continue to be, difficult.

SHIGELLA SPECIES

A number of promising vaccines for *Shigella*, including live attenuated and subunit oral vaccines and a protein-lipopolysaccharide conjugate vaccine, are in the early stages of development. A *Shigella* vaccine could be made relatively quickly, and its impact would be great, but a lack of enthusiasm in the health community presents a significant obstacle to development.

VIBRIO CHOLERAЕ

Though little used, two vaccines for cholera are currently licensed and new oral formulations are under development. The efficacy of the current formulations has not been exhaustively researched; further testing will be necessary to cement the vaccine's place in cholera control efforts. Public health authorities need to focus on developing policy on cholera vaccines in order to ensure better coverage among at-risk groups.

ESCHERICHIA COLI

A vaccine has yet to be licensed for any of the pathogenic *E. coli* strains, which include enterotoxigenic (ETEC), enterohemorrhagic (EHEC), and enteropathogenic (EPEC) forms, but at least one candidate vaccine is in phase I trials. There is some evidence that the killed oral cholera vaccine is protective against *E. coli* infection due to shared toxin antigens. Individuals most likely to enjoy the benefits of an *E. coli* vaccine include small children who travel and traveling members of the military, but the most numerous target population are children in developing countries. Progress in developing *E. coli* vaccines has been slow.

HELICOBACTER PYLORI

Progress in developing a vaccine for *H. pylori* infections (the bacterium now known to trigger stomach ulcers) has been slowed by one major factor: uncertainty about the possible benefits of a vaccine. The level of immunity in humans is not well understood, but it is known that reinfection rates after *H. pylori* infection are high, a fact that casts doubt on the utility of a potential vaccine.

ROTAVIRUS

Since the first vaccine for rotavirus, Rotashield®, was famously removed from the market (see Table 4), no other rotavirus vaccines have been licensed, although two vaccines are in the final stage of development, one of which has been widely tested in middle income countries in Latin America and has recently been licensed by Mexican authorities. Importantly, clinical trials have yet to be carried out in developing countries, where infant mortality rates from rotavirus-induced diarrhea are highest. The serotype distribution of rotavirus, which varies from region to region, may play a role in vaccine efficacy, necessitating reformulation of a vaccine to suit a given population.

NOROVIRUSES

Experimental vaccines for Noroviruses (Norwalk-like viruses) that employ virus-like particles (made in baculoviruses and by other means) are under development. Although short-term immunity to noroviruses does exist, it is not known whether natural or vaccine-induced immunity would be protective over longer periods of time. The existence of multiple pathogenic serotypes may confound efforts to develop an effective vaccine quickly and inexpensively.

VECTOR BORNE AGENTS

MALARIA PARASITES

There is no vaccine currently available for the malaria parasites *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. Multiple clinical trials of a subunit vaccine (a vaccine that contains only a single *Plasmodium* protein or part of a protein) are underway, but the release of a new vaccine is not imminent. A number of outstanding questions about

the cost and efficiency of producing these vaccines persist, but the potential health and economic benefits of a good malaria vaccine are immense. To date, the vaccines tested in humans have induced only limited protective immunity to a natural infection.

DENGUE VIRUSES

Although progress has been slow, a number of vaccines for the Dengue viruses are now in development, including formulations that employ attenuated viruses and genetically recombined viruses. The efficacy of these vaccines is not known. In order to be most useful, a Dengue vaccine should be protective against both Dengue fever and the hemorrhagic fever caused by these viruses. To protect from hemorrhagic shock, the vaccine must be protective against all four serotypes of the virus.

JAPANESE ENCEPHALITIS VIRUSES

Two vaccines for Japanese encephalitis (JE) are currently available. A vaccine that uses the yellow fever virus as a vector and a cell culture-derived vaccine will likely be available soon as well. JE vaccines are manufactured in China, but peer-reviewed data regarding the safety and efficacy of these formulations are lacking.

YELLOW FEVER VIRUS (YF)

The currently available YF vaccine has certain safety problems associated with central nervous system damage and viremia (the presence of the virus in the blood) that should be addressed. No other YF vaccines are being developed as there is little incentive to do so; the risk-benefit ratio of the licensed vaccine is low in areas where YF is endemic (because YF is so devastating) and development expenses are high.

BORRELIA BURGDORFERI

A vaccine for *Borrelia burgdorferi*, the causative agent of Lyme disease, was withdrawn from the market because of safety concerns, limited geographic distribution of the bacterium, and slow sales. Experimental Lyme vaccines are currently being developed that avoid the use of the OspA protein. A vaccine based on OspA could elicit autoimmune reactions because of its homology to synovia, a lubricating fluid found in human joints.

SCHISTOSOMIASIS PARASITES

A vaccine for protection against the parasites responsible for schistosomiasis, *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum* (and occasionally *S. mekongi* and *S. intercalatum*) is not currently available and proposed schistosomiasis vaccines have not yet been subjected to clinical trials. A vaccine would be most useful in those areas of the world where *Schistosoma* infection is difficult to prevent.

Difficulties finding a *Schistosoma* antigen suitable for use in a vaccine and questions about the size of the market for a

potential vaccine have heretofore thwarted development, and a vaccine will likely not be available in the near future.

LEISHMANIA SPECIES

Crude vaccines against Leishmania parasites have been found to be immunogenic, proving that an effective vaccine for leishmaniasis can be developed. Modern formulations are under development, but there has been little interest in these vaccines and, consequently, little funding for these efforts.

HOOKWORM

No human vaccines for hookworm have been licensed, but an experimental formulation is now being tested in humans. For many vaccines in development, especially those designed to protect against diseases not often seen in wealthier nations, such as hookworm, there are often difficulties in convincing prospective manufacturers and funding agencies of the economic benefits of the vaccine. Hookworm vaccine researchers will also likely have to provide evidence of the benefits of a vaccine over other modes of hookworm prevention and treatment.

NOSOCOMIAL AGENTS

STAPHYLOCOCCUS AUREUS

One prospective vaccine for *Staphylococcus aureus*, a common cause of hospital-acquired infections, is undergoing Phase III trials, and others are in preclinical stages of testing. Although vaccines against hospital-associated pathogens may pose new regulatory challenges, the FDA has no guidelines specific for this type of vaccine. It may be difficult to use a vaccine for *S. aureus* in hospital patients, because many of them have compromised immune systems that cannot cope well with a vaccine or may not mount a sufficient immune response to protect them from subsequent exposure to the bacterium. Although the cost of developing a vaccine for *S. aureus* will be high, the cost of continuing without a vaccine would be even higher, given the prevalence and difficulties in antimicrobial treatment of hospital-acquired infections.

Vaccines for certain other hospital-acquired infections, e.g., *Pseudomonas*, *Enterococcus*, Gram-negative enteric bacteria, *Candida*, are in the very early stages of development.

OTHER VIRUSES

HEPATITIS A VIRUS

Very good vaccines for Hepatitis A exist and other experimental formulations are being developed. The cost of Hepatitis A vaccines represents a barrier to their widespread use.

HEPATITIS C VIRUS

There has been a modicum of difficulty in developing a practical Hepatitis C vaccine that induces sufficient immunity from the disease. The genetic variability of the virus, questions about natural immunity, and intellectual property rules have all posed barriers to development. The prevalence of this disease is high. A therapeutic vaccine, which is a formulation designed to boost the immune response to infection rather than prevent infection, would be highly valuable. New opportunities for vaccine development now exist with the recent development of cell culture methods to grow this virus and the use of pseudoviruses to measure neutralizing antibodies

HEPATITIS E VIRUS

A vaccine is not currently available for Hepatitis E, but a promising, experimental virus-like protein (VLP) formulation is being tested in humans. The illness takes its greatest toll in the developing world, where people can least afford vaccines.

CYTOMEGALOVIRUS

Although a vaccine for Cytomegalovirus has yet to be licensed, many different experimental formulations are being developed at this time, two of which have been tested in humans. More information about the existing level of cytomegalovirus immunity in humans, the natural history of the organism, and the expected health benefits of the vaccine is needed before vaccines for a Cytomegalovirus vaccine could be implemented.

MEASLES VIRUS

Measles vaccines have been available for years, but the mode of delivery—by injection—is not optimal for use in developing nations, and currently licensed formulations are not suitable for use in young infants. Efforts are underway at the World Health Organization (WHO) to test and license an aerosol delivery method for a measles vaccine. Also, a new measles formulation is under development that could be used in young infants in developing areas.

RABIES VIRUS

Although a vaccine for rabies exists, the disease remains a problem. Some very good vaccines are available, but economic reasons have kept them from being used in developing countries. In these areas, animal vaccines for rabies are available but are not widely used, a situation that allows the virus to spread among domestic animals, enabling a reservoir of the virus to exist intimately with humans.

OTHER BACTERIA

GROUP B STREPTOCOCCI

Although progress has been made in research on protein-polysaccharide conjugates that could be used in a vaccine for Group B Streptococci (GBS), a vaccine for GBS infection

is not currently available. The legal risk of vaccinating pregnant women (who should be vaccinated to prevent transmission of GBS to their infants during birth) poses a major stumbling block to developing a GBS vaccine. A lack of data on the potential efficacy of a GBS vaccine and intellectual property issues are also probably hindering progress.

OTHER FUNGI

COCCIDIIOIDES IMMITIS AND C. POSADASII

Vaccines available for coccidioidomycosis include subunit vaccines and attenuated vaccines made through genetic engineering, but the market for these products is highly regional.

BARRIERS TO DEVELOPMENT OF NOVEL VACCINES

Barriers to the development of new vaccines are numerous and include legal, technical, regulatory, economic, and other problems.

LEGAL OBSTACLES

Legal obstacles to vaccine development include limits on the flexibility of clinical trials, difficulties in establishing cooperative partnerships between vaccine developers, and litigiousness on the part of the public. Legal barriers can hinder vaccine developers from making constructive testing changes in mid-trial and from using samples from past trials for new purposes. Adding new assays to ongoing trials or initiating new testing on samples from past trials can potentially provide valuable data, but the need for ethical review of such procedures can at times be an impediment to making these changes.

Testing two different vaccine formulations in a heterologous prime-boost strategy, which can be very effective immunologically is also legally problematic, as it is often difficult for two separate companies to reach a legal agreement on applying two experimental products together. One solution to the problem is to wait for one product to be licensed and allow the other company to use that product off-label. However, this process could take many years, and it is possible that neither product would be licensed without the other.

The current public expectation of legal accountability on all matters related to risk and injury significantly inhibits vaccine development out of a fear of litigation on the part of developers.

GENERAL TECHNICAL BARRIERS

Several technical matters also stand in the way of vaccine development. The field suffers from a lack of licensed adjuvants (stimulators that are added to vaccines to enhance

immune response) for subunit vaccines. Adjuvants should be discovered and developed in a more rational way. The recent discovery of mammalian Toll-like receptors offers new approaches for development of novel adjuvants.

Other technical limitations include a lack of immunologic correlates (measures of the effectiveness of vaccines by laboratory assays on a blood sample from the vaccinee) and a lack of immunological tools that can be used to find correlates of protection and understand the phenomenon of sterilizing immunity.

Animal testing resources are inadequate. New and more immunologically defined animal models, including knock-outs and inbred animals, are needed to help define correlates of immunity.

Clinical trial facilities for large-scale vaccine testing, especially in resource-poor settings where the disease of interest is endemic, are needed.

More work in mucosal immunity is needed in order to fully develop oral and nasal vaccine delivery systems. Delivery of vaccines to the mucosal immune system offer substantial advantages over traditional parenteral vaccine delivery via needles.

Blind adherence to old, sometimes outmoded vaccine production methods also obstructs progress. The flu vaccine, for example, is made by growing viruses in fertilized chicken eggs, a method that is both expensive and time-consuming. Developers need to be encouraged to explore more efficient ways of producing vaccines, and regulatory agencies should be receptive to new production methods.

Manufacturing challenges in vaccine development also exist. Achieving sufficient yields of high quality materials poses a continuous challenge. A deficiency of vaccine production facilities capable of producing vaccine pilot lots for clinical trials under Good Manufacturing Practices (GMP) is a problem. In the developing world, a lack of manufacturing expertise limits the availability of affordable vaccines.

Collaborations between the public and private sector can be very fruitful in vaccine development, but conflicts of interest can impede these partnerships, making the transitions from academic research to clinical development to commercialization extremely difficult.

ECONOMIC BARRIERS

Vaccine development is an expensive endeavor. Development costs for a single vaccine average between \$600 million and \$1 billion dollars. The cost of insurance for conducting a clinical trial is also high, particularly in the U.S. Despite the life-saving qualities of vaccines, health authorities and the public alike are reluctant to pay high prices for

these products, a paradox that can translate into low profit margins. This situation may prevent companies from recovering development costs and will certainly jeopardize innovation in the field. With the exception of projects relating to HIV and biowarfare, little public funding is available for vaccine research and development in the U.S.

Biotechnology companies are changing the landscape in vaccine development, but investment dollars from venture capitalists are not flowing like they did a few short years ago, and the biotechnology industry (and, hence, vaccine development) is feeling the repercussions of those cutbacks. Moreover, collaborating with contract research organizations, which often assist biotechnology companies in vaccine development and data management, is extremely complex and expensive.

It is difficult to justify development of vaccines that will have uncertain monetary value. Vaccines for the avian H5 influenza virus strains, for example, may be utterly priceless in the event of a H5 outbreak but nearly worthless if an outbreak never emerges, so it is unlikely that businesses will take much interest in developing an H5 vaccine until a market is assured. Public funding for vaccine development is essential to protect the health of the public in an outbreak situation.

The lack of a “safety net” for compensating those injured in the testing of experimental vaccines complicates the recruitment for clinical trials and poses an economic risk for vaccinees. In the interest of spurring vaccine development, it is recommended that the U.S. government establish a fund to cover developer’s liability in the event of unexpected and non-fault problems with experimental vaccines.

REGULATORY BARRIERS

Development of vaccines faces regulatory hurdles, many of them due to inflexibility of the current rules-based system governing development and testing in the U.S. Regrettably, regulatory restraints on vaccine development do not thwart all malpractice, no matter how comprehensive the rules. Moreover, it is argued that the current system does not improve the safety of vaccines proportionally to the cost of complying with the rules. There are also concerns that The U.S. Food and Drug Administration (FDA) makes decisions on the safety of vaccines based on the desire to preserve individual safety from vaccine risks rather than by a more robust approach in which the risks and benefits for the individual are judged in light of the risks and benefits to society of such vaccines.

Collaborative vaccine efforts between institutions can become ponderous with the obligatory involvement of each institution’s institutional review board—councils assembled to ensure adherence with research standards.

The introduction of the animal rule, which allows developers to prove the efficacy of a vaccine in an animal model if it cannot be ethically tested in humans, has opened the door for developing vaccines that otherwise would never have been tested. However, the practicality of the rule has yet to be proven; not a single vaccine has been licensed based on the animal rule. Defining the correlates of protection in an animal model is difficult and may be inconclusive, making the bridge to human immunogenicity data impossible. Some pathogens do not infect non-human species and even when they do, disease pathogenesis may not be identical to that seen in humans.

New Good Manufacturing Practices (GMP) rules that pertain to vaccine production and “Team Biologics” inspections are becoming costly and complicated. The result may be cancellation of certain vaccines that do not generate enough revenue to cover the costs of compliance.

Lack of harmony between the regulations of different national bodies, including the FDA, the European Agency for the Evaluation of Medicinal Products (EMA), and the Japanese Ministry of Health, Labor, and Welfare, forces vaccine developers to tackle multiple sets of regulations, a process that costs developers money, driving up the price of vaccine development and, hence, the price of that vaccine for the consumer. Many developing countries do not have a qualified national body to decide on and implement the relevant regulations.

There is no precedent for approving adjuvants on their own, a deficiency that prevents fast-tracking of new products. There are no clear rules for how to proceed with new adjuvants and little effort on the part of developers to seek innovative development pathways, so new adjuvants are not being developed.

Finally, one of the most important obstacles to vaccine development is the perception, on the part of regulators and legislators, that vaccines should be low cost. In the interest of public health, governments and individuals should be prepared to pay a certain cost to improve health and avoid suffering. A willingness to pay an appropriate price for vaccines, given their health- and lifesaving attributes, would encourage more research, more innovation, and better, safer vaccines.

MISCELLANEOUS BARRIERS

Adverse reactions and negative outcomes from testing experimental vaccines can hamper development of new vaccines for the same condition or inspire a manufacturer to quit vaccine development altogether. The development of respiratory disease in children who were administered an RSV vaccine has inhibited the development of more vaccines for RSV, and a failure with a vaccine for rotavirus motivated Wyeth to discontinue its vaccine development program.

Clinical trials, although essential, can be very complex endeavors and they may slow the progress of vaccine approval, costing developers money and discouraging subsequent development efforts.

It may be difficult for developers to justify the expense of developing a vaccine for a condition that, clinically speaking, looks a lot like other diseases. If the public cannot perceive or appreciate the benefits of a vaccine for a specific pathogen (*H. influenzae b*, for example) because other pathogens (like pneumococcus or meningococcus) cause similar conditions, they are unlikely to purchase that vaccine. Oftentimes, precise data on disease burden are not available prior to the introduction of a new vaccine even for very distinct diseases. Governments, too, are unlikely to purchase a vaccine if its effect on the burden of a specific disease cannot be accurately estimated.

The relatively low incidence of infectious disease in industrialized countries, where the majority of economic wealth is concentrated, translates into small economic incentives for developing vaccines targeted to developing countries. Vaccines that would be useful in developing countries, like inactivated and live cholera vaccines, Ty21a live typhoid vaccine and others, are most commonly used by travelers from the developed world. Uptake by residents of developing countries has been meager.

CONSEQUENCES OF THE CHANGING REGULATORY ENVIRONMENT

The regulatory landscape for vaccines is changing, and with these changes come several practical consequences for vaccine developers.

Due to changes in federal regulations, the supply of vaccines in the U.S. is often limited based on calculations of theoretical risk, not on real risk, a situation that can spell bad outcomes for public health. The power to prevent the sale of a vaccine is an important instrument in the regulator’s toolbox. In the face of real safety risks, due to vaccine contamination, for example, regulatory intervention that prohibits the sale of a vaccine can save lives. The more regulatory agencies and manufacturers communicate on these issues, the more easily the safest course of action can be determined.

Regulations have become, in some cases, onerous. For example, fulfilling the letter of each FDA requirement in vaccine licensure can be unnecessarily time-consuming and may delay access to promising new vaccines for diseases that result in high levels of morbidity and mortality. Flexibility to consider benefit/risk ratios, especially when very large, should enable provisional licensure of extremely promising formulations that have performed well in Phase II studies.

BOX A.

Influenza Strain H5N1: A Public Health Emergency in the Making

The influenza virus has been with humans for hundreds, if not thousands, of years, but the world may soon face a flu pandemic unlike any it has seen before. A new type of influenza virus called H5N1 poses an almost unprecedented threat to human health. H5N1 could sit dormant for a time and cause problems five or ten years from now or it may never cause a pandemic. It's also possible that we could see the beginnings of an outbreak tomorrow.

The influenza virus is a segmented RNA virus that bears eight genes that can change gradually via point mutations in a process called "drift". Such small changes lead to "minor" flu epidemics every year (minor compared to pandemics; not so minor when the fact that over 30,000 people in the U.S. die each winter from flu is considered). Larger changes, called "shifts," can lead to influenza pandemics. Pandemics strike mankind regularly every 10 to 30 years.

The influenza virus can also change more drastically by exchanging entire genes with other, dissimilar influenza viruses, creating entirely new strains of flu. If a human influenza strain meets up with animal strain, the result could be a virus that can infect both species. This is apparently what happened in 1957 and 1968, when the human influenza virus acquired genes from avian strains and set off major epidemics that cost many, many lives. Reassortment also created the adversary we face today: H5N1, or avian flu.

H5N1 emerged in 1997, when 18 cases of the illness sprang up in Hong Kong. Six of those 18 patients died. In efforts to develop a vaccine for the avian flu, it was discovered that because the virus was derived from an avian strain, it could not be grown in chicken eggs as human influenza strains are grown. Moreover, the H5N1 vaccines that were eventually developed proved to be poorly immunogenic in clinical trials and offered little protection to the immunized. Fortunately, H5N1 could not pass easily from person to person; this limitation stemmed the outbreak.

In late 2003 the avian flu reemerged in Southeast Asia, where 55 cases of the illness were tallied. Thanks to reverse genetics, H5N1 was adapted for growth in chicken eggs and the WHO distributed the adapted strain to vaccine developers for work on a vaccine. The avian flu had a 75% mortality rate in 2003, and there was at least one case in which the virus passed from human to human—a capacity it had apparently acquired since the last outbreak in 1997. It is entirely possible that drift, or reassortment, could enable the virus to become even more adept at passing from human to human. If the virus accomplishes this, a major pandemic could ensue the next time H5N1 emerges.

H5N1 VACCINE PROBLEMS AND SOLUTIONS

A number of practical questions about designing and producing a H5N1 vaccine have arisen:

- Who will pay for development of the H5N1 vaccine?

- Which specific virus should be used for vaccine development? Which will be safest? Which would be most effective?
- How many doses of a prospective H5N1 vaccine should be put in a stockpile?
- How long could doses of a prospective H5N1 vaccine be stored?
- How many doses could be made if we were simply to use the regular system for producing influenza vaccine?
- Can manufacturers keep making the regular annual flu vaccine in the midst of a H5N1 outbreak if necessary?
- In an emergency situation, if the world's entire vaccine manufacturing capacity was dedicated to producing a H5N1 vaccine, manufacturers would not even be able to produce enough doses for the United States.
- What kind of global hierarchy would be established to determine who would receive a dose?
- Since H5N1 affects birds, the virus could theoretically devastate the chicken producing the eggs necessary to produce a H5N1 vaccine. How would this situation be averted?
- Intellectual property laws cover many of the new technologies that would be called upon to produce a H5N1 vaccine, like reverse genetics and some of the adjuvants that might be compatible with the vaccine. In an emergency, how would the legal limitations placed on using these technologies be addressed?

Work with the H5N1 has begun to shed light on the virus, providing clues about how a H5N1 vaccine might be designed and implemented. Based on early experience with H5N1 and because humans are immunologically naïve to the virus, it is likely that a two-dose regimen will be needed. An adjuvant will probably be needed in a vaccine for H5N1. It has been shown that a vaccine against the 1997 H5N1 strain was protective when used in conjunction with adjuvant MF59 and administered in one or two doses.

The intradermal route of injection may be better than the intramuscular route.

Incentives like guaranteed vaccine purchases, tax credits, and indemnification against liability are needed to encourage production of H5N1 vaccines now, while there is still time to build a stockpile.

It may be advisable to vaccinate against H5N1 before the pandemic strikes. Additional vaccine production capacity is needed to avert an infectious disease crisis.

The licensure and manufacturing criteria of the FDA have come to be applied outside the United States in nations where the costs associated with compliance are too high for all but the very largest manufacturers to meet. Unfortunately, large companies are often uninterested in the low-margin vaccines of importance to the developing world, where FDA-style requirements are often put into place. Strong regional regulatory authorities are needed to provide guidance and enforcement in matters of vaccine licensure and safety in areas of the world where a body similar to the FDA is not in place.

SHORTENING THE TIMELINE FOR VACCINE DEVELOPMENT

In an ideal world, safe and effective vaccines would be developed quickly. In the real world, researchers and commercial manufacturers often take the path of least resistance in how they undertake the necessary testing to prove the quality of a given formulation. These tests require time. Realistic timelines for the licensure of a promising vaccine range from a minimum of seven years to as many as 14 years.

Regulation is important and valuable and assures that high standards of safety and efficacy are routinely met and maintained. However, accelerating the availability of new vaccines to the public could save scores of lives. If efficiencies in the regulatory process could be identified and implemented without sacrificing vaccine safety or quality, the time and costs of vaccine development could be reduced, sparing human life and suffering. Consequent increases in returns for vaccine developers would also encourage investment and innovation.

In the U.S., regulatory hurdles could be streamlined, but significant increases in the capacity of the FDA to cope with vaccine projects would be needed to noticeably shorten the development timeline. During the SARS outbreak, in which FDA directed a great deal of attention and time toward preventing an epidemic, it was proven that allotting more resources to contagious disease management gets results. Doubling the manpower at FDA devoted to vaccine licensure, including the recruitment of *bona fide* researchers with hands-on experience in these pathogens, would go a long way toward shortening the time necessary to develop and license new vaccines.

In addition to making vaccine regulation more efficient, other avenues could be tried in an effort to make vaccine development less time-consuming and expensive. Expanding investments in translational research (which takes the findings of health research and tests them in clinical settings) could improve capacity for bringing quality vaccines to market. Improving the procedures involved with institutional review boards (IRBs) would also help. Establishing a time frame for decision-making in these bodies and

enabling IRBs from different institutions to recognize one another's rulings would prevent the loss of time, and, hence, money.

Shortening the length of time needed to develop a vaccine and building infrastructure for the vaccines we need today will help scientists and companies respond to infectious disease emergencies in the future. It would be beneficial, for example, to have several different robust and flexible vaccine platforms available to speed up development of formulations for new and emerging diseases. For example, if DNA vaccines are shown to work, it could be possible to have a universal vector backbone available into which any gene from the new disease organism could be inserted. (Of course, an approach like this would require a great deal of basic research to prove its validity.) The regulatory community also needs to be willing to respond to crisis situations by modifying regulatory requirements for emergency vaccines.

BOX B.

Bioterrorism and Vaccines

Vaccines are available for only two of the many infectious diseases that could potentially be employed by terrorists. Both of these vaccines, smallpox and anthrax, are associated with serious safety concerns. Partly because of these concerns, few individuals have been administered doses of the vaccines, leaving the vast majority of the public vulnerable in the event of an attack.

A major problem in the event of a biowarfare attack is the simultaneous infection of scores of people, and if the agent used in an attack has a short incubation period there would not be enough time to develop a vaccine against an unexpected pathogen. Considerable research efforts are underway to develop vaccines for several bioterrorism agents, but none of these experimental formulations are ready for imminent use in the event of an emergency.

There are few incentives for pharmaceutical companies to develop vaccines against bioterror agents. The opportunity costs associated with involvement in a bioterror vaccine are great, and given the small likelihood of a bioterror attack, the potential for a return on the investments that would be required is utterly uncertain. Public funding, such as that provided by the NIH in recent years, is essential for the development and manufacture of such vaccines.



VACCINE SAFETY

Assuring the safety of each vaccine is essential to the continued integrity of vaccination programs. Both proven and discredited safety issues are of concern to the public and to public health authorities, because even mistaken beliefs about vaccines can impact vaccine acceptance.

The most robust method for evaluating the safety of vaccines is assessment of the relative risks involved in taking or refusing a given vaccine. For the most part, the information necessary to conduct a rigorous risk assessment of vaccines is usually available, but some important factors remain elusive.

It should be noted that, overall, the U.S. system for assuring the safety of vaccines works well. The system protects individuals from unnecessary injury from vaccination and protects public health from major infectious diseases. The safety of vaccines in the U.S. is assured by continuous monitoring throughout the cycle of vaccine development and commercialization. Specific studies are conducted in the pre-licensure phase to assure a minimum level of risk during clinical trials. After licensure, the risks associated with a vaccine are measured more precisely in order to identify any risks that might have escaped detection in smaller scale testing. The Vaccine Adverse Event Reporting System maintained by the Centers for Disease Control and Prevention (CDC) is an important component of vaccine safety monitoring.

PROVEN VACCINE SAFETY PROBLEMS

Over the years, a number of recognized vaccine safety problems have arisen, ranging from relatively mild local reactions to unexplained increases in mortality. Adverse reactions associated with a selection of vaccines are listed in Table 5. In recent years, the safety of vaccines has improved enormously while the tolerance for side effects has declined. The vaccines in Table 5 (oral polio, Rotashield®, whole-cell DTP, smallpox, intranasal influenza), which were associated with side effects are no longer used in most developed countries including the U.S., and have been replaced by safer vaccines.

A number of often-used vaccines can (rarely) elicit either mild local reactions at the site of injection or systemic reactions like fever, rash, joint or muscle pain, or seizures. These vaccines include the diphtheria, tetanus, and whole-cell pertussis (DTP) vaccine and the influenza vaccine.

Some vaccines, including the formalin inactivated measles vaccine and an experimental RSV vaccine, have been shown to induce inappropriate immune responses that actually enhanced the disease they were designed to prevent. This could, in theory, happen with certain other vaccines in development, including HIV vaccines and a vaccine for dengue fever.

In some cases, attenuated live vaccines have proven dangerous for vulnerable subpopulations like the immunocompromised.

PERCEIVED VACCINE SAFETY ISSUES

A number of suspected links between vaccines and certain adverse reactions have been investigated and refuted (Table 6). Other possible links have not been disproved, but they are not supported by the existing data (Table 7).

CONSEQUENCES OF REAL AND PERCEIVED VACCINE SAFETY ISSUES

The public at large is usually ill-equipped to separate fact from fiction in debates over the safety of vaccines. As a result, substantiated adverse effects of vaccines and refuted adverse effects are often one and the same in the eyes of the public. Confirmed adverse effects of vaccines and controversies about suspected adverse effects both result in loss of the public's trust in the government and the public health community and decreased coverage of vaccines in the community. The result can be increases in the diseases these vaccines are made to prevent.

Faced with class action lawsuits stemming from unsubstantiated adverse effects of vaccines, manufacturers have become more cautious about the vaccines they choose to

TABLE 5.**Adverse effects associated with selected vaccines**

VACCINE	ADVERSE EFFECT(S)	COMMENTS
ORAL POLIO	PARALYTIC DISEASE IN VACCINEES AND HIS/HER CONTACTS	AN ESSENTIAL COMPONENT OF THE GLOBAL POLIO ERADICATION CAMPAIGN DESPITE ADVERSE EFFECTS
MEASLES (HIGH DOSE)	INCREASED MORTALITY FROM ALL CAUSES IN FEMALES.	NEVER LICENSED
ROTASHIELD® (FOR ROTAVIRUS)	INTUSSUSCEPTION (BOWEL OBSTRUCTION)	ROTASHIELD® WAS REMOVED FROM THE MARKET FOLLOWING THE DISCOVERY OF A LINK TO INTUSSUSCEPTION.
SWINE FLU VACCINE	GUILLIAN-BARRÉ SYNDROME	
BACILLUS CALMETTE-GUERIN (BCG) (FOR TUBERCULOSIS)	DISSEMINATED BCG INFECTION (BCGOSIS)	
MEASLES, MUMPS, AND RUBELLA	IDIOPATHIC THROMBOCYTOPENIC PURPURA	
	ANAPHYLAXIS	ANAPHYLAXIS RESULTED FROM RARE ALLERGIC REACTIONS TO GELATIN IN THE VACCINE
	FEBRILE SEIZURES	
DIPHTHERIA, TETANUS, AND WHOLE CELL PERTUSSIS	FEBRILE SEIZURES	APPARENTLY DUE TO THE WHOLE CELL PERTUSSIS COMPONENT
INTRANASAL INFLUENZA (FLUMIST) ADJUVANTED WITH WTLT	BELL'S Palsy	NOT A RECOGNIZED COMPLICATION OF LAIV
SMALLPOX	GENERALIZED VACCINIA, ENCEPHALITIS, MYOCARDITIS, ECZEMA VACCINATUM	USE STOPPED AFTER ERADICATION OF SMALLPOX

develop. They may even terminate vaccine projects to prevent the possibility of bad publicity and litigation, outcomes which can cost a large company millions.

VACCINE SAFETY EVALUATION: THE BALANCING OF RISKS

Evaluating the safety of vaccines requires a balancing of risk to benefit ratios. Safety is a relative matter – no action (or failure to act) is without risk. The regulatory definition of safety reflects this need for balance: safety is the relative freedom from harmful effect. The potential for adverse effects from a vaccine must be balanced against the potential benefits of that vaccine. In other words, a safety evaluation must ask not only “what are the bad things that can happen if this vaccine is used?” It must also ask, “what bad things can happen if this vaccine is NOT used?”

The definition of what constitutes an acceptable risk from vaccine exposure varies from region to region. Vaccines are acknowledged to have a two-fold benefit: they can preserve the health of the individual, and through phenomenon of herd immunity vaccines can preserve the health of his or her community. The community also benefits from reduced social costs resulting from diseases prevented by vaccines. In societies where societal and individual rights are balanced, there is a greater tolerance for safety risks associated with vaccines.

Disease-specific factors like incidence and severity, which vary geographically, can also affect tolerance for risks. A vaccine may be better tolerated if the disease it prevents is common or risky. The rotavirus vaccine, for example, which was linked to low rates of bowel obstruction in infants in the U.S. and removed from the market, may have been an acceptable vaccine in the developing world. In these countries, rotavirus infection can be a much more serious

condition. In India, for example, it is estimated that Rotashield® could prevent 1,000 hospitalizations and 200 deaths for every incident of bowel obstruction.

In determining the safety of a vaccine, it is important to avoid confusing risk analysis with cost-benefit analysis. Vaccines will sometimes incur more immediate costs, economically speaking, than they avert. This situation does not discount the value of a given vaccine. The preservation of human health and the prevention of suffering are factors that must come into play in any valid analysis of vaccine safety and they cannot be adequately accounted for in cost-benefit analysis.

Ideally, the acceptable risk to benefit ratio for a given vaccine should be determined prior to vaccine development based on the severity of the disease, its prevalence, and other factors.

There is no substitute for randomized, placebo-controlled trials for assessing the safety and efficacy of vaccines, but other tools exist that are not fully utilized. They include animal models, case control studies, epidemiological data (the CDC's Vaccine Safety Datalink is particularly valuable), and post marketing surveillance.

UNKNOWN COMPONENTS OF RISK

In determining the relative risks associated with vaccines, a number of important factors are either unknown or indefinable. Remote risks are not easy to study prior to licensure, as the number of study subjects in clinical trials is always somewhat limited and rare occurrences are hard to discern. New systems are needed for determining the incidence of these potential effects. Long term risks, too, are difficult to identify in the pre-licensure phase.

As more vaccines are developed for use by teens and adults, the epidemiology of diseases that are most prevalent in these groups needs to be studied in detail. The baseline incidence of systemic lupus erythematosus and multiple sclerosis, for example, should be determined so that possible interactions between vaccines and these conditions can be rigorously evaluated.

TABLE 6.

Suspected links between vaccines and adverse effects that have been disproved.

VACCINE	DISPROVED ADVERSE EFFECT
MMR	AUTISM INFLAMMATORY BOWEL DISEASE
PERTUSSIS	CHRONIC ENCEPHALOPATHY
POLIO	CONTRACTING HIV
THIMEROSAL (A PRESERVATIVE)	AUTISM
HEPATITIS B	MULTIPLE SCLEROSIS
HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE AND HEPATITIS B	DIABETES

TABLE 7.

Suspected links between vaccines and adverse effects that are unsubstantiated by research.

VACCINE	UNSUBSTANTIATED ADVERSE EFFECT
THIMEROSAL (A PRESERVATIVE)	NEURODEVELOPMENTAL DELAYS
LYME	AUTOIMMUNE DISORDERS
BOVINE SERUM (USED TO CULTURE VIRUS COMPRISING VACCINES)	PRION DISEASES
ANTHRAX	GULF WAR SYNDROME
ALUMINUM PRODUCTS (VACCINE COMPONENTS)	MACROPHAGIC MYOFASCIITIS ASTHMA
DTP	ATOPY
PEDIATRIC VACCINES (E.G., DTP)	SUDDEN INFANT DEATH SYNDROME



RESEARCH ISSUES

The research surrounding vaccines is evolving rapidly, yielding novel methods and approaches for exploration and development. Although the landscape is changing and progress is being made, scientific barriers to vaccine development remain.

PROMISING SCIENTIFIC METHODS AND APPROACHES

A number of new approaches have become available that could directly or indirectly impact the ability to develop better vaccines.

Improved diagnostics, data systems, bioinformatics, and surveillance techniques have all enabled researchers to better define the burdens of infectious diseases, knowledge that drives the development of new vaccines. The ability to identify target agents has improved too, providing a detailed understanding of both the pathogenesis of these organisms and their genomes.

Novel approaches using live bacterial and viral vectors are very promising and could allow for mucosal delivery of vaccines and prime-boost regimens that are useful for therapeutic vaccines. The use of non-living antigen delivery systems like proteosomes, lipids, cochleates, virus-like particles, and genes (e.g., replication incompetent vectors and replicons) also shows great potential for improving vaccines.

The use of transgenic plants to produce antigens is a promising area, but very high technical hurdles must be overcome before adequate yield and purity can be achieved. Transgenic animals may also eventually be a suitable source of antigens.

Progress has been made in our understanding of adjuvants and their modes of action—they are no longer a purely empiric, unknown “black box.” The discovery of mammalian Toll-like receptors, which can act as adjuvant receptors, has opened up the possibility of customizing vaccines to elicit the desired type of immune response and

avoid certain side-effects. It is also possible to make chimeric adjuvants that target more than one Toll-like receptor, stimulating more than one type of immune response. Finally, it may be possible to use cytokines and other biologic immunomodulators as potent adjuvants.

Improved modes of vaccine delivery, like needle-free mucosal, and transcutaneous methods, could expand the uptake of vaccines and, in turn, drive renewed interest and investment in vaccine development.

There are many innovative approaches available for vaccine development, but often it is unknown how these approaches match up against one another. There are few ways to make head-to-head comparisons of delivery systems, vectors, etc., because it is not in the interest of any party to develop these modes of comparison. Validated assays, common reagents, and common peptides are needed in order to make effective, meaningful comparisons. In government-funded development projects, comparisons to find the optimal set of techniques should be encouraged.

SCIENTIFIC UNKNOWN SURROUNDING VACCINES

The science surrounding vaccines is by no means complete. From fundamental questions about how vaccines work to more specific issues regarding multivalent vaccines, a great deal of discovery lies ahead.

Despite all the success of vaccines, science still has not fully explained how, exactly, vaccines work. Even less is known in cases where vaccines failed to work. A better understanding of the heterogeneity of human responses to vaccines, including the possible genetic underpinnings of immune responses and adverse events, is needed.

The ways by which different types of protective immunity (e.g., innate and adaptive) are regulated is also poorly understood, as are the induction of long-lasting immunity and high-affinity responses.

The roles of T cells in vaccine-induced immunity are not well understood. The ways T cells protect the body and the relationships between T cell phenotype and biological activity require more study.

There is a need for more information about immune responses in pregnant women and fetuses, specifically whether cytokines (proteins that mediate the immune response) can lead to injury of the fetus. The immunological immaturity of infants is also poorly understood.

The human immune response to chronic infection is little understood; grasping the mechanisms (both human and microbial) that allow for persistent infection and immune evasion would enable better manipulation of the system. Conversely, the ability of the body to completely clear an infection requires study to enable development of better therapeutic vaccines to aid this process.

Mucosal protection is important to vaccine development but it is still not well understood. The immune system can be manipulated to direct responses to specific areas (e.g., the lungs or nasal membranes). Further study of how the body protects the mucosa is required.

Vaccine development would benefit immensely from an understanding of how to target antigens toward tailored immune responses.

Oral formulations like polio, rotavirus, cholera, and Shigella vaccines have proven less effective in the developing world but the reasons for this irregularity are not understood. This requires further study so that vaccines can be optimized for use in all markets.

Multivalent vaccines can evoke enhanced responses to some component antigens and depressed responses to other components. The mechanism for differential responses like this is not known and the phenomenon is not predictable using animal models.

EDUCATION AND TRAINING ISSUES

The effort to develop more and better vaccines to protect human health does not end when scientific, legal, technical, and regulatory hurdles are overcome. Issues concerning collaboration, education, and training need to be addressed as well.

THE NEED FOR MULTIDISCIPLINARY COLLABORATION

Taking a vaccine concept from basic research to development requires that coalitions of investigators work together toward their common goal. Large-scale projects that combine the efforts of multiple investigators have

proven more effective in producing vaccines than have small, disconnected ventures. Collaborative efforts help investigators learn from one another and ensure better transparency of clinical findings. Lack of collaboration results in wasted and redundant efforts.

Multidisciplinary centers to coordinate effective collaborations between academia and industry could help carry vaccines from the bench to the clinic. These types of partnerships are not common in many areas and should be encouraged.

Funding agencies can encourage multidisciplinary collaboration in research through requirements in their requests for proposals.

Outside of research, other collaborations could encourage acceptance and uptake of vaccines. Collaborations between vaccine advocates and disease advocacy groups could advance the goals of both groups. For example, vaccine advocates and asthma awareness groups could work together to bring a vaccine for respiratory syncytial virus to market.

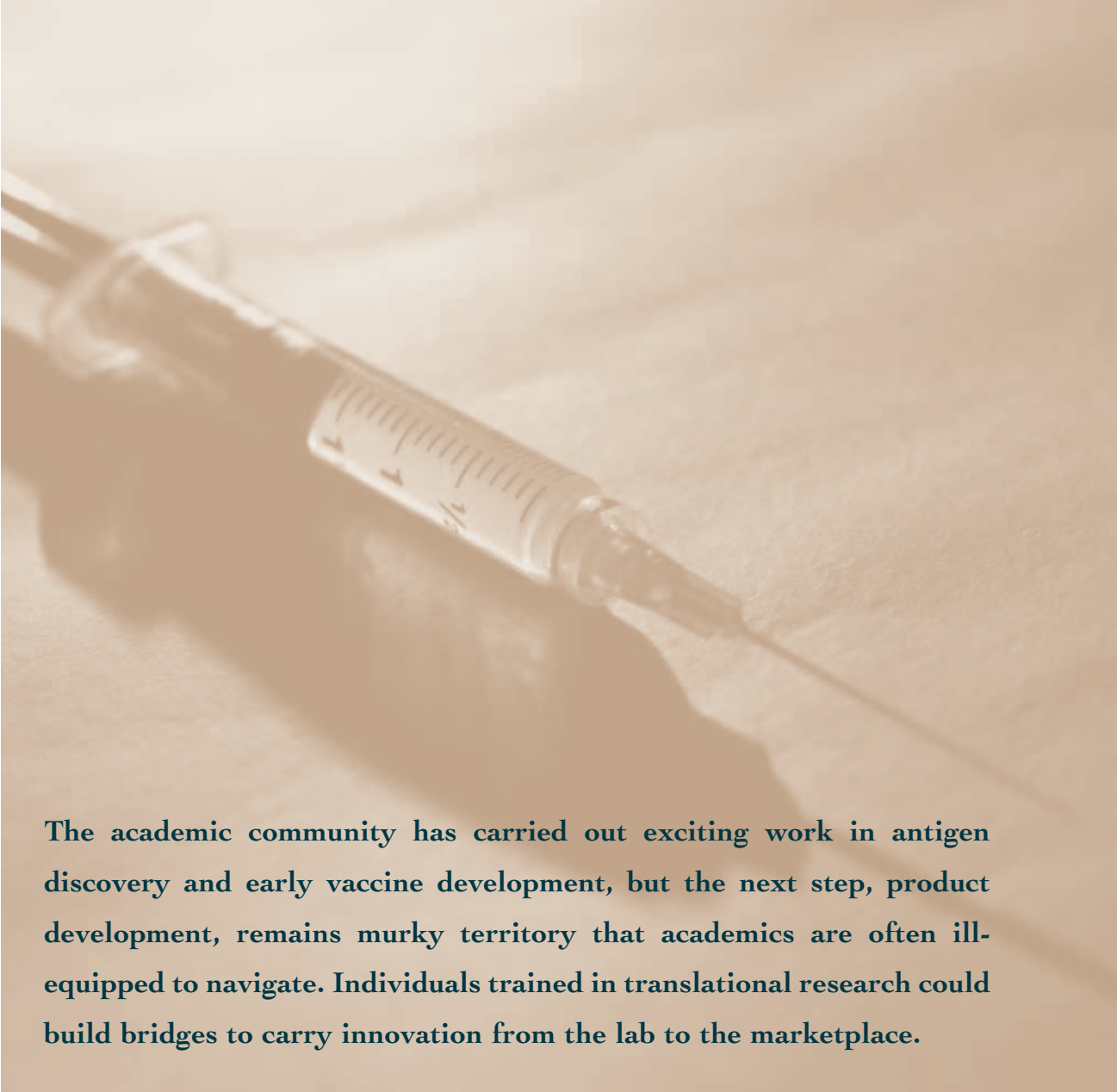
Encouraging the participation of the broader community could help to neutralize the voices of those individuals with unfounded and irrational arguments against vaccines.

Contact between vaccine advocates and responsible members of the mass media could help promote an even-handed analysis of both the benefits and drawbacks of vaccines.

INTERNATIONAL COLLABORATION

International collaboration is an increasingly important issue in vaccine work and productive cooperation should be encouraged. Vaccine developers and clinical trial sites are often located in different areas of the world. Where clinical trials are in developing countries, establishing a productive collaboration requires building trust, empowering host country researchers and their communities to be full partners in the planning, conduct and reporting of the trial, and strengthening trial site capacity.

Scientists involved in basic vaccine research are rarely confronted with limitations on international collaboration unless funding agencies impose restrictions on where funds can be spent. Collaborations between investigators from the U.S. and European Union are problematic, as government grants often put constraints on expenditures. More harmonization is needed between funding agencies in order to foster these collaborations. Consolidation within the pharmaceutical industry has led to huge international companies that play ever larger roles in developing and manufacturing vaccines throughout the world. Increasing collaboration among manufacturers, academic and government researchers, funding agencies, and regulatory agencies in multiple countries will be essential in future vaccine development.



The academic community has carried out exciting work in antigen discovery and early vaccine development, but the next step, product development, remains murky territory that academics are often ill-equipped to navigate. Individuals trained in translational research could build bridges to carry innovation from the lab to the marketplace.

EDUCATION AND TRAINING NEEDS

Educating and training scientists for future work in vaccines is critical to continuing the public health successes vaccines have brought about.

Developing programs that grant masters degrees in biotechnology would deepen the pool of qualified individuals needed to support vaccine process development, quality assurance and quality control programs, and other areas of vaccine development. Programs that place master's-level students in laboratories to gain experience prior to graduation would be helpful.

There is currently a scarcity of trained personnel available to work in vaccine process development. It is in the interest of the vaccine industry to address this shortfall. Establishing a

pool of people skilled in process development will require development of a curriculum, qualified instructors from academia or industry, and on-the-job training.

Training is also needed in translational research. The academic community has carried out exciting work in antigen discovery and early vaccine development, but the next step, product development, remains murky territory that academics are often ill-equipped to navigate. Individuals trained in translational research could build bridges to carry innovation from the lab to the marketplace.

Establishing schools of public health in developing nations would enable those nations to expand their sometimes meager expertise in public health matters.

COMMUNICATING THE IMPORTANCE OF VACCINATION TO THE PUBLIC

Maintaining public confidence in vaccines is essential. Both the mass media and the education system can be used to inform the public about the benefits of vaccination.

In the U.S., as in other industrialized nations where individual rights are paramount, the overarching problem with respect to vaccines and the public is how to achieve high immunization coverage with vaccines that cause adverse reactions. The successes of vaccination efforts, the dangers of infectious diseases, and the safety of vaccines need to be publicized to overcome public misgivings and encourage vaccine uptake. Physicians knowledgeable in the subject could give voice to the benefits of vaccination.

The mass media is an effective tool in getting a message to the public. The use of high profile spokespersons, product placement, and advertisements in the popular press are all techniques used by commercial interests that could be used to advantage in advertising the importance of vaccination.

Most health-related news stories selected for broadcast or print are negative. News related to the positive outcomes of vaccination efforts should be made available and promoted to the popular press.

With vaccines, there is a need to target different messages to different audiences. The elderly, for example, would benefit from a campaign that emphasized the benefits to their own health of making sure their grandchildren are immunized. Parents would benefit from messages that convey the risks involved in failing to vaccinate their children.

Information about vaccines could also be introduced in educational contexts. Teaching high school students about epidemiology and offering lessons about the positive effects of vaccines to the parents of children of all ages could encourage vaccine uptake. Pre-natal classes for expectant mothers are another good platform for this type of information.

Physicians are inadequately trained in immunology and vaccinology and, as a result, are often inadequately prepared to relay information about the benefits and risks of vaccines to their patients. Vaccine education in medical schools and continuing education on vaccine-related topics for health care workers should be better developed and promulgated.

The government can get involved in communicating messages about vaccines by sponsoring a "National Vaccine Awareness Day," such as the National HIV Vaccine Awareness Day held in May, or through activities carried out by the National Center for Health Marketing.

To the public, vaccines are somewhat contentious. In conveying information about vaccines, it is important that the

messenger be a neutral body, possibly a governmental organization, but not an industry group.

ENCOURAGING BROADER USE OF EXISTING VACCINES

A number of routes could be followed for encouraging the broader use of existing vaccines. They include:

- Increasing public funding for the procurement and delivery of vaccines,
- Increasing transfer of technology to settings where cost of manufacture can be significantly decreased,
- Enforcing vaccination requirements for enrollment in day care centers and schools,
- Making vaccines available in convenient locations, including grocery stores and schools,
- Providing incentives for physicians to follow vaccine recommendations,
- Requiring that all medical insurance plans support vaccination,
- Advertising by public health organizations, and
- Publicizing political support for vaccines.

In the developing world, as compared with developed nations, problems with vaccine uptake may be less related to public perceptions and more related to vaccine availability and affordability. Politicians in those countries should be educated on the importance of vaccines and funding for the procurement and delivery of vaccines should be increased. The WHO plays an important role in encouraging and facilitating vaccine use in poor countries but could play a larger role if more funding was available.



RECOMMENDATIONS

Vaccines have helped eradicate the worst infectious diseases in the developed world. Research and development must continue the progress of the past and address those diseases that have eluded the development of effective vaccines and the diseases that continue to devastate regions where vaccines have been unavailable. Research is also needed to improve existing vaccines.

The misperception that vaccines should fulfill a net cost-savings is a major obstacle to vaccine development. Governments and individuals should be prepared to pay a certain cost to improve health and avoid suffering. Vaccine development is hampered by the current pricing structure in the U.S., which for some diseases fails to allow adequate compensation for the companies that develop vaccines in the early years following licensure. Paying prices for vaccines that take into account their health- and lifesaving attributes, would encourage more research, more innovation, and better, safer vaccines.

The field of vaccine development suffers from a dearth of potent adjuvants licensed for human use. Adjuvants should be discovered and developed in a more rational way than they have in the past, for example, by using the newly discovered mammalian Toll-like receptors.

A lack of serologic correlates and limitations of immunological tools that can be used to find correlates of protection also presents a serious limit on vaccine development. These tools should be developed or improved promptly in order to ensure optimal progress in the field.

The safety of vaccines needs to be determined by a balancing of risk to benefit ratios by comparing the potential for adverse effects from a vaccine with its potential benefits. With respect to vaccine safety, it is critical to avoid confusing risk analysis with cost-benefit analysis. Vaccines will sometimes incur more costs, economically speaking, than they avert, a situation that does not reduce the value of a

given vaccine. Better public health tools are needed to measure the benefits of vaccines.

Many innovative approaches available for vaccine development are available, but there are few ways to make head-to-head comparisons of delivery systems, vectors, etc., because it is not in the interest of any party to develop these modes of comparison. Validated assays, common reagents, and common peptides are needed in order to make effective, meaningful comparisons of approaches to vaccine development and intellectual property issues that inhibit comparisons should be resolved.

Multidisciplinary centers that coordinate collaborations between academia and industry could help carry vaccines from the bench to the clinic, a breach that is often difficult to traverse. These types of centers, which should be government funded if not government owned, should be developed and promoted.

Vaccine developers and clinical trial sites are often located in different areas of the world and international suppliers are playing ever larger roles in manufacturing. As a result, international collaboration is becoming increasingly important in vaccine work. Productive cooperation between professionals of different nations should be encouraged.

Most health-related news stories are negative. In the interest of promoting vaccine uptake and public health, news related to the positive outcomes of vaccination efforts should be made available and promoted to the popular press.

