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SCIENCE AND SOCIETY

Vaccine safety—vaccine benefits: science and the public's perception

Christopher B. Wilson and Edgar K. Marcuse

The development of cowpox vaccination by Jenner led to the development of immunology as a scientific discipline. The subsequent eradication of smallpox and the remarkable effects of other vaccines are among the most important contributions of biomedical science to human health. Today, the need for new vaccines has never been greater. However, in developed countries, the public's fear of vaccine-preventable diseases has waned, and awareness of potential adverse effects has increased, which is threatening vaccine acceptance. To further the control of disease by vaccination, we must develop safe and effective new vaccines to combat infectious diseases, and address the public's concerns.

The discipline of immunology developed from observations in the fields of public health and clinical medicine. In the fifth century BC, Thucydides noted that individuals who recovered from plague did not develop disease again, and similar observations of 'immunity' to plague were made in Europe in the fourteenth century^{1,2}. The observation that mild smallpox infection protected against disease on subsequent exposure led to the practice of variolation — the inoculation of dried pus from smallpox pustules into the skin or nose. This was first practised in India and China, and then introduced in 1721

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Online links

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in England by Lady Montague, and in New England by Cotton Mather³. Jenner's clinical trial of cowpox virus vaccination, and publication of *Variolae Vaccinae* in 1798, gave birth to the field of immunology, but neither an understanding of the basis for its efficacy nor universal acceptance of this practice were soon to follow^{3,4}. Instead, scientific and public scepticism and alarm were common early responses (FIG. 1).

The subsequent formulation of the germ theory of disease by Koch and Pasteur, and von Berhing's identification of neutralizing factors for toxins, provided a foundation for the mechanistic understanding of protective immunity⁵. In the ensuing years, vaccines for more than 20 infectious diseases have been developed, and in 1977, Jenner's original experiment was brought to full fruition when smallpox was eradicated worldwide⁶. Immunization is one of the most stunning and economically effective contributions of biomedical science to human health. So, immunologists can be proud of the fundamental biomedical insights that have arisen from the field, and of the practical application of these insights in the prevention of disease.

Advances of the last century allow us to better understand the successes (and failures) of past vaccines, and enable a more rational and diverse approach to new vaccine development. An example is the development of polysaccharide–protein conjugate vaccines

Figure 1 | **The Cow-Pock.** *The Cow-Pock or the Wonderful Effects of the New Inoculation!* by James Gillray was published in England in 1802 by the Anti-Vaccine Society. The etching, which shows Edward Jenner among patients in the Small Pox and Inoculation Hospital at St Pancras (London), suggests the transformation into cows of individuals vaccinated by Jenner. Reproduced with permission from The Wellcome Library, London.

against *Haemophilus influenzae* type b. These arose from observations showing: that antibodies to type b capsular polysaccharide are protective; that polysaccharides do not induce T-cell help and are not immunogenic in early life; and that linkage of polysaccharide to protein results in a T-cell-dependent antibody response to both components. Routine use of these vaccines has nearly eliminated meningitis and other diseases caused by *H. influenzae* type b⁶. Advances in our understanding of the determinants of protective immunity and immunological memory, of the mechanisms by which adjuvants affect the quality and magnitude of immunological responses, and of microbial genomics, offer the promise for new and more effective vaccines in the near future.

Public concerns and vaccine safety

In recent years, a vocal minority in the developed world has questioned the safety and net benefits of vaccines. Vaccines are unique among medical interventions in that they are given to healthy individuals to prevent diseases that often do not pose an immediate threat to the recipient. Many vaccine-preventable diseases are now so infrequent that the only context in which many individuals have heard of these diseases is when hypothetical adverse effects of the relevant vaccine are presented by the

media as fact in an emotionally gripping story. We illustrate, through examples of real and falsely attributed adverse reactions to vaccines, the effects on vaccine use and development.

“...a perceived risk of a vaccine might outweigh concerns about the disease it is designed to prevent. Perceptions, be they true or false, drive behaviour.”

Whooping cough. Whooping cough vaccines were developed in the late 1940s, by formalin inactivation of whole *Bordetella pertussis*, and were later combined with diphtheria and tetanus toxoids to create the DTP vaccine. Widespread early childhood immunization led to a marked reduction in the incidence of whooping cough. Because encephalopathy and encephalitis were well-recognized complications of smallpox vaccine⁷, encephalopathy presenting soon after immunization with a pertussis-containing vaccine was attributed to the vaccine⁸. As awareness of the severity of this disease faded, public concern emerged

regarding potential adverse reactions to the vaccine, including seizures, infantile spasms, encephalopathy and sudden infant death syndrome (SIDS)^{9,10}. As a result, DTP vaccine usage declined in several countries, which was followed by a resurgence of the disease¹¹ (FIG. 2). It was later determined that DTP does not cause SIDS^{12,13}, infantile spasms¹⁴ or epilepsy¹⁵. In some children, DTP does cause transient fever, hypotonic-hyporesponsive episodes, protracted inconsolable crying and seizures, and might rarely cause acute encephalopathy (<1:100,000 attributable risk)¹⁶, but there is no clear evidence that any of these acute events are followed by chronic neurological disability^{17,18}. The negative publicity that precipitated the decline in vaccine usage and resurgence of pertussis-related disease also motivated research to improve our understanding of the antigens that induce protective immunity. In the early 1980s, Japanese investigators developed acellular pertussis vaccines composed of one or more protein antigens, which are now available in combination with tetanus and diphtheria toxoids as DTap. These vaccines have much lower rates of adverse effects and have largely replaced formalin-inactivated pertussis vaccines in developed nations, but owing to their greater cost, not in developing nations.

Poliomyelitis. Decades before the development of molecular methods would allow the engineering of live-attenuated viral vaccines, an attenuated poliovirus vaccine for oral administration (oral polio vaccine, or OPV) was developed by empirical, sequential passage of virulent viruses in heterologous cell-culture systems. Shortly after its introduction, sporadic cases of vaccine-associated paralytic poliomyelitis (VAPP) were noted (~1:750,000 recipients)¹⁹. The continued occurrence of VAPP following the virtual elimination of wild-type poliomyelitis from the Western Hemisphere in 1991 prompted a change from OPV to inactivated poliovirus vaccine (BOX 1) in the United States, as was already the practice in many countries of the developed world. OPV remains the vaccine of choice in the drive to eradicate poliomyelitis worldwide, and has worked successfully in regions where vaccine coverage is high. In two regions where OPV coverage was low, paralytic polio due to transmission of vaccine-derived polio viruses has recently been described, perhaps reflecting the accumulation of genetic changes in vaccine-strain virus sufficient to restore neurovirulence and transmissibility following sequential passage between susceptible individuals²⁰.

Figure 2 | **The effects of adverse public perceptions of whole-cell pertussis vaccine on pertussis disease.** The left panel shows the incidence of pertussis disease in countries with sustained vaccine use. The right panel shows the incidence of pertussis disease in countries in which vaccine use declined in relation to public anti-vaccine movements; the timing of the anti-vaccine movements is highlighted (in yellow), and for England and Wales, vaccine coverage during the period is shown in the inset. Adapted with permission from REF. 11.

Curiously, these rare, but real, adverse effects of OPV have not received media attention comparable with that prompted by a false adverse effect. In 1992, an article in *Rolling Stone* magazine suggested that a candidate poliovirus vaccine derived from virus cultured in kidney cells from African green monkeys (which are known to carry simian immunodeficiency virus; SIV_{AGM}) and tested in the Congo was the source from which human immunodeficiency virus (HIV)

arose²¹. Because SIV_{AGM} is genetically distant from HIV-1, the hypothesis proposed in *Rolling Stone* was implausible. In 1999, a book entitled *The River: A Journey to the Source of HIV and AIDS*²² renewed public concern by proposing that HIV was introduced into the Congo by poliomyelitis vaccine prepared in chimpanzee kidney cells contaminated by a simian immunodeficiency virus (SIV_{CPZ}) that evolved into HIV-1. This hypothesis was plausible, as SIV_{CPZ} is closely

related to HIV-1; however, several groups have shown conclusively that the vaccines used in the Congo contained no chimpanzee DNA²¹. These and other data have closed the door on the OPV–AIDS hypothesis in scientific circles, but not all public sceptics have been converted.

Current vaccine controversies

Whether real, alleged but unproven, or incorrect, a perceived risk of a vaccine might outweigh concerns about the disease it is designed to prevent. Perceptions, be they true or false, drive behaviour. Although this might seem to be scientifically irrational behaviour, several truths contribute to such decisions: the safety of biological products is not absolute; rare adverse effects of vaccines might not be apparent in pre-licensing studies; public (and scientific) concerns about adverse effects have contributed to the development of safer vaccines; and if you or someone dear to you is affected, it matters little to you that the adverse event is rare.

In the past 15 years, vaccines against *H. influenzae* type b, hepatitis A and B, rotavirus (BOX 2), *Streptococcus pneumoniae*, varicella, meningococcus C and Lyme disease have been introduced. In the United States, children are now required to receive 23 (or more) vaccine doses by the age of six. These vaccines have led to a marked reduction in the incidence of many of these diseases. At the same time, there has been a striking increase in the apparent prevalence of some chronic and neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), autism, allergy and autoimmune diseases^{23–26}. The temporal association between these events has led some to propose that the vaccines are causally related to an increase in the incidence of these disorders.

Reports by Wakefield and colleagues^{27,28} in the United Kingdom indicated that, following the administration of the measles, mumps and rubella (MMR) virus vaccine, vaccine-strain measles virus persists in the gut of certain at-risk children, and, through a complex hypothetical pathway, contributes to the development of autism. This hypothesis received widespread media attention in the United Kingdom and Ireland, and was followed by substantial public concern and decreased use of MMR in some regions^{29–31}. This concern has crossed the Atlantic, prompting media concern and congressional hearings in the United States. Studies and expert panels in the United Kingdom and United States^{32–34} concluded that the apparent increase in the rate of autism is not

Box 1 | Polio vaccines: Salk, Sabin and the Cutter incident

Poliomyelitis became epidemic in industrialized countries in the late nineteenth century, when improved hygiene postponed exposure beyond infancy, resulting in an accumulation of sufficient numbers of susceptible individuals to sustain epidemics. Public fear and Franklin Roosevelt's paralysis as a result of polio led to the creation of the National Foundation for Infantile Paralysis in the United States, which funded research that culminated in the licensing of an inactivated poliovirus vaccine (IPV; the Salk vaccine) in 1955. Weeks later, mass vaccination was halted when vaccine-associated cases of disease were recognized. Ultimately, 260 cases were attributed to insufficient inactivation of virus in two lots of vaccine manufactured by Cutter Biologicals. Since then, no cases of paralysis have been associated with the more than 90 million doses of IPV. The incidence of poliomyelitis fell by 95% between 1955 and 1961, at which time IPV was replaced by oral poliovirus vaccine (OPV; the Sabin vaccine)⁴. Simian virus 40 (SV40), which is oncogenic in several species, was later found to contaminate many lots of IPV derived from viruses cultivated in rhesus monkey kidney cells. Although some vaccines developed antibodies to SV40, there is no evidence that this resulted in an increase in the rate of cancer⁵⁰. Nonetheless, culture systems were changed, and today, poliovirus vaccines are produced either in well-characterized continuous cell lines or cells from monkeys raised in SV40-free colonies.

causally related to MMR vaccine, although data are, at present, inadequate to fully exclude the possibility that MMR might be a contributing factor in a rare child³⁴. In France, concern has revolved around the potential induction of **multiple sclerosis** by hepatitis B vaccination, prompting its withdrawal from routine use in some groups, and widespread public concern (BOX 3).

The increased prevalence of **type I diabetes** and **asthma** in many countries in the developed world has been linked by some to the prevention of infectious diseases and microbial contact through better hygiene and vaccination^{23,25,35–37}. There is some evidence that children with more frequent infections in early life have a lower rate of allergic diseases, including asthma, in later life^{23,25,35–37}, but the epidemiological evidence is conflicting^{38,39}. The hypothesis, which states that frequent infections protect against atopic disease, fits with the notion that microbes trigger the production of cytokines by cells of the innate immune system, for example, interleukin-12 (IL-12) and type 1 interferons, which favour the development of T helper (T_H)1 T-cell-mediated responses. Some propose that, in the absence of such signals, the infant's immune response to non-microbial environmental antigens, particularly in children with a genetic predisposition, is more likely to deviate to an allergic, T_H2 response^{23,36,37}. Because infection is known to decrease the risk for type I diabetes in genetically prone rat and mouse models²⁶, if these principles apply in at-risk humans, reduced contact with infectious agents might increase their risk. However, even if this 'hygiene hypothesis' has merit, the contribution of vaccine-induced prevention is likely to be minor^{26,40}, as relatively few infections are prevented by immunization.

Non-antigen-specific effects have also been proposed. Many vaccines contain alum, an adjuvant that favours the development of T_H2 responses⁴¹. Whether or not the frequency and amounts of alum administered are sufficient to influence the nature of ongoing immune responses to intercurrent infections, or to do so in a subset of children with a genetic predisposition to allergic disease, is uncertain. Comparative data from West Africa showed that immunization with DTP vaccine, which contains alum, increased the risk of allergy in children, whereas immunization with BCG (Bacillus Calmette–Guérin) decreased this risk and overall mortality³⁵. However, potential confounding variables might account for these differences. Finally, almost 25% of US parents are concerned that the number of vaccines administered

“...predictions that infectious diseases would cease to be an important threat to human health have been followed by a more sobering reality.”

‘overload’ the capacity of the infant's immature immune system, perhaps impairing immunity to other infections or altering the body's tolerance to self-antigens⁴² — a concern for which there is no clear scientific basis. Concerns have also been raised about the potential for thimerosal⁴³, which was included in a number of vaccine formulations as a preservative, to contribute to the development of neurodevelopmental disorders, including autism. The active ingredient in thimerosal is ethylmercury, and mercury is a known neurotoxin⁴⁴. The increased number of routine childhood immunizations in the United States resulted in an increase in the total amount of ethylmercury received by young children, at the same time that the apparent incidence of autism has increased. Although the amounts of ethylmercury

received are below those shown to cause neurotoxicity, theoretical concerns led to the removal of thimerosal from vaccines manufactured in the United States⁴⁴. Further study is needed to determine the risk, if any, of these doses of thimerosal⁴³. Thimerosal has not been removed from vaccine formulations provided by the World Health Organization, owing to concerns that the resultant increase in cost would limit vaccine availability. Similarly, the presence of bovine serum in vaccine preparations has raised theoretical concerns about the transmission of bovine spongiform encephalopathy (BSE); although unlikely, a finite (<1:10⁹) risk cannot be excluded.

At the same time that public trust in vaccines is threatened, the impetus for the development of new vaccines is great. Earlier predictions that infectious diseases would cease to be an important threat to human health have been followed by a more sobering reality. Infection currently accounts for ~25% of all deaths worldwide, new infectious diseases have emerged as global threats, and there has been a resurgence of many diseases for which we lack effective vaccines⁴⁵. We, in the developed world, are no longer safe from infections that plague the developing world, as shown by the HIV epidemic. The pressure to bring prototype HIV vaccines to early clinical trials, particularly in

Box 2 | Rotavirus vaccine: licensed 1998, withdrawn 1999

“...if one is culpable for vaccine related deaths, then one is also culpable for deaths caused by withholding the vaccine”⁵¹.

Rhesus–human reassortant rotavirus vaccine, the first of a new generation of live recombinant viral vaccines, was developed to prevent a diarrhoeal disease that causes substantial morbidity in the developed world and more than 600,000 deaths per year in the developing world. A total of 10,000 children received the vaccine in 27 clinical trials in nine countries. Five cases of intussusception (in which the terminal ileum telescopes inside the colon, producing intestinal obstruction) occurred in 5 out of 10,054 vaccines and 1 out of 4633 placebo recipients. This is an uncommon but serious disorder, occurring primarily between 3–12 months of life. Intussusception might be initiated by enlarged germinal centres in Peyer's patches, which indicates that an over-exuberant intestinal immune response might underlie the disorder. However, mice given the vaccine do not develop Peyer's patch hyperplasia, even though virus is present in Peyer's patches⁵². Because there were relatively few cases in the trials, and wild-type infection does not cause intussusception⁵³, the relationship between this vaccine and intussusception seemed likely to be coincidental. Vaccine licensing was not delayed, but further monitoring was assured and cases were tracked. 10 months after licensing and administration of ~1.5 million doses in the United States, 13 cases of intussusception had been reported, and vaccination was suspended. Epidemiological studies confirmed an excess of cases following the first dose of rotavirus vaccine, which was withdrawn in October 1999 (REF. 53). Some believe this episode indicates that the United States' post-licensing vaccine safety system works, whereas others view it as evidence that the pre-licensing vaccine system failed. To detect an adverse event with an incidence equivalent to the excess risk attributable to rotavirus vaccine (~1:10,000), a trial involving 40,000 children would be needed. Such larger pre-clinical trials would increase safety, but delay vaccine availability and increase cost. Withdrawal of the vaccine means that it will not be available to the developing world, where it could prevent vastly more deaths than it might cause.

Box 3 | Hepatitis B and multiple sclerosis

Following a mass hepatitis B immunization campaign in France in 1996, a group of neurologists reported several cases of multiple sclerosis (MS) in vaccinated women. This attracted the attention of the French media and then of the international popular press. Two subsequent studies found a nonsignificant increase in MS among vaccinees, and a meeting of experts convened by French authorities in 1998 concluded that there was no credible evidence for an association between hepatitis B and MS. Nonetheless, the French minister of health advised that the school-based hepatitis B immunization programme be suspended, and public health authorities in some other countries took similar actions. An expert panel convened by the World Health Organization did not find evidence of a causal relationship between the hepatitis B vaccine and MS, found weak evidence supporting the hypothesis that the vaccine might trigger symptomatic disease in at-risk individuals, and concluded that the benefits of hepatitis B immunization outweighed the risk and that no change in hepatitis B immunization policy was warranted⁵⁴. Two rigorous studies found no association of hepatitis B with the onset of MS, and no evidence that hepatitis B increased the risk of short-term relapse of MS^{55,56}. Controversy, low vaccine acceptance and litigation alleging that MS is caused by hepatitis B continue in France. Worldwide, hepatitis B immunization continues and has reduced the rate of childhood liver cancer⁵⁷.

Africa, is great^{46,47}. This has led some public figures to dismiss scientific concerns that hypothetical negative effects of a candidate vaccine on protection might go unnoticed in initial clinical trials⁴⁷. Some in the developed world have used such issues as fuel for their own concerns about vaccine safety. They ask whether the enthusiasm for the triumphs achieved through vaccination will lead to the introduction of new vaccines, including vaccines against HIV, the full safety of which will not be known, and that they and their loved ones will be the unwitting experimental subjects in whom adverse effects will first become apparent.

Call to action

What must we do to allay these fears and to restore and sustain the public's trust? First, advances in immunology must be exploited to develop more effective, safer vaccines, particularly for diseases of global importance. We must carefully assess the safety and efficacy of each vaccine, when administered alone or in combination with other vaccines. We must ask if vaccines alter the risk of allergic and autoimmune diseases, and understand genetic factors that influence immunogenicity or predispose individuals to adverse effects. Finally, immunologists, along with scientists from other fields, public health officials and physicians, must participate in a frank public dialogue with those to whom vaccines will be given, stating clearly what we know for certain, what we suspect, but for which we lack compelling proof, and what we do not know^{48,49}. The debate about vaccine safety takes place in three courts: the court of medicine and science, the court of public opinion and the legal courtrooms. The rules of

evidence — what constitutes proof of causation — differ in these venues, and therefore so might the judgements rendered. Science must be the final arbiter, but we must explain the science more clearly and effectively to a public whose scepticism reflects their struggle to understand information from diverse sources of varying validity, including the web (see the web sites listed in the links box below). Both our individual credibility and the credibility — and therefore the potential — of the entire collaborative enterprise of immunization depend ultimately on both the rigour of our scientific practice and our ability to communicate this to the public.

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National Immunization Program

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