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The legacy of Edward Jenner

More vaccines of different types are reaching ever more people

See p 1210

Two hundred years after the pioneering clinical experiments of Edward Jenner, who inoculated humans with cowpox to prevent smallpox, we find ourselves at the threshold of a golden age of vaccinology. Much attention has recently been directed at the advances in modern biotechnology that are giving rise to exciting new vaccine candidates. Nevertheless, a long and arduous journey lies between being an innovative concept and becoming a licensed product that can serve as a public health tool. In fact, few concepts survive to become products. Less well appreciated are the advances in clinical vaccine testing that allow a vaccine to progress towards licensing; the epidemiological techniques devised to appraise its effectiveness after licensing, when the vaccine is used under real life conditions; and the tactics used to achieve high levels of vaccine coverage, particularly in less developed countries.

Biotechnology has opened entire new approaches to vaccine development, such as the rational and precise attenuation of bacteria and viruses to serve as live vaccines,[1] the direct inoculation with plasmid DNA encoding protective antigens ("naked DNA" vaccines), and the microencapsulation of antigens to enhance immunogenicity and modulate the kinetics and type of immune response.[2] Consequently, at various stages in the pipeline we find vastly improved vaccines against infectious diseases for which vaccines already exist—for example, acellular pertussis vaccines containing purified antigens[3] and a recombinant, single dose, live oral cholera vaccine[1]— together with new vaccines against diseases for which immunoprophylaxis was previously unavailable (malaria, rotavirus,[4] and Lyme disease). Notably, several rotavirus vaccines that are advanced in clinical trials follow a "Jennerian" approach in which an animal (rhesus monkey or bovine) rotavirus strain is genetically manipulated (reassortant viruses) to express human rotavirus neutralisation antigens.[4]

Vaccines are tested in a series of stepwise clinical trials. Phase 1 trials, performed in small numbers of adults, are early dose-response tests to detect common adverse reactions and provide an initial glimpse of whether relevant immune responses are generated. Most vaccine candidates never progress beyond phase 1. Phase 2 trials, which assess the vaccine in increasingly larger numbers of subjects, are typically placebo controlled to measure the rate of adverse reactions versus background rates of complaints. The level of shedding of a live intranasal influenza vaccine or of a recombinant live attenuated *Vibrio cholerae* O1 oral vaccine would also be examined in phase 2 trials, as would their propensity to be transmitted to household contacts and to survive in the environment.[5] For vaccines that will ultimately be used in infants and children, phase 1 and 2 trials must be undertaken in progressively younger subjects.

Particularly demanding is the design of phase 2 clinical trials to evaluate the reactogenicity and immunogenicity of the new multivalent combination vaccines in infants. As additional vaccines—such as hepatitis B, *Haemophilus influenzae* type b conjugate, and multiple component acellular pertussis vaccines—enter infant immunisation regimens, a way must be devised to administer them along with the fewest inoculations along with existing parenteral vaccines. The ultimate objective is to combine vaccine antigens into a single inoculation. This raises the theoretical possibility of interactions,[6] so phase 2 trials must show that acceptable immune responses to all antigens can indeed be stimulated without undue reactogenicity. Phase 1 and 2 trials of candidate AIDS vaccines also require special considerations.

In some cases, as with vaccines to prevent influenza,[7] shigella dysentery,[8] or *Plasmodium falciparum* malaria,[9] preliminary assessments of efficacy can be obtained through carefully performed experimental challenge studies with wild type organisms in fully informed adult volunteers. Such modern day challenge studies are a direct legacy of Edward Jenner's experiments, although today the study protocols undergo stringent ethical review, and children, such as Jenner's young subject, James Phipps, would not be allowed to participate.

Large scale, randomised, controlled field trials remain the gold standard for showing the efficacy of a vaccine.[3,10] Such trials tend to be expensive, require several years to complete, and are subject to the vagaries of year to year variation in the incidence of the disease. Moreover, in prelicensure efficacy trials the protective activity of a vaccine is measured under ideal conditions, with extra staff and with only fully vaccinated subjects included in calculations of efficacy. Therefore the practicality of use of the vaccine within a programme is not readily estimated. Estimating efficacy after licensing usually involves case-control studies, which are relatively inexpensive and simple to perform but have inherent limitations that can distort the estimation of efficacy.[11] A few controlled postlicensure trials have directly measured the effectiveness of vaccine under real life, programmatic conditions.[12]

Enhanced postlicensure epidemiological surveillance has proved its value by showing herd immunity effects (as with *H influenzae* type b conjugate vaccine) and consequences in those who are not the targets of the vaccine—for example, the rare occurrence of vaccine associated paralytic poliomyelitis in household contacts of infants who have received Sabin live oral polio vaccine.

The ultimate triumph of vaccines is disease eradication. In the mid-1970s smallpox vaccine deployed following special epidemiological strategies succeeded in eradicating the disease that Jenner attempted to prevent in the 1790s. Polio has been eradicated from the western hemisphere, and worldwide eradication is now a realistic goal. The World Health Organisation's expanded programme on immunisation, descended from the smallpox eradication programme, has devised practical solutions to maintaining a "cold chain" and delivering vaccines under field conditions in less developed countries. During the past decade the percentage of the world's infants who receive the basic vaccines of the expanded programme (BCG, DPT, oral polio, and measles) has risen from about 40% to over 80%.

Vaccines have come to be recognised by public health authorities as one of the most cost effective interventions available. Across the world, in both industrialised and developing countries, more vaccines of different types are being administered to increasingly larger segments of the population. This is the greatest tribute to Edward Jenner, who started it all 200 years ago.

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Mass polio vaccination

Eradication by 2000 is a realistic goal

Albert Sabin always emphasised that the global eradication of wild poliovirus was possible but that to achieve eradication in developing countries would require mass administration of oral polio vaccine. Experiences in Cuba and Czechoslovakia have proved the effectiveness of this approach, but it was only with its deployment in Brazil in the 1980s that its role in eradicating the virus from a broad geographical area was realised.[1] After 40 years of mass administration of oral and inactive poliovirus vaccines a pattern of impact is emerging. Both the vaccines have proved records of safety and efficacy, and there is now no doubt that applying oral polio vaccine over short periods and on a mass scale can control poliomyelitis in any country, irrespective of its geographical location or level of sanitation.

The World Health Organisation has played a vital part in the development and use of polio vaccines since their inception. Since 1973 it has been directly responsible for the custody and distribution of the Sabin strains of the oral polio vaccine and has supervised the production laboratories.[2] In 1974 it started the expanded programme on immunisation covering six childhood diseases, including poliomyelitis, and progress has been such that in 1988 the organisation declared its commitment to the goal of global eradication of poliomyelitis by 2000.[3]

Eradication is defined as zero cases of paralytic poliomyelitis due to wild poliovirus infection and the absence of environmental circulation of wild poliovirus: three years' absence of wild poliovirus qualifies a region as having eradicated polio. The World Health Organisation recommends four strategies for achieving this goal: increasing and sustaining coverage with oral polio vaccine; conducting national immunisation days; developing surveillance for acute flaccid paralysis, including laboratory confirmation; and "mopping up" vaccination campaigns.[4] Routine vaccination and annual immunisation campaigns can greatly reduce the incidence of disease[5] but are not enough to eradicate the virus, so the expanded programme is now helping countries to transform their national disease prevention programmes into, in the case of poliomyelitis, disease eradication programmes.[6]

From 1988 to 1994 the number of reported cases of poliomyelitis fell by 84%, from 25 711 to 4184. Cases from India in 1994 accounted for 93% of the regional total and 62% of the global total,[7] but the disease has practically disappeared from many developed countries in the Americas, Europe, and Western Pacific regions.[8] Most countries in southern and northern Africa have also recently achieved their eradication targets.[4]

Since 1988 importation of wild poliovirus from parts of South East Asia has accounted for many outbreaks or sporadic cases of polio in countries previously free of the disease in Europe, the Middle East, and North America.[4] Because South East Asia remains a major global reservoir of polioviruses, full implementation of the World Health Organisation's recommended polio eradication strategies in this region is a high priority.

The mass polio vaccination campaign now going on in most developing countries involves giving two doses of oral polio vaccine to all children in the target age group (generally below 5 years of age) irrespective of prior vaccination history, with an interval of four to six weeks between the doses. The "mopping up" vaccination campaign involves door to door administration of two doses of oral polio vaccine to all young children in areas where stool tests show that wild poliovirus circulation persists at low levels during the final stages of eradication. The aim is to reduce the circulation of wild poliovirus in these pockets. The campaign is being conducted alongside the routine vaccination of children with three doses of oral polio vaccine at 2, 3, and 4 months of age.

Wild poliovirus is prevalent in seven of 10 countries in South East Asia, and six of these seven countries completed