17 Responsibilities of sponsors after successful Phase 3 vaccine efficacy trials
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We lack viable political and financial mechanisms to ensure the rapid uptake of effective new vaccines into nascent vaccine programs. This raises a number of questions as to the role of clinical trial sponsors after an efficacy trial is over. How does one apportion responsibilities among multiple trial sponsors? Sponsors could include the vaccine developer/manufacture who provides the vaccine for the clinical trial, international public health funding agencies who provide some or all of the funding, as well as academic or governmental institutions given legal permission by regulatory agencies and ethics boards to conduct and monitor the trial. Trial sponsors also differ. In some cases the vaccine sponsor needs the data to obtain licensure in an industrialized country, but in others the driving force is the strong interest of public sector agencies with the vaccine producer simply having agreed to provide the requisite vaccine doses. Do the capabilities of the host country immunization program matter for example, so post-trial "responsibilities" of sponsors differ for trials in extremely poor developing countries vs. trials in "emerging nations" vs. trials in industrialized countries? What may be financially and politically possible for sponsors for a trial in one country (e.g., the Doualaa with a population of approx. 7 million) would be much more difficult for another (e.g., Bangladesh, with its 180 million people). Finally, who decides whether a trial was sufficiently "successful" to warrant introduction, and how are those responsibilities affected by subsequent post-licensure "effectiveness" trials? Despite these complexities, it seems possible to elaborate some general principles regardless of the precise context. How we resolve these issues has implications for the willingness of trial sponsors to support trials in various countries, as well as for the rapid introduction of new vaccines directed against diseases of significant public health importance.

18 A post-licensure selective vaccination demonstrating the impact of programmatic use of Hib-conjugate vaccine in Chilean infants.
Lagos R. Levine MM.

In 1992 the Institute of Public Health of Chile licensed PRP-OMP and PRP-T Hib conjugate vaccines for use in infants and young children. Such decision rendered the acknowledgment of the local regulatory authority of the safety, immunogenicity and inherent biological activity of these products. However doubts remained among Public Health and EPI officials about whether the impact after programmatic use of Hib-conjugate vaccines would justify their high cost. Consequently, the Ministry of Health undertook a post-licensure selective vaccination to evaluate the effectiveness of Hib-conjugate vaccines under programmatic conditions. This would allow a more informed decision on whether to introduce Hib vaccine into the EPI. During 12 months (November 1992 to October 1993) the EPI clinics of 30 ambulatory health centers in Santiago implemented PRP-T vaccine combined with DTP vaccine, whereas 35 similar health centers administered only DTP vaccine. Standardized bacteriologic surveillance for invasive Hib disease was maintained throughout the study and 3 private hospitals that admitted children in Santiago. Over a period of 30 months, 4 cases of invasive Hib diseases were detected among infants and children served by PRP-T/DTP health centers, vs 40 cases in the population assigned to health centers that administered DTP alone. Thus, in an intent-to-vaccine effectiveness analysis PPR-T conferred 90% protection against invasive Hib infection. Vaccine effectiveness against meningitis was 91.5% (95% CI 91.4%, 91.7%) and 80% against pneumonia and empyema. This post-licensure evaluation provided a clear demonstration of the impact of programmatic use of Hib-conjugate vaccine in diminishing the burden of Hib invasive infections in Chilean infants. Based on this evidence, the Ministry of Health decided to implement systematic use Hib-conjugate vaccine in the EPI, beginning in July 1996.

19 AIDS Exceptionalism in the Vaccine Arena: Additional Obstacles for HIV Vaccine Trials

Involving in 1991, HIV has already caused more than 40 million infections worldwide, 90% of them in developing countries. In 1998 alone, 2.5 million people died of AIDS and 8.8 million became infected with HIV. Although an HIV vaccine would be the most cost-efficient intervention to control this pandemic, its development is hampered by "myths and misconceptions", which makes it unfortunately "exceptional". Although the scientific challenges presented by HIV vaccine development should not be underestimated, many lessons can be learned from the experience obtained in the development of other vaccines. Issues that tend to paralyze the HIV vaccine field (genetic variability of the virus, lack of an adequate animal model, no information on potential immune correlates of protection, difficulty in inducing sterilizing immunity) have been solved with other vaccines by incremental knowledge obtained through multiple vaccine trials, including large scale efficacy trials. AIDS vaccine development may also be quantitatively (although not perhaps qualitatively) different from other vaccines in relation to the degree of public attention it attracts, its political visibility, the involvement of affected communities in the design and implementation of trials, and the renewed attention to ethical issues related to medical research in human volunteers.

20 Overview of Potential Bioterrorist Biological Agents and Countermeasures. G.W. Korch. Virology Division, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland 21702

The range of biological pathogens potentially available for use as weapons exceeds from simple protein toxins through viral, bacterial or protozoal organisms. Agents that would be anticipated in the setting of a large-scale infection or intoxication event would most likely be delivered as a small particle aerosol, be relatively easy to produce, be stable during storage, and be rapidly disseminated. The Department of Defense develops vaccines, therapeutics and diagnostics as countermeasures for a number of toxins, viral and bacterial threats. Programs to develop safe and effective vaccines against an aerosol or other delivery of these agents incorporate both classical approaches as well as newer strategies for vaccine development and delivery. These newer approaches are based on recombinant technologies for production of protective immunogens, as well as new delivery platforms, such as viral replicons. Diagnostic capabilities emphasize the development of specific and rapid, early identification assays for antigen, antibody or nucleic acid followed by confirmatory assays. Rapid assessment of antibiotic resistance profiles are also important requirements for proper intervention. The DoD has been at the forefront of developing broad-based educational programs for military personnel which are now being applied to actual responders and primary care physicians.