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Some Problems Related to Risk-Benefit Assessments in Clinical Testing of New Vaccines by Gunnar Bjune and Truls W. Gedde-Dahl

Since 1975 Norway has experienced the highest incidence of disease caused by serogroup B meningococci (MCdB) in Europe. The disease has mainly afflicted children and teenagers. The fatality has been about 10 percent, and another 20 percent have survived with sequelae.[1-2] An outer membrane vesicle vaccine was developed at National Institute of Public Health (NIPH) in Oslo and passed successfully through phase II trials including about 7,000 adults. In October 1988 we started a placebo-controlled, double-blind, school-randomized efficacy trial, phase III, in all Norwegian secondary schools.[3] The Norwegian Government guaranteed compensation to participants in cases of any damage caused by the vaccine. Two injections of vaccine or placebo were administered during a period of four months to a total of 172,000 subjects. Side effects and possible complications were reported instantly to the NIPH and, if judged "serious," by phone to the Ethical Review Committee (ERC).[4-5] ERC was also continuously informed about reported cases of possible MCdB. During the trial ERC was the only body that could check for an individual's vaccination status, whether placebo-injected, vaccinated, or nonparticipant. The trial was closed and analyzed 3 June 1991 and showed significant protection (p=0.012) with a protection rate of 57.4 percent and a 95 percent confidence interval of 28-90 percent.[6]

Eleven adverse events were initially reported as "serious." Four were in the placebo group and seven among vaccinees. Of the latter, four were various neurological conditions of unknown etiology. As soon as the protective effect could be assessed against observed side effects and serious events recorded, it was decided that the former placebo group should be offered vaccine. Thus, the phase III persons in the relevant cohorts immediately continued (in this case partly rearranged) in an extended, open phase IV trial (IVb). This sort of comparison in fact started as a half open phase IV trial (IVa) simultaneously with the proper phase III trial. Those included in phase III, of whom about half were vaccinated, were compared to those in the same cohorts who did not participate. All the vaccinated individuals (140,000) were compared with all nonvaccinated in the same cohorts (95,000) acting as controls. All cases of possible MCd and vaccine side effects as well as any case of relevant neurological diseases were recorded and will be analyzed at fixed intervals through July 1994.

During the clinical testing of this vaccine we were confronted with several ethical problems, some of which are inherent in any large-scale testing of vaccines in large groups in natural target populations. General problems related to the risk-benefit assessments will be discussed in this paper from the perspective of a vaccine developer. In another paper we discuss problems related to informed consent in young adolescents who were the subjects in the major protection trial.[7]

Are Vaccine Trials Therapeutic or Nontherapeutic Experiments?

In any research involving human beings there must be a reasonable balance of risks and benefits. In The Helsinki Declaration this balance is seen from the individual participant's point of view.[8] For a new drug that can potentially or most likely heal or improve the patient's disease, benefits are fairly noncontroversial. In phase I studies of organ toxicity and drug metabolism in healthy volunteers, however, since the individual's health gain is zero, the risk ought to be minimal.[9] This is a classical example of a nontherapeutic experiment.

The more serious the disease, the higher is the level of acceptable risks inherent in the therapy to be tested. Ideally, the risks in a nontherapeutic trial involving children should not exceed those of ordinary daily life.

Gunnar Bjune, MD, PhD, *is senior physician at the National Institute of Public Health, Oslo, Norway, and directed a protection trial with a new vaccine against meningococcal-B-disease 1988-91;* **Truls W. Gedde-Dahl, PhD,** *is biostatistician at the same institute and participated in designing the clinical trials.*

Phase I trials are made manageable by involving a minimal number of test subjects, often including the researchers themselves. The research proceeds slowly and cautiously with an intensive-care-unit type monitoring of the participants' vital functions. The careful monitoring is expensive and cumbersome. Consequently, the researchers want to involve patients as soon as possible, to proceed to a therapeutic setting where a higher level of risk is permitted by regulations and ethical codes.

In vaccine trials there are no "patients" in that only a small number of the vaccinees will ever become victims of the disease even if no effective vaccine is given. Vaccine trials are thus commonly defined as nontherapeutic. Consequently, there is a general requirement for pretrial projections of very low risk. Some have argued that this is not fair: like patients in a drug trial, they contend, participants in a vaccine trial may benefit by being protected against a future health threat. However, since phase I to phase III vaccine trials cannot refer to more than a very marginal and uncertain health benefit to participants, we concur that they should be considered nontherapeutic. As soon as vaccine testing passes into phase IV we will have some knowledge about the vaccine's protective efficacy. For diseases which are perceived by the individual as a personal threat, whether on the basis of prevalence, severity, or cultural attitudes, clinical testing of an efficacious vaccine (phase IV) must be regarded as a therapeutic trial. The distinction between therapeutic and nontherapeutic biomedical research is actually problematic for any trial with a placebo control group, and the terminology should probably be revised.[10]

The Problem of "Unknown Risks"

Risk calculations in vaccine trials may be seen as *qualitatively* different from those of drug trials due to the large number of volunteers participating. There are four risk categories we must consider:

1. Risks inherent in the administration procedure, e.g. the injection.

2. Toxic components in the vaccine such as bacterial toxins, additives, etc.

3. Risks of immunological reactions, particularly severe allergic reactions.

4. Unknown risks.

A correctly executed injection carries a known, but negligible risk.

The contents of a vaccine are usually totally nontoxic in the dosages to be used. In the meningococcal-B-vaccine, the only toxin of concern is lipopolysaccharides (endotoxin) that can be measured and extensively tested in animals before any human experiments are undertaken.[11]

The antigenic molecules in a vaccine generally belong to the known universe of natural molecules to which we are all exposed, and usually carry a minimal risk for eliciting allergic reactions.

What remains is the frightening concept of serious "unknown risks." What can we know about "unknown risks" before we start clinical testing? By definition, we know nothing! The only thing we can "know" about unknown risks, is what we experience *during testing*. At any stage we can know how many individuals are tested, and whether—so far—any serious event has been reported.

The level of theoretical, maximal risk for a serious reaction can be calculated on the basis that the injection has passed uneventfully in all N previously tested subjects (where N is the number of previously tested subjects).[12] When the true proportion affected by a serious vaccination complication in the infinitely large population is designated P, the probability that one vaccinee will be unaffected is $(1-P)$, and the probability for getting N unaffected will be $(1-P)^N$. Using a 95-percent confidence interval corresponding to type I risk, the probability for such an extreme result under the null-hypothesis will be:

$$p = (1-P)^N$$

At the time of pretrial review of the protocol, the ethical committee has to make sure that:

1. The trial is planned in steps with group sizes and safety precautions that seem justified in the light of the maximal, theoretical risk calculations at any given time;

2. the system to diagnose and report any serious event is of sufficiently high quality and speed;

3. the investigators have a realistic and efficient plan for immediate termination of vaccination if reports indicate that the vaccine has caused serious reactions; and

4. any large-scale clinical trial where "unknown risks" constitute a potential threat to the safety of the participants have an independent ethical monitoring committee with authority to ask for immediate termination of the trial if justified by observed incidents.

Neurological Diseases of Unknown Etiology

The most feared situation in any vaccine trial is that cases of severe neurological disease of unknown etiology will be reported among the participants in the first weeks after an injection. According to current beliefs, such cases must be regarded as possibly related etiologically to vaccination.

We have in current use two vaccines known to cause such diseases: the sheep-brain-derived rabies vaccine, which causes about one case of myeloencephalitis in 400 vaccinated individuals,[13] and the live attenuated poliovaccine, which is responsible for one case of vaccine paralysis in 1 million vaccinees.[14] In addition, the whole-virus influenza vaccine is suspected of very rarely causing polyradiculomyelitis (Guillain-Barré Syndrome),[15] and until about ten years ago the DPT vaccine was suspected of causing sudden infant deaths and severe brain damage.[16] Except for the two first vaccines where the cause-effect relationship is established, a group of severe central nervous system diseases is presently thought to be triggered in a few susceptible individuals by drugs, various infections, vaccines, or combinations of these.

No testable mechanisms have been discovered, and our knowledge of possible antigens that might trigger such reactions is rudimentary. Only meticulous registration of any case of such diseases among vaccinees and in a comparable control group can demonstrate whether there is an association. This a painful exercise and usually includes several years of recording what the public, and sometimes even the authorities, might perceive as vaccine complications. A less meticulous registration will keep the vaccine "clean" during its introduction, but will only postpone the problem to a stage where it is much more difficult to deal with.

Owing to the rare spontaneous occurrence of such conditions in the population, different measures should be taken for such events in different phases of vaccine testing:

1. A single case of such a disease reported during a small-

scale trial (phase I or II) should lead to immediate suspension of the trial. Maximal efforts should be made to identify a possible causal relationship with the vaccine. If the chance for a relationship is not negligible, the candidate vaccine should probably be excluded from further clinical testing.

2. In large-scale testing (phase III or IV), the size of the population itself makes it very likely that a few such cases will be detected, if the detection system is working adequately. The measures taken should be adjusted accordingly. The investigators are obliged to look very carefully for a possible causal relation with both statistical and experimental biological tools, but as the outcome of this research will be indicative at best, the ethical committee must be prepared to accept further clinical testing under strict supervision.

Provided the investigators have a sufficiently effective system for reporting adverse events, the consequence of a more restrictive attitude would be to stop most new vaccine development at this stage.

The Risk Problem in Individual vs. Societal Contexts

The Helsinki Declaration is firm in its insistence that "in research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject."[17] The point has been criticized both by representatives of developing countries and by epidemiological scientists. This is understandable, as developing countries for economical reasons must go on using the sheep-brain-derived rabies vaccine, for example, while simultaneously new vaccine development for the major Third World infections is severely hampered by restrictions on clinical testing. Epidemiological research commonly offers benefits only for the society and not for the individual participant.

When we proceeded from phase III to phase IV trials of MedB vaccine among Norwegian adolescents, we had records of single cases of severe neurological disease of unknown etiology among vaccinees. At the same time, we also had data for vaccine efficacy showing that further use of the vaccine would save a predictable number of persons from death and disability. If the disease is relatively rare, we admittedly offer a vaccine that is more for the benefit of the society than for the individual. If the vaccine also has the potential of interrupting the transmission of the infecting agent, the gain of the society is greatly enhanced with minimal effect for the individual.

During the last five years of smallpox eradication, more people died from vaccine complications than from smallpox itself. Was the campaign unethical because of this, or is the question of no interest because the vaccine was not an experimental vaccine? At present there is a detrimental lack of both phase IV trials of vaccines and post-marketing studies for drugs.[18] The effect of a very restrictive interpretation of The Helsinki Declaration, considering all such trials as designed to respond to societies' needs, can thus be that we continue to use tools in disease control that have never been tested for performance in practical, routine use.

The society also runs risks in undertaking—or omitting—clinical testing. The interests at stake are not those of the trial participants, but those of future users of the new intervention. We believe that the Declaration should be revised to state that investigators have an obligation to arrange for some sort of phase IV trials. Ethical committees should be more active in demanding follow-up after phase III has shown protection in a defined population.

The "Nocebo" Effect

The word *placebo* literally means "I will please you." In drug trials the "placebo effect" leads to analytical problems because it adds to the apparent pharmacological effect of the drug. Only when a placebo control is used can this be corrected for. In vaccine trials we deal with it's counterpart "nocebo," literally "I will harm you."[19] Based on past experience with vaccinations, the test subjects expect side effects. They are also informed that certain problems might occur—and they do indeed feel them.[20] Contrary to the situation in a drug trial, there are no expectations for "feeling good" after a vaccination. In various phase II trials 20 to 40 percent of controls have reported various systemic ailments, such as fatigue, nausea, or dizziness, after injection of the placebo preparation. The frequency of such reactions has not been significantly higher among vaccinees than among placebo-injected individuals.

Generally, these ailments decrease with time after the injection and with increasing motivation for participation. Yet from the West Indies, instant death has been reported as a nocebo effect. In vaccine trials, the majority of the nocebo-induced ailments are minor. Still, they add significant harm to the participants compared to the trauma of injections and blood sampling. Blood sampling is seen by some as the upper limit for acceptable harm to test subjects in nontherapeutic trials. If this is the view of the ethical review committee, the limits are in reality too narrow for vaccine testing where nocebo effects add to the discomfort. The information required to be disclosed to participants is probably a significant cause of nocebo ailments. Providing "good information" to volunteers should not enhance their expectation of side-effects or threaten the blinding of the trial.[21]

The Risk of Ecological Side Effects

The public health objectives for the use of a vaccine can be:

1. Eradication of the disease in question. If the vaccine interrupts the chain of transmission and the causative microorganism is found exclusively in man, a generally high vaccination coverage can totally eradicate the disease from the face of the earth. These factors helped much in the eradication of smallpox. However, it was isolation and containment assisted by a high vaccination coverage around the surveillance-traced suspected cases that led to its final eradication.

2. Elimination of the disease. If a vaccine affords full protection to the vaccinees but does nothing to the infectious reservoir, as e.g., the tetanus vaccine, the disease will reappear as soon as the immunization program is interrupted (given that hygienic factors are not changed simultaneously).

3. Control of the disease. Widespread use of the vaccine can prevent the disease from being so prevalent that it represents a health burden to the general public.

For many infectious diseases circulation of the causative agent or closely related microbes provides the population with a substantial "natural immunity." If the vaccine inter-

feres with the circulation of the microbe without fully eradicating it, a large number of unprotected individuals will build up before the microbe again appears in the population. The result might be an increased disease problem or a higher rate of severe complications in the intermediate or long run. Let us presume there is a vaccine against meningococcal disease that prevents carriage of meningococci by healthy individuals. Most of the meningococcal strains in carriers never cause disease, but on the contrary contribute to immunity in the nonvaccinated population. A reduction of carriage rate of these "useful variants" of the bacteria could thus decrease the natural resistance of those not vaccinated.

Such ecological side effects of a future use of the vaccine are usually a matter of no concern to a commercial vaccine developer. It is handed over to the ethical committee to evaluate, and is frequently ignored also by the committee.

Ethical review should pay attention to the possibility of ecological side effects and request the investigators to secure relevant samples and data to assess these side effects at the end of the trial. Such data can usually be collected during phase II and III trials, but can rarely be evaluated precisely until larger scale phase IV studies are conducted.

Consequences

New vaccine development has recently entered a revolutionary stage due to developments in gene technology.[22] This technology could potentially give us vaccines to prevent nearly twenty million deaths annually and more than half of the world's physical disability. In addition, the same technologies give new speed to development of contraceptive vaccines, anti-cancer vaccines, and possibly vaccines to prevent conception of offspring with genetic diseases and birth defects. Modern vaccine research thus constitutes a major challenge for medical ethics.

These possibilities are not science fiction. A large number of new vaccines are already at an advanced stage of basic research, mostly in universities or other governmentally controlled research institutions. Some of them have entered clinical trials, while the majority are due for clinical testing in the very near future. However, during the last thirty years most government-based production facilities in the industrialized world have been closed.[23] Production facilities in developing countries are few and have so far usually been substandard with regard to quality control. Due to the recent opening up of the world economy, production facilities in former communist countries are also in deep trouble owing to stricter quality control regulations. Costs of large-scale clinical testing have been sky rocketing after the swine influenza event in the U.S. in 1976. The bulk of the health problem that can be attacked by new vaccines is located in poor, developing countries. These countries will not be able to buy new vaccines at a price that could give the industry a reasonable profit for investment.

The intellectual and academic "profits" are still high enough to support basic vaccine research in governmental institutions. However, when a new and promising vaccine candidate is developed in the laboratory the vaccine is most often patented by a commercial company. Unfortunately, the prospects of profit are too poor to justify production and efficacy testing for the time being. The patents, however, are cheap to acquire and can be activated later. Since World War II, nearly all wars have been fought in the tropics. New vaccines to protect military personnel from the North have thus become a very interesting future market. Due to the high cost of efficacy testing, the marketing period protected by a patent is too short to make any new vaccine available at a reasonable price, whatever the cost of production. To protect the vaccine against cheap copies, the commercial producers have taken the lead in setting standards for quality control. By establishing and patenting a complicated control method, they can protect a new gene-technology-based product even if the product itself is very simple to manufacture. Due to fear of these "mysterious" products, governmental control authorities very rarely have the courage to overrule such self-inflicted control measures.

Some solutions to these problems have been suggested by the scientific community:

1. Public funding should secure basic research and development and clinical testing according to openly discussed priorities. The industry should be invited to produce the vaccine on contract for production costs plus a reasonable profit. There should be an international body for collaboration between governmentally financed vaccine R&D and industrial production expertise.

2. Quality control of vaccines should take proper and balanced care of what is useful for developing countries. An international body for quality control, like that already established for drugs useful in developing countries, should include vaccines.

3. As clinical trials (phase III and IV) are unanimously seen as essential, their practical feasibility should not be hampered by unbalanced application of the text of ethical rules. Special ethical guidelines for clinical trials with vaccines should be established, either by flexible interpretations or amendments of The Helsinki Declaration or by considering large-scale vaccine trials (phase III and IV) as a special case of epidemiological research in the new CIOMS *International Guidelines for Ethical Review of Epidemiological Studies*.[24]

Our Main Conclusion

Ethical guidelines for clinical testing of vaccines should pay specific attention to the problems of how to handle "unknown risks," how to record and follow up on cases of neurological disease of unknown etiology, how to inform participants to minimize the "nocebo" effect, and how to safeguard against ecological side effects.

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A Study of the System of Protection for Human Subjects

The NIH has awarded a contract for a comprehensive study of the system for protection of human subjects.[1] The only previous comprehensive national assessment of the IRB system was conducted in the mid-1970s for the National Commission for the Protection of Human Subjects.[2] The study's findings helped to shape the Commission's recommendations about the system for protecting human research subjects, which in turn had an influential role on the content of the 1981 regulations.[3] In the years that have passed since the Commission's study and the 1981 regulations, sweeping changes have occurred in the biomedical, behavioral, and social science research that falls under the purview of the human subjects protection program. In light of these changes, the NIH determined that it was timely to examine how well the system had been able to adapt. After consultations with the extramural research community and a feasibility study, the NIH drafted the framework for a comprehensive study of the performance of the human subjects protection system. This provided the basis for an RFP that was issued in August 1991 (RFP NIH-OD-91-12).

As described in NIH's RFP, the study has a number of major, interrelated objectives. These include assessing how the current system operates to protect the rights and welfare of research subjects and the "costs and burdens" of the program to the institutional groups implementing the regulations. The goal is to develop data-based recommendations concerning federal or institutional-level changes in policies and procedures that "would be likely to improve the program's performance." These and other topics will be examined through a variety of specific research questions and measures dealing with four aspects of the IRB system: (1) outcomes of IRB review, (2) the volume and content of the work being done by IRBs (output), (3) the operating procedures used by the IRBs (process), and (4) the resources (time and financial) required to operate the system. The study methodology includes interviews and surveys with IRB staff and members, investigators, research subjects, and institutional and governmental officials; field research; document analysis; and a comprehensive review and analysis of the literature. As early planning progresses, the research and IRB communities are invited to communicate with the project staff regarding salient issues. In particular, project staff would appreciate information about any unpublished studies or research-in-progress that could be included in the literature review.[4]

References

1. A contract for the two-year study was awarded to James Bell Associates, Arlington, VA. in September 1992. The study is being directed by James B. Bell, MA, principal investigator; the co-PIs are Bradford Gray, PhD, and Judith P. Swazey, PhD. Dr. Charles MacKay, NIH, is the project officer.
2. Gray, BH, Cooke, RA and Tannenbaum, AS: Research involving human subjects *Science* 201 (22 September 1978): 1094-1101.
3. 45 CFR 46. Subpart A. In June 1991, Subpart A was replaced by regulations that apply to 16 federal agencies and departments involved in research with human subjects (86 CFR 28004). The FDA simultaneously published modifications of its human subjects regulations in 21 CFR 50 and 56 to incorporate provisions of the common rule.
4. Please contact Judith C. Watkins, Program Analyst, 12 Dartmouth St., Boston, MA 02118; phone 617-538-3420.

In October Sen. Tom Harkin of Iowa, chairman of the subcommittee that oversees the NIH budget, asked director Bernadine Healy to allow a former constituent who is dying of brain cancer to receive a form of gene therapy that NIH's Recombinant DNA Advisory Committee (RAC) had rejected for lack of safety and efficacy data. Healy has not approved the "compassionate exemption," but the RAC has been asked to develop policy to cover such requests.— ***B-JC***