Review Article

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Current topics in research ethics in vaccine studies

BACKGROUND

About 7.6 million children under the age of five die every year, according to 2010 figures,[1] out of these 2.4 million children die from vaccine preventable diseases.[2] The problem is compounded by the absence of effective therapies for many infectious diseases. Obviously, new, more cost-effective and improved vaccines are needed today and in the future.

Vaccines have some distinct features than drugs. Unlike therapeutic molecules, vaccines have preventive role against specific infectious diseases. The target population is healthy people, mostly children and infants; as a result, tolerability of adverse events is less. Additionally, vaccines are highly complex substances derived from living microorganisms and their quality and safety needs to be demonstrated on a lot-to-lot basis. Naturally, these factors have some bearing on the clinical trials of vaccines. Here we discuss some of the current ethical issues in vaccine clinical trials.

Pediatric trials

Most of the vaccine studies are conducted in children, some of them in infants and even in newborns because that is where you want to catch them for prevention of an infection. However, children by themselves are unable to consent, and the vaccinator has to accept a legal guardian's agreement. Also, one would expect children to experience more adverse reactions than adults. For these and many other reasons, it is generally agreed that vaccine studies are, at least primarily, unethical in children if the relevant investigation can be done among adults. The main problem here is, however, that many infections are characteristically only pediatric diseases, or at least, those infections are specially harmful to the youngest.

One therefore needs to seek for a difficult balance between the true and ostensible need of a vaccine in the pediatric population. The CIOMS rightly states that "Before undertaking research involving children, the investigator must ensure that–the research might not be equally well be carried out in adults; and the purpose of the research is to obtain knowledge relevant to the health needs of children."[3]

Parental consent

More in developing countries than elsewhere, parents or guardians of children may have little or no understanding of research trials. They may be unfamiliar with concepts such as "informed consent" and "confidentiality" and may not understand the scientific terms and processes involved in trials, including the use of randomization and placebos. Yet these parents will be called upon to give consent on behalf of their small children, or to explain to their older heirs (children) what is happening in the trial.

Another concern is consent of an appropriate legal representative in the absence of parental consent. Recently a demonstration project on a vaccine was conducted in India. An investigation was prompted after press reports of some deaths. Though the deaths were not found caused by the vaccine, consent obtained from hostel wardens in some subjects living in hostels was questioned.[4]

Need for the trial

Before launching a trial in children one must show that there is compelling need to use children to establish safety, immunogenicity, effectiveness or efficacy of the vaccine. Such a trial would not be justified if the child comes from

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population in which that particular disease is not a problem. Malaria vaccine cannot be tested soon in Europe or North America.

An absolute care must be taken to ensure that socioeconomic inequalities between industrialized and developing countries are not exploited i.e., that children in a poor country are not asked to undertake risks to produce a vaccine that, for economic or other reasons, would primarily benefit their counterparts in industrialized countries. At the same time, research should not be impeded that aims to reduce the inequality of health care and to benefit pediatric populations in need in developing countries.

Selection of control

If a good vaccine is already in use in some other country or community which is more or less comparable to site where the trial is planned, that vaccine should be used as the comparator. If such a vaccine does not exist, a placebo "vaccine" may be used, provided the set-up is thoroughly explained to the participants, their families and the community. Placebo controls are ethically acceptable when there is no proven vaccine for the indication for which the candidate vaccine is to be tested.[5,6]

A modification of this setting is that the placebo recipients receive the true vaccine later–but all this has to be explained in understandable words to the participants.

An alternative to the use of placebo is to give another vaccine that provides comparable benefit against another disease, or more willingly, against similar disease caused by different agents. This was the approach in Finland in the 1970s, when the first vaccines against bacterial meningitis (due to Neisseria meningitidis and H. influenza) were tested in children.[7] Here it was important these two types of meningitis were equally common in that community. For some vaccines, the choice is not difficult since there are no effective interventions so far, e.g., malaria or HIV vaccines.

In Indonesia, an exceptional approach was taken on 1998-2002.[8] Half of children received traditional DTP (diphtheria-tetanus-pertussis) vaccine, whereas the other half of children got DTP with H. influenza type B (Hib) component. Thus, all children were not in an equivalent position, but the setup was considered justified because in the absence of disease burden data and vaccine efficacy data in the region, the trial was deemed helpful for the decision whether or not to introduce Hib vaccination in Indonesia and the whole region.

When, instead of clinical efficacy, "only" immunogenicity (antibody production) is measured, the rules of equipoise are looser. The comparator vaccine may function more as "compensation" to the child in the trial's control arm. For instance, meningococcal C conjugate vaccine in a pneumococcal vaccine trial, or rabies vaccine in a Japanese encephalitis vaccine trial does not restore equipoise but benefit the child who would not otherwise receive that vaccine.

Age de-escalation

Age de-escalation means that phase I and II trials are conducted first in adults, then in older children, and finally, if relevant, in small children. Epidemiology of the disease, the risks/benefits of the vaccine for each age group, and the safety profile are all factors to be taken into account in de-escalation.

However, if a new vaccine is only for infants, trials in older children may expose them to unnecessary risks without giving any benefit to these too "old" vaccinees. Rotavirus vaccines are good examples in this category. Sometimes adult participants can be used in the first trials, although they are of no help in the efficacy trials.

Sometimes there are grounds to use child participants already in phase I trials. This is the case if the new vaccine would likely cause problems in adults (but not in children) because of prior immunity in adults e.g., DTP vaccine.

Participation of adolescents

Only a few vaccines as targeted just for adolescents: examples are human papillomavirus (HPV) and herpes virus (HSV) vaccines. However, adolescents may be used in the de-escalation studies before progressing to small children. The participation of adolescents often involves complex legal, ethical issues and operational issues.

Informed consent is problematic, because adolescents often have the intellectual and emotional capacity to provide consent, but do not have the legal right to consent. Also their views may not be the same as their parents' views, and appropriate confidentiality can be difficult to maintain. An extreme would be a situation in which the youth disagrees but the parents agree the trial, or in which a willing adolescent would be included in the absence of parental consent.

The participation of adolescent girls is further complicated by the potential or soon materializing pregnancy. Not only would it perhaps risk the young mother and the fetus, but also raise complex issues regarding the consent, confidentiality and legal liability. Routine pregnancy testing of adolescent girls prior to the inclusion in a trial would also have its cultural problems.

Limitations of informed consent

Obtaining informed consent in a developing country has its own problems and should be seen as a process which begins from the voluntary decision to participate in the study. The decision should be based on sufficient information prior to the trial entry. The informed consent form should be simple enough to be understood by the often not-too-educated individual, or in case of a child, by parents or legal guardian, but still comprehensive to explain the concepts, potential risks and benefits, implications of the use of a placebo or other comparator, care that will be provided, and the indemnity for injury or death arising from the trial. Importantly, it must be stated clearly that a withdrawal from study is allowed at any time without giving an explanation for the decision. If the circumstances of the trial change significantly, the consent form is to be changed accordingly, and the whole study warrant discussion with the already enrolled participants. Another consent is then to be obtained.

The problems in getting valid consent are heightened in developing countries where people may be unfamiliar with scientific research, concepts and vocabulary. Thus, the expectations may be unrealistic. Also the individual's full autonomy might become endangered because of the society's cultural and/or gender norms, or the family or spousal pressure. All of these challenges are further complicated when the trial deals with children.

Child's assent

In the case of a child, every effort should be made to explain to him/her also, in language that is understandable to the child, what the participation means, as regards to potential risks (discomfort, time spent, etc.) and benefits, The investigators should document the child's assent.

Community consent

Since an informed consent may be culturally sensitive, family or community discussions are sometimes necessary, albeit the community consent should not be considered as a substitute for the individual consent. There may also be tension between the ethical responsibility to maintain individual confidentiality, and cultural norms that press for "shared confidentiality". Within appropriate boundaries of confidentiality, it may be useful to have an impartial witness/observer present during an oral consent particularly if verbal rather than signed consent is sought. Such witnessed consent must be recorded in the trial files.

Potential for inducement

The improved medical care provided during the trial may constitute an inducement and may impact on the willingness to participate. Indeed, trial participants often accept the trial in the belief that they will receive improved treatment. It is important to explain that participation will not necessarily ensure protection against disease. In case of a study using placebo, the entire set-up and the meaning of randomization should be explained, including the fact that the participant might fall in the placebo group. Any care or other benefits that perhaps are offered should be described.

Another concern is if the parents see an opportunity for economic benefits, they may encourage enrolling their and perhaps other children in trials in which those should not necessarily be included. All efforts should be made to avoid any exploitation, and to minimize all mental, emotional and physical harm.

Standard of care

In case of vaccine trials in developing countries, the situation is tricky because of a high burden of disease and low standards of health care in that community. With the contribution of local authorities, a standard of care should be offered. This means an improvement in the health conditions of participants, and that it is sustainable. These efforts need an approval from the local ethics committees.

Duration of follow-up

An active follow-up should extend at least to the end of the trial. In case of an adverse effect, the, follow-up should be continued for an additional six months. In high mortality populations, it may be desirable to analyse long-term mortality changes and to follow-up participants for a number of years. Passive follow-up is advisable even longer, and if existing mechanisms can be used for this purpose.

Long-term follow-up may complicate a trial substantially and greatly increase the costs. Therefore, gathering only passive data may suffice. Creative follow-up should be contemplated, both for safety and long-term protection. The high titer measles vaccine was studied in some African countries, however on a long term follow up, it was discovered that female mortality was higher following the vaccine,[9] which resulted in abandoning the use of the vaccine. This important finding was detected only because of long-term follow-up.

Screening of subjects

Vaccine trials need to be conducted in healthy people and hence, the screening for inclusion/exclusion criteria is very critical. Enrolment of children with underlying medical conditions can complicate the safety outcomes. A recent vaccine trial in India brought forth this issue. A death was reported in the study after an infant had received a licensed vaccine used as a control. The investigation revealed that the infant who died had a pre-existing medical condition.[10] It is recognized that physical screening of young infants has limitations;

however, every effort should be made to ascertain the health status. In case of suspicious cases, it is better to err on the safer side.

CONCLUSIONS

Vaccine clinical research needs to deal with certain ethical issues because of the inherent nature of these trials. The issues are more complicated since the research mostly happens in pediatric populations in developing countries. Keeping in mind these issues while designing research on vaccines is critical.

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