

Ethical considerations arising from
vaccine trials conducted in
paediatric populations
with high disease burden
in developing countries

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Abbreviations and acronyms

ARI	acute respiratory infections
CDC	Centers for Disease Control
CESP	Confederation of European Specialists in Paediatrics
CIOMS	Council for International Organizations of Medical Sciences
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EFGCP	European Forum for Good Clinical Practice
FDA	Food and Drug Administration
GCPG	good clinical practice guidelines
GLP	good laboratory practice
GMP	good manufacturing practice
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes virus
ICH	International Conference on Harmonisation
NCI	National Cancer Institute
NIH	national institutes of health
OED	Oxford English Dictionary
OHRP	Office for Human Research Protection
PHR	Partnerships for Health Reform
POP	proof of principle

RSV	respiratory syncytial virus
SCRIHS	WHO Secretariat Committee on Research involving Human Subjects
STI	sexually transmitted infection
UNESCO	United Nations Educational Scientific and Cultural Organization
WMA	World Medical Association

Glossary¹

Access (OED²) (v.) the action of going or coming to or into; coming into the presence of, or into contact with; approach, entrance (n.) The state or faculty of being approached; accessibility.

The presence or absence of physical, economic, or cultural barriers that people might face in using health services. Physical barriers are usually interpreted to mean those related to the general supply and availability of health services and distance from health facilities. Economic barriers are usually interpreted to mean those related to the cost of seeking and obtaining health care, in relation to a patient's or household's income. Cultural barriers relate to social or community perceptions about receiving or knowing about certain health services.

Assent (OED) agreement with a statement, an abstract proposition, or a proposal that does not concern oneself; mental acceptance or; official, judicial, or formal concurrence of will; sanction; the action or instrument that signifies such concurrence; compliance with a desire.

A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent;

The agreement to participate in a project given by a child who lacks the capacity to give full consent. Where a parent or guardian gives the necessary consent to a project involving a child, the child's assent must be obtained if this is possible.

Available (OED) capable of being employed with advantage or turned to account; *hence*, capable of being made use of, at one's disposal, within one's reach.

Identifies the presence or absence of needed health care services.

Benefit (OED) (*n.*) a thing well done; a good or noble deed; a kindness; a favour, gift; advantage, profit, good; gain;

(*v.*) to do good to, to be of advantage or profit to; to improve, help forward; to receive benefit, to get advantage; to profit;

Valued or desired outcome; advantage.

Advantage; in evaluating risks and benefits, the Institutional Review Board (IRB) should consider only those risks and benefits that may result

¹ This section was contributed by Dr Abha Saxena, WHO/SCRIHS, based on various resources (see Appendix 2).

² Oxford English Dictionary, Oxford University Press, Oxford, 2003.

from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research);

Gains, whether material or not, accruing to an individual or a community;

money, care, or other services to which an individual is entitled by virtue of insurance.

Community (OED) 1. as a quality or state: the quality of appertaining to or being held by all in common; joint or common ownership, tenure, liability, etc.; common character; quality in common; commonness, agreement, identity;

2. a body of individuals: the body of those having common or equal rights or rank, as distinguished from the privileged classes; the body of commons; the commonalty; a body of people organized into a political, municipal, or social unity; a body of men living in the same locality; the people of a country (or district) as a whole; the general body to which all alike belong, the public; a body of persons living together, and practising, more or less, community of goods.

Compensation (OED) that which is given in recompense, an equivalent rendered, remuneration, amends; amends or recompense *for* loss or damage.

Payment or medical care provided to participants injured in research. This does not refer to payment (remuneration) for participation in research.

Consent: (OED) voluntary agreement to or acquiescence in what another proposes or desires; compliance, concurrence, permission.

The right of persons who participate in research to know what shall or shall not happen to them. The Institutional Review Board (IRB) must judge whether three conditions are met: disclosure of information (participant has been provided full information regarding the research), comprehension (participant fully understands all ramifications of the research), and voluntariness (participant is volunteering free of coercion and undue influence);

a person's voluntary agreement, based on adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure.

DSMB Data Safety Monitoring Board independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically; required that a majority of the members be drawn from outside the institution (or institute) conducting the study; membership is usually comprised of experts in the fields of medicine and science that are applicable to the study, statistical experts, lay representatives, and others who can offer an unbiased assessment of the study progress.

Equipoise	<p>(OED) (<i>n.</i>) equality or equal distribution of weight; a condition of perfect balance or equilibrium; a counterpoise; a balancing or equivalent force; (<i>v.</i>) to counterbalance.</p> <p>A state of genuine uncertainty on the part of the expert medical community regarding the comparative therapeutic merits of each arm in a trial.</p>
Equity	<p>(OED) in general: the quality of being equal or fair; fairness, impartiality; even-handed dealing; what is fair and right; something that is fair and right; in jurisprudence: the recourse to general principles of justice to correct or supplement the provisions of the law.</p> <p>Equity of a statute: the construction of a statute according to its reason and spirit, so as to make it apply to cases for which it does not expressly provide.</p> <p>Principle of being fair to all, with reference to a defined and recognized set of values. Equity in health implies that ideally everyone should have a fair opportunity attain their full health potential and, more pragmatically, that no one should be disadvantaged from achieving this potential. That is, everyone should have geographical and financial access to available resources in health care. There are two kinds of equity. Horizontal equity is the principle that says that those who are in identical or similar circumstances should pay similar amounts in taxes (or contributions) and should receive similar amounts in benefits. Vertical equity is the principle that says that those who are in different circumstances with respect to a characteristic of concern for equity should, correspondingly, be treated differently; e.g. those with greater economic capacity pay more; those with greater need receive more;</p> <p>Not necessarily the same as equality, it relates in general to ethical judgements about the fairness of income and wealth distribution, cost and benefit distributions, accessibility of health services, exposure to health-threatening hazards, and so forth. Several measures are used depending on preferences of the community.</p>
ERB	<p>Ethics Review Board; ethics committee also synonymous with Institutional Review Board (IRB); the formally appointed review committee at an institution established to ensure that research involving human participants is designed to conform to relevant ethical standards.</p>
Ethics	<p>(OED) the science of morals; the department of study concerned with the principles of human duty; the moral principles or system of a particular leader or school of thought; the rules of conduct recognized in certain associations or departments of human life; the whole field of moral science, including besides ethics properly so called, the science of law whether civil, political, or international.</p>
GCP	<p>Good clinical practice; standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.</p>

Incentive	<p>Of or pertaining to a system of payments, concessions, etc., to encourage harder work or a particular choice of work;</p> <p>Factors that motivate a person or group to behave in a certain way;</p> <p>Rewards for desired behaviour. Now used regarding rewards for decreasing hospital and physician costs, and for encouraging patients to be frugal in demands for health care. Sometimes incentives are negative, for example, when a patient is required to pay the first dollars for a service (deductibles). This is a “disincentive” to seek the care, and thus an incentive to be frugal.</p>
Indemnification	<p>(OED) the action of compensating for actual loss or damage sustained, trouble or annoyance; the recompense so rendered;</p> <p>Insurance benefits that are provided in cash to the beneficiary rather than in service (service benefits). Indemnity benefits are usual with commercial insurance.</p>
Inducement	<p>(OED) something attractive by which a person is led on or persuaded to action; any ground or reason which leads or inclines one to a belief or course of action; a moving cause; an incentive.</p>
Justice	<p>(OED) the quality of being (morally) just or righteous; the principle of just dealing; the exhibition of this quality or principle in action; just conduct; integrity, rectitude; conformity (of an action or thing) to moral right, or to reason, truth, or fact; rightfulness; fairness; correctness; propriety; exercise of authority or power in maintenance of right; vindication of right by assignment of reward or punishment; requital of desert.</p> <p>One of three main principles relevant to research involving human subjects; fairness in distribution or what is deserved; ethical principle requiring attention to equal or fair distribution of burdens and benefits; criteria to be considered: experience, age, deprivation, competence, merit, and position; five formulations of justice: (1) to each person an equal share (2) to each person according to individual need (3) to each person according to individual effort (4) to each person according to societal contribution (5) to each person according to merit.</p>
Monitor	<p>(OED) to guide as a monitor; to check or regulate the technical quality of without causing any interruption or disturbance; to observe, supervise, or keep under review; to keep under observation; to measure or test at intervals, esp. for the purpose of regulation or control.</p> <p>The continuous oversight of an activity to assist in its supervision and to see that it proceeds according to plan. Monitoring involves the specification of methods to measure activity, use of resources, and response to services against agreed criteria.</p>
Placebo	<p>(OED) a substance or procedure which a patient accepts as a medicine or therapy but which actually has no specific therapeutic activity for his condition or is prescribed in the belief that it has no such activity.</p>

RCT	Randomized control trial. In an RCT, participants are randomly assigned either to an intervention group (e.g. a drug treatment) or to a control group (e.g. a placebo treatment). Both groups are followed up over a specified period of time and the effects of the intervention on specific outcomes (dependent variables) defined at the outset are analysed (e.g. serum cholesterol levels, death rates, remission rates).
Reimbursement:	(OED) to repay or make up to one (a sum expended); to refund; Payment to a health facility or physician from the government, insurance company, or other fund holder for services rendered; The payment to a hospital, other provider, or anyone, after the fact, an amount equal to the institution's or individual's expenses.
Sponsor:	(OED) one who enters into an engagement, makes a formal promise or pledge, on behalf of another; a surety; one who pays, or contributes towards, the cost of a broadcast programme or other spectacle, <i>spec.</i> in return for commercial advertisement.
Voluntary:	(OED) performed or done of one's own free will, impulse, or choice; not constrained, prompted, or suggested by another; Free of coercion, duress, or undue inducement; used in the health and disability care and research contexts to refer to a consumer's or participant's decision to receive health or disability care or to participate (or continue to participate) in a research activity.

Preface

Each year, millions of children¹ in developing countries suffer from infectious diseases. Of these, more than 2.7 million children under five² die from diseases that are potentially preventable by vaccines. In light of these unacceptable rates of morbidity and mortality, the development or improvement of vaccines to meet the needs of children in developing countries continues to be one of the highest priorities, with the attendant requirement for an increasing number of trials to evaluate new vaccines. The necessity for such research is heightened by the absence of effective therapies for many infectious diseases and the reality that many of the drugs presently prescribed for children have never been properly clinically evaluated for use in children.³

A cautious approach is appropriate in the conduct of vaccine trials among children in any circumstances because of their particular vulnerability in view of their inability to give informed consent and their sometimes greater potential to adverse reaction to vaccines. Increased vigilance is necessary with respect to vaccine trials among children in developing countries, because they are made much more vulnerable by poverty, underdevelopment and high disease burden. Such trials involve not only significant scientific challenges but also complex economic and ethical considerations, which relate to the cost of the vaccine development process, as well as to the creation of equitable access to the vaccines resulting from the research. Health imperatives urge that these issues are speedily and appropriately addressed, so that trials among children in developing countries can go forward to allow evaluation of vaccines that may provide substantial health benefits to the children in these countries.

While many existing documents provide guidance on ethical issues in biomedical research and some specifically address vaccine research, few were drafted with a focus on the particular ethical issues posed by vaccine trials among children in developing countries. Current ethical guidance to assist ethics committees, sponsors and investigators involved in such trials in developing countries is sparse. As part of an effort to address this situation, the World Health Organization (WHO) held a meeting in Accra, Ghana on 26–28 November 2002 to consider various ethical issues that might arise during the performance of vaccine trials in paediatric populations in developing countries. The objectives of the meeting were:

- to identify ethical issues that have arisen or are likely to arise in the conduct of such trials;

¹ As defined by the Convention on the Rights of the Child, Article 1: "...a child means every human being below the age of eighteen years unless, under the law applicable to the child, majority is attained earlier."

² WHO 2001 estimate

³ Barrett, J, "Why aren't more Pediatric Clinical Trials Performed?", *Applied Clinical Trials*, July 1st, 2002; Crawley, F. and Smith, R. N., "Striking a Balance: concerted action for children's medicines", *International Journal of Pharmaceutical Medicines*, 2002; Steinbrook, R., "Testing Medicines in Children", *Health Policy Report*, *New England Journal of Medicine*, 31 October 2002; *Better Medicines for Children: proposed regulatory actions on pediatric medical products*, EC Consultation Document, 28 February 2002 http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2002/feb/cd_pediatrics_en.pdf.

- to explore possible solutions to address such ethical concerns;
- to produce a document that outlines some of the relevant considerations that might assist those involved in such trials, e.g. governments, communities, ethical committees, sponsors, funding agencies and investigators.

This document is the result of that meeting. It highlights some of the critical ethical issues that should be considered in vaccine development and evaluation, largely from the perspective of those conducting trials among paediatric populations in developing countries. (See list of participants, Annex 1.) Each section of the document comprises subsections entitled “**Considerations**”, summarizing the points that participants at the meeting considered most relevant to the topic at hand, and “**Discussion**” noting some of the broader issues that pertain to these points.

This document is not intended to be definitive, as issues relevant to the ethics of paediatric vaccine trials in developing countries are broad and wide-ranging. It should be considered within the framework of other documents giving guidance on the conduct of medical research involving human participants. These include: the Nuremberg Code, the Declaration of Helsinki, the Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research; Ethical and policy issues in international research: clinical trials in developing countries, Bethesda, MD, USA, National Bioethics Advisory Commission 2001; Opinion of the European Group on Ethics and New Technologies to the European Commission, Ethical aspects of clinical research in developing countries, 2003; the International Ethical Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences (CIOMS) in 2003; the report on the ethics of research related to healthcare in developing countries, Nuffield Council on Bioethics (2002); the WHO Good Clinical Practice Guidelines (WHO GCP) (1995); the International Conference on Harmonisation's Good Clinical Practice (ICH GCP) Guidelines (1996); the EU Directive on Implementing GCP; the UNESCO Guidelines on the Human Genome; the WHO/TDR Guidelines. (For a list of background documents to the meeting, see Annex I.)

1. Ethical and scientific imperative to conduct vaccine trials among children in developing countries with high disease burden

1.1 Considerations

In order to respond more effectively and quickly to the enormous disease burden among children in developing countries, greater efforts should be made to conduct vaccine trials among such children. This would facilitate the introduction of effective vaccines to the populations in most need. Such trials must be based on sound science and be conducted ethically.

1.2 Discussion

It is generally recognized that it is not ethical to conduct research on children if the relevant investigation could be done equally well among adults.¹ However, there is a huge disease burden among children in the developing world and a paucity of research being done that directly relates to the health needs of children. There is a special need to develop vaccines appropriate to children in developing country settings, because of the potentially high and rapid impact on disease burden.

The disease burden among children in developing countries challenges the international community, as well as national and local communities, to find the appropriate balance between the need for urgency, and the need to meet safety and other ethical requirements in evaluating vaccines in paediatric populations.² The characterization of vaccine trials as a moral imperative for children (and adults) in developing countries compels an ethical assessment regarding whether more harm is done by inaction than by action – that is, whether more harm is done by not undertaking trials that have the potential to do good, than is done by undertaking trials that might cause harm.³

¹ “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.” CIOMS Guideline 14: Research involving children. See also the British Paediatric Association’s Working Party on Ethics of Research in Children, 1980.

² The need for continuing research is incorporated in the Helsinki Declaration, paragraph 6 which states: “Even the best proven prophylactic, diagnostic and therapeutic methods must be continually challenged through research for their effectiveness, efficiency, accessibility and quality.”

³ In the US, most drugs have not been evaluated in children prior to registration. In an attempt to rectify this problem, the FDA has added special patent incentives for products tested in children and some US\$200 million has been provided for NIH to undertake studies for children. Though this situation does not apply to vaccines currently, it illustrates the growing recognition of the import of the failure to test drugs (or produce vaccines) for children and the need to address it.

2. Vulnerability of child participants in research

2.1 Considerations

In vaccine trials conducted in developing countries, children are particularly vulnerable as research participants because of the poverty, underdevelopment and high disease burden they experience. Where trials in paediatric populations are critical to the development or evaluation of vaccines, every effort should be made to address the vulnerability of children as participants, so that such trials are implemented in an ethical manner.

2.2 Discussion

Child participants in research can be viewed as vulnerable from a number of perspectives. Depending on age, their physical, mental and emotional development is incomplete. They are largely dependent on others for their well-being and for the protection of their interests. Because they have less power, knowledge, education, resources and strength than adults do, they are more susceptible to coercion, harm, exploitation, deception or unfair treatment. In some communities, children may also be subject to harmful cultural and gender norms that increase their vulnerability to exploitation, physical and psychological violence, and illness and disease. Also, up to a specific age, they are not considered to be constitutionally, and/or legally, capable of making independent decisions or providing informed consent. They depend on their parents or guardians to make decisions about their health, including their participation in research trials.

Child participants in research in developing countries are especially vulnerable due to their medical, social and economic circumstances. If they live in conditions of poverty and underdevelopment, they – as well as their parents and guardians – are likely to have inadequate access to education, information, health care and social support. In addition to not being able to afford health care, treatment and medicines, the health care infrastructure around them may be underdeveloped and under-financed. It may not provide the best interventions available in other parts of the world. Furthermore, the health of many children in disease-endemic developing countries is seriously compromised by under-nourishment, lack of sanitation and safe drinking water, and exposure to various endemic disease-carrying vectors. Their inadequate education and health care and poor state of health may make them vulnerable to coercion and exploitation and may make it difficult for them to give appropriate assent to participation in vaccine trials.

The parents or guardians of children in developing countries may have little or no understanding of the conduct 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 minor children, and to support those children and explain to them what is happening as the trial progresses. Moreover, the

economic pressures on parents could encourage them to enrol their children in trials, if they saw an opportunity for economic benefits.

Finally, given the special vulnerability of child participants in vaccine trials in developing countries, particular efforts should be made to address their vulnerability and protect them from any exploitation, and from mental, emotional and physical harm. The following paragraphs describe some of the considerations that should form part of these efforts. The different aspects considered include the balance of benefits and risks, the choice of control groups, the selection of participants, vaccine development strategies, the informed consent process, the appropriate standard of care, post-trial access to efficacious vaccines, trial management and oversight, and follow-up of participants after a trial has ended.

3. Benefits and risks

3.1 Considerations

In order to justify exposing child participants to the possible risks posed by a vaccine trial, it must be shown that there is compelling need to use such children in order to establish safety, immunogenicity or efficacy (as appropriate). Such a trial would not be justified if the population from which the children come will not benefit from use of the vaccine subsequent to the trial if it is shown to be efficacious. The choice of the particular group of children to be included in a trial requires clear justification in terms of: (a) the scientific need to use that population, and (b) an equitable sharing of benefits and risks among possible groups. The nature and identity of the child population selected should be explicitly discussed in the protocol in these terms.

3.2 Discussion

Care must be taken to ensure that socioeconomic inequalities between industrialized and developing countries are not exploited such that research is carried out in developing countries that has little relevance to the population under study, i.e. asking children in developing countries to undertake risks to produce a vaccine that, for economic or other reasons, would primarily be of benefit to children in industrialized countries. At the same time, research should not be impeded that aims to reduce the inequality of health care and to benefit paediatric populations in need in developing countries.

In this context, the protocol for a trial should describe the objective to be achieved for the population from which the participants come, and the nature of the benefits and risks involved for the participants. Questions of equity in terms of sharing benefits and risks should also be explicitly addressed. This involves stating why particular groups of children (age, gender, ethnic background, health profile) in particular communities are being selected as participants, or are being excluded. Trial sponsors should consult communities in appropriate ways to seek their reactions and approval with regard to the choice of participants. Particular care and consideration should be given to populations that are especially vulnerable and to “over-researched” populations.

4. Equipoise and choice of control/comparator interventions

4.1 Considerations

In general, clinical equipoise should exist for randomized controlled trials of vaccines, and the choice of the control/comparator should be that which (a) will best establish the value of the candidate vaccine and (b) will improve the health and/or medical care of the participants. Where a vaccine of established efficacy for the condition under study exists and it is already in use in the country or community in which the trial will be conducted, it should be used as the comparator. Where no effective vaccine exists, a placebo may be appropriate, with special care being taken to explain to participants, their families and the community, its purpose and that it will have no protective effect. An alternative to a placebo is the use of another vaccine that provides health benefit to the child participants but is not expected to affect the outcomes measured in the trial. There should be community participation in reaching a decision on the choice of comparator.¹

4.2 Discussion

It is a general ethical principle that a state of clinical equipoise should exist with respect to the interventions being used and compared in a randomized controlled trial. Among other things, equipoise assures that the potential benefits justify the risks undertaken. A state of clinical equipoise may arise in several different ways. Early clinical evidence without sufficient statistical power may suggest that a new treatment provides additional benefits over existing treatment, or may point to a potential benefit for a condition for which no comparable intervention exists. Or equipoise may arise where there is no consensus within the medical community on the relative efficacy of competing interventions. For some experimental vaccines, clinical equipoise is easily demonstrated as no interventions have shown clinically important efficacy so far, e.g. malaria or HIV vaccines.²

The search for equipoise is relevant to the selection of the control or comparator intervention, which may involve three possible choices: (a) an established effective intervention, i.e. a licensed vaccine formulation that has (some) protective effect against the primary end-point of interest, e.g. using the licensed 7-valent conjugate pneumococcal vaccine in an efficacy trial evaluating a 11-valent conjugate candidate (see Annex III); (b) an inactive placebo; (c) an active control, i.e. a vaccine that provides some benefit to the child participant but is unrelated to the condition under study and has no effect on the primary end-point of interest in the study, e.g. using meningococcal C conjugate vaccine in the

¹ For more detailed guidance and discussion on this complex subject, see Guideline 11, International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS, August 2002.

² However, it may be difficult to maintain that equipoise continues to exist in some cases of the vaccine development process. Randomized controlled efficacy trials often do not involve equipoise, as vaccines in Phase III testing have a reasonable chance to work and have already been proven reasonably safe. Yet phase III trials may be necessary to establish efficacy conclusively.

control arm of a pneumococcal conjugate vaccine trial, which had invasive pneumococcal disease as end-point.

When a licensed and effective vaccine is available, by default this would be the comparator of choice for the control group. Any exception to this rule should be fully justified to, and carefully reviewed by, relevant ethics committees. Where an effective vaccine exists it may be used as the control even if it was not previously in general use in the community. In such circumstances, it is particularly important to define and implement mechanisms by which the vaccine found to be most efficacious in the trial is made available as soon as possible in the community from which the trial population was drawn.

When no licensed and effective vaccine exists, it may be acceptable to use a placebo as the comparator. Given its complexity, the concept of a placebo and why it is required in the trial should be thoroughly explained to the parents or guardians of child participants as part of the informed consent process. It is suggested that WHO assemble the experience of investigators in conveying the concepts of “placebo” and “randomized controlled trial”.

The administration of an inactive placebo by injection involves pain and discomfort without any corresponding benefit. Rather than a placebo, it may be considered preferable to use a comparator that comprises a vaccine unrelated to the condition under study that would provide some benefit to child participants (an “active control”). Care should be taken in the choice of a control vaccine to ensure that the scientific integrity of the trial is not compromised, including trial end-points (as may occur if the control vaccine affects the incidence of the disease under study or may mask the measurement of an adverse effect of the trial vaccine).

The use of an alternative vaccine as comparator does not provide a resolution to the lack of equipoise, but functions more as a compensation to a child participant in the control arm of a trial. For instance, the use of meningococcal C conjugate vaccine in a pneumococcal vaccine trial or of rabies vaccine in a Japanese encephalitis vaccine trial does not restore equipoise or provide an automatic justification for conducting a randomized controlled trial. However, such vaccines do benefit the child and are ones that the child would not otherwise receive.

The use of an active control should also be fully explained during community negotiations that precede the trial and form part of the informed consent process. An active control should not become an undue inducement to parents to enrol their children in the trial so as to obtain for them a vaccine, which they otherwise could not afford.

5. Where equipoise does not exist (exceptions to use of established effective vaccine as comparator)

5.1 Considerations

In some cases, it may be justifiable to use a placebo, or a vaccine unrelated to the outcome of interest, as the comparator, even though an established effective vaccine exists. This may be necessary to establish the public health benefits of the candidate vaccine in a particular setting. However, community considerations should not be allowed to override the needs and well-being of individual participants in the trial. Such a strategy should be subject to particularly stringent ethical review and should be discussed and agreed upon with the community from which participants are drawn. The existence of a placebo arm should be properly explained as part of the informed consent process. Parents or guardians of child participants should be informed that equipoise does not exist and that there is an established effective vaccine, which may be of benefit to their child. The reasons for not including this vaccine in the control arm should be fully explained.

5.2 Discussion

In both industrialized and developing countries, a vaccine is only introduced into public health programmes if the level of efficacy, and the consequent reduction in morbidity and mortality, justifies the cost of introducing and delivering the new vaccine. Such considerations are of special relevance in developing countries, where the overall level of resources for health programmes is low. Thus, a trial which does not use the established effective intervention as comparator (for example, a vaccine that has been proven efficacious in the industrialized world) might be justified in a developing country on the basis that such a trial is necessary to establish if efficacy is sufficiently high in the developing country setting to justify general use of the candidate vaccine in that setting (see Annex III).

In such circumstances, equipoise does not exist with respect to individual participants as there is a reasonable expectation that efficacy is greater than zero, but it is judged that the need for information that will inform public health strategies outweighs the lack of equipoise. Examples where such trials have been justified have involved: (a) not using the 7-valent conjugate vaccine licensed in the United States as the comparator in the trial of the 9-valent pneumococcal conjugate vaccine in the Gambia; and (b) a *Haemophilus influenzae* type b (Hib) conjugate vaccine trial in Lombok, Indonesia, despite widespread use of this vaccine in the industrialized world (For a more complete discussion of these two examples, see box below and Annex III).

Any decision not to use the established “effective” vaccine as the comparator should form a part of community discussions and agreement. Such discussions may, for example, include information that the vaccine has been established to be effective in other countries, but the effectiveness in the local community is uncertain. It should also be made explicit in the consent process that a vaccine exists that has already demonstrated clear benefit, albeit in

other communities, and that the child participant in this trial will not receive it if he or she was in the control group. Where applicable, the consent form should also indicate that the vaccine might be available on the private market. Such a situation, as well as the need to obtain proxy consent in paediatric trials, place greater responsibility on local ethics review boards in evaluating such trials. It also compels that government and/or sponsors make a firm commitment before the trial begins regarding future access to the vaccine, if it is shown to be sufficiently efficacious in the developing country population.

The trial of a Hib conjugate vaccine in Lombok, Indonesia, involves a randomized controlled trial to evaluate the efficacy of a Hib PRP-T (Polymer of D-ribose Ribitol Phosphate-Tetanus) vaccine against pneumonia. Although the efficacy of the vaccine in preventing invasive disease in susceptible children exposed to Hib had already been well established, a randomized controlled trial was considered justified because: (a) the burden of disease in Indonesia and other Asian countries was not well quantified; (b) the lack of information regarding its public health benefit has prevented the implementation of a Hib vaccination policy in Asia; and (c) the results of the trial would help to inform policy for Hib vaccine introduction in Indonesia and the region.

However, Hib conjugate vaccines are also registered in Indonesia and are available in the private market, albeit at a very high cost. Parents thus have the option of procuring the vaccine for their children on the private market. In such a situation, parents of children participating in the trial should be informed as part of the consent process of the availability of the vaccine, its safety and efficacy in other populations, and its potential to benefit the particular child whose enrolment in the study is being sought. The responsibility for providing this information rests on the investigator and/or the sponsor of such a trial.

6. Improved survival as end-point

6.1 Considerations

Vaccine trials with improved child survival or prevention of severe disease as outcomes are ethically justifiable if the effects of the intervention on prevention of mortality or severe disease are unknown. These studies should be undertaken after standards of care and prevention are agreed in order to improve survival for all trial participants, as a result of services provided by the trial. Stopping rules should be defined before the trial begins.

6.2 Discussion

Improved survival as an end-point is similar to other severe outcomes of a trial. Furthermore, a difference in survival rates is the most powerful outcome to trigger public health action. An evaluation of this end-point is desirable with regard to all vaccines where such information is unknown and an impact on survival is expected.

However, for vaccine trials in healthy individuals, measurement of mortality or incidence of severe disease as end-points may involve emotional issues, particularly where this is not clear or expected (in contrast to trials of treatment of life-threatening disease, for example, where survival studies are accepted, and hence emotional issues are diminished). In such cases, the community should be made aware of the implications of survival or reduction of severe disease as end-points and should have a chance to discuss it in community negotiations. These end-points should be fully explained to participants so that their informed consent indicates understanding and acceptance of them.

Many diseases are life threatening in developing countries because of the absence of appropriate treatments in the community, even though simple interventions may be very effective. In the context of a trial, improved levels of medical care are provided in the trial community as part of the trial activities. This may enable the treatment of diseases that may otherwise have been life threatening. Clearly if such improvements to medical care can be made in the context of a trial, it would be unethical to not implement them, even though it may diminish the incidence of the occurrence of a primary trial end-point. The improvement in the level of the standard of the care that might be provided to the trial community for the duration of the trial should be discussed fully in advance of the trial with the local community and with the health service providers. An issue that will be important to discuss is the sustainability of such improvements, once the additional resource that may be provided as part of the trial ceases.

7. Development pathway

7.1 Considerations

It may be ethically and scientifically justified to conduct vaccine trials first in developing countries among populations that carry the highest burden of disease, or to conduct these simultaneously with trials in industrialized countries, given the need: (a) to develop vaccines quickly for diseases of high burden in developing countries, and (b) to evaluate them under conditions that pertain to developing countries. Strategies should be devised in light of conditions in relevant developing and industrialized countries including the disease burden, the nature of the health risks and safety issues, and the potential benefits to the populations involved.

7.2 Discussion

Traditionally, vaccines have been developed and first evaluated in industrialized countries with eventual application in the developing world. In recent years, there has been greater recognition of the need to give priority to the development of preventive interventions against diseases endemic in developing countries and/or under conditions of high disease burden. Not only do the diseases endemic in developing countries involve compelling public health needs, but they also pose challenges unique to the conditions found in developing countries in terms of vaccine development and distribution. Strategies that involve development of vaccine in developing countries are likely to provide regulators and advisory bodies more complete knowledge of the risks and benefits of the vaccine in the developing country population, and therefore enable them to make more informed decisions about the acceptable risk–benefit ratio relative to the candidate vaccine under the conditions in which it will be used.

A number of considerations may influence the choice of the development pathway. One important consideration is that the health risks created by a particular disease may vary considerably between industrialized and developing countries. For example, while pneumonia and diarrhoea may represent relatively easily treated causes of morbidity in industrialized countries, these are conditions that are associated with high rates of mortality in developing countries, particularly among children. Differences in health conditions might also mean that different weight might be given in the risk–benefit analysis in developing countries as opposed to industrialized countries. For instance, whereas authorities in an industrialized country might assign a particular significance to certain adverse events, authorities in developing countries might assign different significance due to their consideration of the risks and benefits that pertain in their setting. Such differences in the risk/benefit ratio may mean that candidate vaccines that would not be considered for trials in an industrialized country could offer significant benefits in developing countries. On the other hand, it may be difficult in some developing countries to assess the causal relationships between the vaccine and observed “side effects”, due to the potential presence of other naturally occurring pathological manifestations.

It has been the usual practice to conduct phases I and II in the industrialized country manufacturing the vaccine, prior to conducting trials in developing countries. Such a strategy precludes accusations of using participants from developing countries as “experimental subjects” and/or of attempting to develop vaccines where costs are thought, rightly or wrongly, to be lower. It also means that safety issues may be addressed in subjects who may be at no or low risk of the target disease and who have a low risk of incidental morbidity or mortality. In developing countries, where there may be high background rates of disease, the occurrence of such diseases in the context of a trial may be mistakenly interpreted as a consequence of vaccine administration, such as neonatal death or high fever due to DPT, etc., and that might cast doubts on the safety of the candidate vaccine. However, in such situations, placebo arms might be used in phase I and II trials to evaluate these effects. (Examples given in box below.)

There may be countervailing reasons to conduct phase I and II trials in developing countries first, or to conduct them simultaneously in developing and industrialized countries.

- First, if the product being developed will not eventually provide benefits or will provide only marginal benefits to the populations in industrialized countries (e.g. a malaria vaccine), it may not be ethically acceptable to expose participants from these populations to the risks involved, particularly the safety issues involved in a phase I trial.
- Second, there may be an urgency to instigate vaccine development as soon as possible in countries where the major disease burden is found (e.g. rotavirus vaccines).

For diseases that represent a burden in both industrialized countries and developing countries, it may be advisable to conduct trials (all phases) in close parallel in both settings. Issues of appropriate vaccine formulations should be addressed, and regulatory agencies should be in a position to evaluate the data from both types of country. One current trend is to move phase III trials more rapidly to the countries where efficacy can be tested. For example, phase I and II studies of HIV vaccines have been conducted in close parallel in Oxford (UK) and Nairobi, with the plan to conduct phase III studies in developing countries. A similar approach has been adopted in the development of some malaria vaccines. Generally, it is highly desirable that vaccines be evaluated as quickly as possible (phase III) in locations where the burden of the target disease is greatest.

With regard to the development of vaccines for children in developing countries, there is ethical tension between favouring speed to develop these vaccines faster and being more conservative for the sake of safety (see section below). Arguments in support of both approaches can be found, and a case-by-case analysis is warranted. Special safety issues may arise and may require additional consideration with regard to premature infants, neonates, and immunodeficient individuals. Furthermore, vaccines that may be developed for “endemic” or “orphan” diseases may use novel technologies that have not previously been tested in industrialized country populations. The use of such technologies for the first time in developing country populations may be interpreted as using vulnerable populations to test new technologies with no safety track record. Special justification should be provided for the use in paediatric populations of new vaccine concepts, such as new viral vector vaccines, DNA vaccines,¹ new adjuvants, and immunomodulators.

¹ Report of WHO meeting on Safety of DNA Vaccines, Geneva, Switzerland, March 16th, 2001

Simultaneous trials or trials designed for developing countries may address the difficult situation that arises when observation of rare adverse effects in the industrialized world precludes the development of the vaccine in the developing world where the vaccine may have an overall beneficial public health impact.¹ The complex issues to be considered in a strategy for simultaneous development can be demonstrated by the case of the tetravalent rhesus reassortant rotavirus vaccine. When there was evidence that the vaccine was associated with intussusception in a small proportion of vaccinated infants in an industrialized country, the vaccine was withdrawn from the market, and planned trials with the vaccine in the developing country population were suspended. As a result, the vaccine could not complete evaluation in developing countries, though if it had proven efficacious in such settings, it would have had a tremendously beneficial public health impact. Hence, it is very likely that the risk/benefit ratio would have been very favourable. On the other hand, to knowingly expose children to a product that is known or suspected to induce a potentially life-threatening complication, however low the risk, may pose difficult ethical issues, though it is a fact that all vaccines carry some such risk. (For more complete discussion, see Annex IV.)

¹ It could be argued that this issue arose with regard to action taken by the US Federal Drug Administration in the development of RSV and pneumococcal vaccines.

8. Age de-escalation in vaccine trials

8.1 Considerations

Age de-escalation – conducting phase I and II trials first in adults, then in older children and finally in the target age group – in order to avoid undue risks to younger child participants may be appropriate, but must be assessed with reference to a number of factors, such as the epidemiology of the disease for which the vaccine is prepared, the risks/benefits of the vaccine for each age group, and the safety profile of the vaccine. Ethics review committees will need to consider such strategies carefully, seeking the advice of independent experts in the field to assist their decision-making. A strategy of age de-escalation should be discussed with the community, from which participants come and receive its approval.

8.2 Discussion

Generally, children should not be included in the first phase I trials of a new candidate vaccine because they are unable to give their own consent and because of the potential risks involved. However, there are a number of considerations that may affect whether it is appropriate to assess the safety of a vaccine in adults or older children before progressing to young children or infants. In the case of the development of vaccines for infants, trials in older children may expose them to risks even though they cannot benefit from the vaccine. This may be acceptable for adult participants who are able to choose freely to take risks without corresponding benefits. It would be less acceptable in the case of adolescents or toddler participants, who are unable to provide informed consent, and would likewise be exposed to potential risks without benefit (see Annex II for discussion on age descalation in malaria vaccine trials).

Furthermore, some diseases induce only partial immunity. Adults who have been repeatedly exposed would have high levels of immunity and young infants with no prior exposure would have no immunity. The level of immunity in adolescents and children falls in between these two groups. In such cases, a live vaccine may have a different safety profile in each age group, and gradual age de-escalation may be a desirable option. An example of this is the live attenuated vaccine against respiratory syncytial virus (RSV).¹ Immunity following natural infection by RSV is not complete, and repeated infections occur. However, each successive infection is less severe, because of immunity conferred by previous infections. Live attenuated vaccines may thus have few side-effects in partially immune older children, but have a higher level of side-effects in naive infants.

On the other hand, it may be necessary to use child participants in phase I trials based on scientific justification or ethical considerations. For example, phase I trials conducted with child participants might be justified if testing in adults would be risky because of the presence of prior immunity in the adults, e.g. anaphylaxis or hyper-immune reaction. Phase I

¹ See Crowe, J.E. Jr., “Respiratory syncytial virus vaccine development”, *Vaccine* 2002:20: S32-S37

trials conducted with child participants from developing countries can also be conceived if the vaccine had previously been extensively tested or used in children in industrialized countries. For products that have undergone phase I testing in adults in industrialized countries, this testing should often be repeated in adults in developing countries before they are undertaken in children, lest there be differences in the safety profile in different ethnic groups or in those with different levels of prior exposure to the infection.

9. Adolescent participation in vaccine trials

9.1 Considerations

The participation of adolescents in vaccine trials would be justified where adolescents may be the target population for vaccines against diseases acquired during or after adolescence, e.g. vaccines for HIV, human papillomavirus (HPV), herpes virus (HSV) or other sexually transmitted infections. Studies in adolescents would be indicated if there is evidence that a candidate vaccine would not work as well in adolescents as in adults or if specific safety, immunogenicity or efficacy data would be needed for an adolescent vaccine indication. Because the participation of adolescents often involves complex legal, ethical issues and operational issues, vaccine trials with adolescents require clear parameters regarding their participation, including how assent and consent is to be obtained and confidentiality protected. Such parameters should be devised with community input and agreement.

9.2 Discussion

There is major unmet under-appreciated need for effective vaccines for adolescents, e.g. hepatitis B virus (HBV), human papillomavirus, HIV, and other sexually transmitted infection (STI), in particular. This imperative is just as great as for infants. As with the participation of any person legally unable to give informed consent, the participation of adolescents should be justified by scientific need, i.e. the need to establish safety, immunogenicity and/or efficacy of a vaccine for their particular age group with regard to a disease that affects them. Adolescent participation in trials may not be justified where protection data can be obtained from studies in adults and where there is no scientific evidence to suggest that the data from adults are not applicable to adolescents. In such situations, another option for consideration, if appropriate, would be to conduct clinical trials in adults, with smaller safety and immunogenicity studies in adolescents to bridge data from adults to adolescents. Decisions on use of the vaccine in this age group may be made based on non-inferiority in immune response in comparison to the adult population.

The participation of adolescents in HIV vaccine trials is complicated by a number of issues including the need to be tested for HIV infection in order to participate in such trials as well as the lack of a clear correlate of protection and the ethical imperative of having an adolescent indication for any HIV vaccine. Guidance Points 17 and 18 of the UNAIDS guidance document *Ethical considerations in HIV preventive vaccine research* generally promote the conduct of HIV vaccine trials among children and adolescents, including girls, given the particular vulnerability to HIV infection of these populations.¹ The lack of knowledge of immunological correlates of protection against HIV infection does not allow the design of HIV vaccine bridging studies from adults to adolescents. Therefore, at the present time, in order to establish an adolescent indication for an HIV vaccine, adolescents will need to either be included in phase III trials or separate efficacy trials will need to be

¹ UNAIDS/00.07E, May 2000, Geneva

planned, a very expensive prospect. As a consequence, phase I/II trials in this age group will need to be completed to assess safety prior to enrolling adolescents in phase III trials. A logical approach would be to monitor phase I/II work in adults and only as candidate vaccine phase III trials are being planned complete phase I/II work in adolescents, allowing for delayed enrolment in phase III trials. Similar considerations apply to human papillomavirus.

Adolescents present issues of particular complexity with regard to informed consent, because they often have the intellectual and emotional capacity to provide consent, but are not *legally* able to consent. Furthermore, their views and their parents' views on their participation may differ. There may also be difficult issues regarding the maintenance of appropriate confidentiality with regard to adolescents. While it is considered ethically unacceptable to include adolescents in a trial against their will, even if there was parental approval, it may be considered ethically acceptable, but illegal, to include a willing adolescent in the absence of parental consent. In some cultures, adolescent girls may not be able to exercise true autonomy in light of gender norms and the influence of their parents or partners. The participation of adolescent girls is further complicated by the fact that they may be, or may become, pregnant. Not only does pregnancy pose possible risks for the young mother and the fetus, but it also raises complex issues regarding informed consent, confidentiality and legal liability. In addition, the need for pregnancy testing of adolescents prior to inclusion in a trial presents special problems.

Issues of consent and confidentiality concerning minors, including adolescents, are matters governed by national and/or local law, but local laws and practice may be complicated with regard to adolescent consent. Married adolescents may or may not be able to give legal consent. Adolescent parents may be able to give legal consent to have their children vaccinated, but may not be able to give legal consent for themselves to participate in a vaccine trial. Adolescents seeking birth control, treatment for sexually transmitted infections and testing for HIV may or may not be able to obtain these without the consent of their parents.

Thus, there is need for a clear understanding of local law and practice, as well as for strategies that address the complexities particular to adolescent participation. When adolescent girls are participating, special efforts may be needed to ensure that they are truly able to exercise autonomy and provide assent to participation. Where appropriate, pregnancy testing should be considered to minimize the risk of harm to the mother and fetus. Given the controversies that may attend adolescent participation, it is important that there has been community discussion and agreement regarding the parameters of their participation.

10. Proof of principle or candidate antigen trials

10.1 Considerations

Proof of principle (POP) trials or candidate antigen trials can be part of non-traditional vaccine development in situations where correlates of protection/immunity are not defined (e.g. malaria and HIV) and the trial is needed to provide proof of principle that a particular vaccination strategy can provide protection against disease. Because POP trials are unlikely to result directly in a product that will benefit, in the short or medium term, the children of the community from which participants are drawn, there should be significant scientific and ethical justification for doing POP trials with child participants. POP trials should not be done with child participants when the issues being addressed in such trials can be addressed adequately by the use of adult participants. In every case where a POP trial is being conducted, the consent form should be explicit if the community and the participants are not likely to benefit from the particular product used in the trial in terms of gaining eventual access to it.

10.2 Discussion

A proof of principle trial is essentially an experiment to prove whether a certain approach will work, rather than a trial of a specific product that is intended for public health use. POP products often go through “iterative product development” wherein the product is modified or improved a number of times before it goes to licensure. Examples of POP trials include HIV candidate vaccines that are chosen in order to provide information on the degree of protection conferred to a vaccinated individual by an antigen, or information on a type of immune response, but are not intended to be used routinely as a final product. POP trials can therefore be useful, or necessary, to speed up product development, but agreements regarding future access are not possible, since the product may never be registered or the trial’s sponsor may not be intending to, or capable of, bringing the candidate vaccine to licensing, manufacture and distribution.

Such trials, in which the product has no immediate potential public health benefit, could be ethically acceptable, though they require careful scrutiny by ethics review committees. The ethics review committee may need to be convinced that there is a well-defined development pathway that would lead eventually to a product for public health use in the community in which the trial is being conducted, especially for phase III trials with such products. Furthermore, the consent form should clearly explain to participants that the trial is a POP trial, and the product being evaluated will not be available for use by the community. This will be a difficult concept to convey, especially in communities with a lack of understanding of modern scientific principles and of contemporary regulatory affairs. Such situations place an additional burden on ethics committees to ensure that consent is truly “informed”.

Because children are not able to give informed consent and should generally not be exposed to risks without the possibility of compensating benefits, POP trials among children should

be limited to situations where the scientific questions cannot be answered by studies in adults. Studies in children should generally not be initiated if the data generated are not likely to be used for licensing. If POP trials are to be conducted in children, ethics committees should ensure at least that the vaccine candidates are produced using GMP and GLP standards, are reproducible, and that there is appropriate regulatory oversight for pre-clinical safety, stability, potency and purity testing.

11. Informed consent/ confidentiality

11.1 Considerations

Special efforts should be made to overcome any challenges to obtaining informed consent in a developing country. Informed consent should be seen as a process – beginning with the voluntary decision to participate based upon information conveyed, both to the community and to the individual participant, prior to trial entry and as evidenced by the consent form, and continuing throughout the trial in terms of ensuring adequate ongoing comprehension and voluntariness. The informed consent form should be sufficiently simple to be understandable, yet comprehensive enough to explain the concepts, the potential risks and benefits, the implications of the use of a placebo or other comparator, the care that will be provided, and the indemnity for injury or death arising from the trial. Every effort should be made to involve the child or adolescent in the consent process to the level of the minor’s capacity and understanding. Based on capacity, the minor’s assent to participation should be evidenced at the beginning of the trial and throughout his/her participation.

11.2 Discussion

Obtaining informed consent in the complicated research setting of vaccine trials presents a number of challenges. These challenges are heightened in developing countries where potential participants may be unfamiliar with scientific research, its concepts and vocabulary; may have unrealistic or erroneous expectations of health benefits and/or care; and may be unable to act with full autonomy due to possible influences on individual action, e.g. cultural and gender norms, community and/or family/spousal pressure. All of these challenges are further complicated in situations involving proxy consent obtained from the parents or guardians of a child participant.

Cultural differences most likely exist between a developing country hosting a trial and sponsors in industrialized countries. These differences should be taken into account in the process of obtaining informed consent. Investigators should be sensitive to possible influences on consent – primarily those of community elders, spouses and other family members. Though it is natural that such people influence potential participants, care should be taken to ensure that involvement is truly voluntary on the part of both the parent who is providing the proxy consent for his/her child and on the part of the child who is participating. In cultures where women do not have equal status with men, care should be taken to ensure that the mother also agrees that her child become a participant. In cases of illiteracy, oral consent may be acceptable, if understanding is sufficient and consent is witnessed and documented.

In the case of children, parents usually make the decision regarding participation. Therefore, it is important to assess whether the children also assent (agree to participate voluntarily without coercion). To the extent that the child’s capacity allows, every effort should be made to explain to the child, in language that is understandable to the child, the nature of the

child's participation, the potential risks (including discomfort, time spent, etc.) and benefits, and the purpose of the trial. In the case of older children/adolescents, investigators should document the child evidencing his/her assent.

The means by which to obtain informed consent should also be culturally sensitive. This may involve community discussion, family discussion and individual consultation. However, community consent should not be considered as a substitute for 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 process, particularly if verbal rather than signed consent is sought. Such witnessed consent should be recorded in the trial records.

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 to participate in the belief that they will receive improved treatment. It is important to explain clearly to those participating in a vaccine trial (and to the parents in the case of child participants) that participation will not necessarily ensure protection against disease. The use of a placebo and randomization should be explained, including the fact that the participant might be one of those who receive a placebo and that the candidate vaccine may offer no protection. Any care or other benefits that are offered should be described.

It is necessary to ensure that there is sufficient comprehension and that the consent form is a document that is easily and actually understood. A number of factors might affect comprehension, such as: (a) the unavailability of terms for clinical concepts in local languages, (b) cultural/socioeconomic barriers, including authority issues inherent in the doctor/patient and investigator/participant relationships, and (c) regulatory and legal requirements that the form include extensive explanations. At present, there is tension between producing a form that acts as protection from liability for sponsors and investigators and a form that is understandable by participants, particularly by those in developing countries. Whenever possible, research should be conducted to check that participants in a trial have fully understood the nature of the investigation in which they are participating and have appreciated the explanation of possible risks and benefits provided during the informed consent process.

The informed consent form should explain the purpose, procedures, risks and benefits, comparator, care and indemnification in the trial. If there is no equipoise between the treatment groups, this should be explained in the form. Also, if relevant, the fact that the trial is a proof of principle trial should be explained in the informed consent form and process. In essence, parents considering the participation of their child should have adequate comprehension of every aspect of the trial relevant to the safety and well-being of their child, so that they are able to choose freely on an informed basis, without coercion or undue inducement, in the context of their particular circumstances.

Though informed consent is obtained before participation in the trial begins and is evidenced by a consent form, participation throughout the trial should remain both voluntary and informed. Thus, the form should explain that the parent and/or child can opt out of the trial at any time, and investigators should continue to explain to participants what is happening throughout the trial process. Where the circumstances of the trial change significantly, it would be necessary to revise the consent form, discuss it with already enrolled participants, and obtain their consent to the new set of circumstances.

Some situations, such as “home enrolment”, may involve a number of aspects that make it more likely that informed consent is truly informed and voluntary. Several visits over a period of weeks may improve the process. An example of home enrolment is when the families of potential participants become involved before the delivery of their babies, trust has time to develop, and clinical services are given to study members by the study doctor, who can then check if parents have understood the nature of the trial. The signature of the participant, or their witnessed consent, and in the case of children, that of their parents, is a last step that formalizes the consent process.

12. Standard of care

12.1 Considerations

In the conduct of paediatric vaccine trials in developing countries, trial sponsors and investigators should try to address and contribute to the improvement of public health in the situation of poor communities that experience a high burden of disease and low standards of health care. Through a process of consultation and agreement with local authorities before the trial, a standard of care should be offered that: (a) improves the health conditions of the trial participants and community, and (b) is sustainable. The standard of care should be approved by both the local ethics review committee, as well as by the appropriate ethics review committee in the country from which the sponsor comes. The trial should be conducted in such a way so as to ensure that it strengthens (notably through infrastructure, training, etc.) existing health services.

12.2 Discussion

There has been, and continues to be, an ongoing debate about the standard of care that should be provided for trial participants and to the community from whom participants are drawn. This document will not conclude that debate. In the context of vaccine trials, the reality is that many of the diseases endemic in developing countries and against which new vaccines are needed have disappeared from industrialized countries due to improvements in the standard of living (e.g. water-borne diseases and malaria). In many instances, vaccination in developing countries would address these diseases more readily and in a shorter time frame than the time frame required for improvement in the socioeconomic situation. In this sense, if one were able to deploy the “best proven intervention”, there would be no need for certain vaccine developments.

Query: Is the “established intervention” attainable as the standard of care for pneumonia? If this standard were to become the universal standard, treatment of childhood pneumonia may include care that is out of the socioeconomic realities of many children’s lives, e.g. intensive care and ventilatory support. This would be unattainable in developing countries that do not have such facilities, and if introduced as part of the trial, would lead to imbalances in the health services of the country, potentially leading to long-term damage to the country. A more sustainable level of care may consist of basic management of pneumonia, primary ARI case management with CTX, and adequate hospital care in line with the guidance provided in the WHO manual for managing sick children.¹

¹ *Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries*, WHO/FCH/CAH/00.1, 2000, Geneva

² *Management of the child with a serious infection or severe malnutrition. Guidelines for care at the first-referral level in developing countries*, WHO/FCH/CAH/00.1, 2000, Geneva

Given this reality, it is necessary to consider the standard of care within the context of the standards of the country and the community hosting the trial, with every effort being made to improve it. The level of care provided should be defined prior to the trial's initiation through a process of community consultation and agreement, including with the local and national health services, where appropriate. This consultation should identify what the community considers appropriate and what the sponsors and other partners have to support. In discussions with the government, local community, etc., it is important to define clearly, prior to the start of the trial, what and what not will be provided in the context of the trial, to whom and for how long. The ethics review committees in the host country and sponsoring country should agree on the standard of care, with recognition that the former committee is likely to be much better informed with respect to what is appropriate and acceptable in a local context. The standard of care should not be compromised to serve the project, but neither should care be provided in a way that will generate undue inducement to enrol children into the trial.

In the process of consultations, the standard of care to be provided should be discussed and decided first with regard to trial participants, i.e. those taking the risks involved in the trial; then if appropriate and possible, with regard to siblings and/or family members, and the community at large. The first level of concern should be the disease that is the focus of the trial. The second level of concern might involve other health and social conditions, within trial resources. Any measures regarding standard of care during a trial should be agreed to and supported by local health care providers to ensure sustainability.

Various levels of care might include, e.g.:

- best preventive method/other vaccine;
- best management of condition of interest;
- good general health care for study children;
- good health care for the community;
- access to a proven intervention during and after the trial, including access to antiretroviral therapy if relevant. On this particular issue, see also the proceedings of the WHO-UNAIDS Consultation on “Treating People with Intercurrent Infection in HIV Prevention Trials”, Geneva, 17 and 18 July 2003.

13. Duration of follow-up

13.1 Considerations

Where there are no regulatory requirements for the duration of follow-up in paediatric vaccine trials, active follow-up should extend at least to the end of the trial, or longer, depending upon safety issues encountered. Some regulations for children's vaccines require that at a minimum all children be followed for six months after completion of their vaccination for serious adverse effects.¹ For those who have presented serious adverse effects during the study, follow-up should be continued for an additional six months after the end of the study. In high mortality populations, it may be desirable to analyse long-term mortality changes and to follow-up participants for a number of years.

13.2 Discussion

Active follow-up should extend to the end of a paediatric trial, depending on the situation and the safety issues. Passive follow-up is advisable for a few more years. Registry/identification mechanisms can be used for this purpose.

Long-term safety issues are important, though long-term follow-up may complicate a trial substantially and greatly increase its cost. Active or passive data gathering can be combined for short-term follow-up, whereas passive data gathering will be more relevant for long-term follow-up. Creative follow-up studies should be contemplated, both for safety and for long-term protection, like sentinel surveillance, case-control studies, etc. The effect of the high titre measles vaccine was detected only because long-term follow-up was being undertaken. For this reason, there are advantages in undertaking trials in areas where sustained demographic surveillance is in place for other reasons.

Other parameters to be followed in the longer term might include:

- modification of disease epidemiology as a result of vaccination (disease patterns);
- duration of protection;
- impact of public health intervention with the vaccine;
- change of distribution of pathogen types in the environment.

¹ WHO Guidelines on Clinical evaluation of vaccines: regulatory expectations, Geneva, adopted 2001, in press.

14. Compensation for expenses and indemnification/insurance

14.1 Considerations

The level of reimbursement or compensation for participation should be fair, but should not constitute undue inducement to participate. The local ethics committee should provide guidance on the level of appropriate compensation in light of the nature of the participation, cultural traditions, and the circumstances of the trial. Protocols should also provide for indemnity for injuries or conditions related to the intervention and/or arising from the conduct of the trial. Clinical trial insurance should be in place to provide for medical care for injury or death related to the trial.

14.2 Discussion

Practice with regard to reimbursement of cost, or compensation, differs significantly according to what is considered fair and acceptable locally. Usually, reimbursement of costs or compensation is calculated to put the participant in the “same place” he or she would have been if they had not participated – in other words to reimburse for any costs incurred for participation, such as time spent and expenses (e.g. travel to and from the study site). In some situations, it will be appropriate to compensate families of trial participants, particularly where parents incur costs because of the participation of their child. Local ethics review committees can best evaluate the appropriateness of compensation in the context of local cultural, social and economic conditions.

Compensation may take different forms and should respond to the nature of the participation. In some places, compensation has taken the form of health care. In Oxford, payment has been based on a calculation of the number of hours spent by participants.

15. Oversight/regulatory framework

15.1 Considerations

All paediatric trials should be subject to strong regulatory and ethical review in order to protect the best interests of child participants, and should be conducted in accordance with GCP guidelines with adequate provision for strict monitoring of adverse events. The international framework for regulation and ethical review should be improved in terms of development of guidance relevant to paediatric trials. Where necessary, efforts should be made at the national level to build and improve the capacity of national and local regulatory and ethical review bodies. In multi-site trials or in trials involving ethics committees in more than one country, regulatory and ethical review bodies should share information and concerns, and should have a mechanism by which to resolve differences.

15.2 Discussion

Ethical and regulatory review should be a central aspect of all vaccine trials, particularly those involving child participants. However, a strong international ethical and regulatory framework does not yet exist, and national frameworks differ markedly in capacities. The overriding challenge is to create an ethical environment at both the international and national levels for the protection of child participants and the communities from which they come.

Vaccine trials often involve sponsors and investigators from multiple institutions, which lead to a complex process of ethical and regulatory review, and sometimes to conflicting requests regarding the conduct of the trial. In general, regulatory agencies have the responsibility to ensure that products being tested in human subjects do not pose an undue risk. This responsibility is greater in the case of trials involving children. Regulatory bodies are also well placed to deal with issues pertinent to the licensing of a new product, taking into account its safety and efficacy. Regulatory agencies are probably not the bodies best placed to oversee the public health aspects of a vaccine trial and to make ethical judgements with respect to end-points. There is need for appropriate mechanisms to ensure appropriate regulatory oversight for products of public health importance tested in developing countries. Such mechanisms should take into consideration the risk–benefit ratios relevant to the epidemiological situations in the countries where the products are being evaluated. International organizations such as WHO have a role in exploring and establishing such mechanisms.

Like regulatory bodies, ethics review committees are also concerned with safety and risks. This overlap in responsibilities between regulatory bodies and ethics review committees sometimes results in differences in assessments that are difficult to resolve. (For an example, see Annex III on the Gambia Pneumococcal Vaccine Trial). Because of the sometimes confusing and overlapping roles of regulatory authorities, ethics review committees and

other bodies involved in the trials, there is also need to put into place mechanisms to ensure communication among these bodies about ethical issues.

Another aspect of regulation is that performed by clinical trial monitors. Monitors are required to check the accuracy and validity of data collected during the course of the trial. However, such monitoring more often involves checking for consistency between the trial forms and the source documents, and often fails to provide serious scientific and ethical oversight. While such monitoring may fulfil regulatory requirements, it may fall short of the level of oversight that may be required for trials in children in developing countries.

In principle, competent and independent local ethics review committees are best placed to decide issues of local relevance and their judgement should be given significant weight in these matters. They are aware of the particular cultural and social realities relevant in their communities, may also best represent the views and values of the community and be more closely in tune with the needs and concerns of participants. Though the ethics review committee in the country of the sponsor organization may be best placed to address many of the scientific issues that are involved, the ethics review committee in the host country should have the capacity to analyse the scientific validity of the project from its point of view and to monitor the conduct of the trial through independent steering committees or Data Safety Monitoring Boards. In addition to safety issues, the local ethics review committee may also be best placed to deal with the well-being of study participants and the appropriateness of particular end-points. In multi-centre trials, dialogue should be ensured among all ethics review committees involved in the trial, and, where possible and acceptable, it may be advisable to identify or create a “central” ethics review committee.

In some developing countries, local ethics review committees are providing excellent ethical review. However, in others, the committees suffer from: (a) inadequate composition and training, (b) inadequate knowledge of scientific trials and product development, (c) lack of transparency and independence, and (d) poorly defined monitoring responsibilities. In addition, they may be overwhelmed by the increase in regulatory demands, and by the numbers and complexity of clinical trials. Where these are problems, there is a need to strengthen local ethics review committees, especially with regard to the issues raised in paediatric trials. It is suggested that, where necessary, WHO and other international agencies have an important role in building the capacity of local ethics committees.

16. Trial management

16.1 Considerations

Trial managers should respond quickly and appropriately to developments within the trial or to developments in the context of other research that has a bearing on the course of the trial. Data Safety Monitoring Boards should share information and recommendations with trial managers and the relevant ethics review committee. Broader consultation may also be appropriate with the community and government health officials. There is need to develop a system by which to collect and share general and relevant information among trials.

16.2 Discussion

There is a need for those managing trials to be able to respond to developments that might, or should, affect the design or conduct of the trial. Such developments may occur in the context of the trial itself, or may occur in the context of other trials but be relevant to the one in question. This information may be useful to stimulate action in areas not dealt with in the trial, and/or to avoid repetition of harmful or negative results or studies. The Data Safety Monitoring Board (DSMB) has access to relevant codes and has the statistical capacity to make appropriate judgements. When it becomes aware of serious adverse effects, it should share these, along with its recommendations, with relevant ethics review committees at an appropriate time, with care being taken that these committees are not overloaded with reports on individual cases. Large international trials may require both an independent DSMB as well as an independent steering/advisory committee.

The first level of decision about significant changes to the design or conduct of a trial should be taken after consultations among the investigators and the trial bodies: the DSMB, the ethics review committee(s), and the sponsor(s). The second level of decision might involve consultations with health system officials and the communities from which participants are drawn.

In the pneumococcus vaccine trial conducted in the Philippines, the vaccine manufacturer decided to stop commercial development of the vaccine, while it was undergoing phase III testing. After initial consultations, the investigators and trial bodies decided to continue with the trial. Community representatives were then consulted. A new consent form was drafted to reflect the developments and this was used to inform the children already enrolled, as well as children newly enrolled. Families of children who had already completed the trial were also informed. Original study outcomes were maintained. (For fuller discussion, see Annex III.)

It is also important and necessary that the results of completed trials, and important relevant interim results from ongoing trials, be shared rapidly among the scientific community so that trial participants in similar trials are not exposed to unnecessary risks, and problems are not duplicated because of lack of awareness. Thus, there is a need to collect general information about serious adverse effects and to share this information with those for whom it may be

relevant. Such information sharing generally relies on a voluntary system capturing information that trial groups are willing to share, and dealing, as necessary, with issues of appropriate confidentiality. Issues with respect to safety may be gathered centrally for multiple trials by regulatory agencies. WHO programmes have facilitated information sharing about vaccine trials for some diseases, e.g., pneumonia, but not for others, e.g. malaria. It is suggested that WHO and regulatory agencies develop and improve mechanisms by which to share appropriate information.

17. Access to the products of the trial

17.1 Considerations

The community from which participants are drawn in a vaccine trial has the right to benefit from the results of the trial in a reasonable time. Steps should be taken from the outset of trial design to ensure that provision is made for the trial community to benefit from early access to any product of the trial, as well as to infrastructure and knowledge brought by the trial. Access issues should form a part of negotiations among community representatives, government, health authorities and trial sponsors during the design of the trial, through decisions on participation, and at all levels of product development, with a view to finding a sustainable solution that gives preference to the participating community/country in light of the product being developed. Access to the vaccine by child participants in the control group should be provided at the end of the trial if the vaccine would still be expected to offer health benefits to this group (e.g. they had not passed the age of disease risk).

17.2 Discussion

The community should be considered by the sponsoring group as a partner in the development of the vaccine. Indeed, if a community has contributed to the development of a vaccine, it could be said that the community has some degree of “ownership” in the product, and the sponsor has an obligation to return to the community a benefit for the contribution made. In the context of that obligation, the local or national government, together with the sponsor, has the key role in defining the best way to facilitate access to the product. The issue of post-trial access will become most relevant with respect to phase III trials and becomes especially relevant once the product has been shown to be efficacious and is potentially available. However, issues of access should be discussed at all levels of clinical development of the product.

Governments should negotiate with sponsors regarding the nature, coverage and time frame of the access to be given. In some instances, governments enter agreements with sponsors in which the sponsors agree to provide a vaccine for a certain number of years to the community after the demonstration of efficacy. Governments should also be willing to commit themselves to provide support beyond what the trial sponsors will provide, but their ability to do this will usually depend on the pricing of the product. The vaccine should be given to control participants at the end of a vaccine trial/product development if efficacy has been demonstrated and the disease/vaccine is still relevant for the age of the control group. (See Annex III for discussion of pros and cons of providing vaccine to the control group at the end of the trial.)

Access should be ensured not only to the vaccine, but also to public health infrastructure and knowledge that the vaccine trial has generated. If services are provided in the context of a trial or in the context of creating access, attention should be given to the sustainability of those services, which should ideally strengthen the local health infrastructure.

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General

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Annex 3:

Some ethical considerations regarding malaria vaccine trials¹

General ethical issues

Malaria vaccine trials in children must meet the general ethical standards that apply to all intervention studies in children, such as obtaining a full ethical review, obtaining informed consent, and provision of high standards of care during the trial. However, such trials also raise some specific issues that are considered below.

Specific issues concerning malaria vaccines

Novel vaccine formulations and use of new adjuvants

Inducing protective immunity to malaria is not easy. Multiple infections are required to induce natural immunity, and this usually provides only partial protection against the clinical consequences of the infection, but not against the infection itself. The task of inducing artificially a level of protection as good as, or better than, that acquired following many years of natural exposure is a daunting task and one that is likely to require vaccines based on mixtures of antigens and the use of novel delivery systems and/or novel adjuvants. The situation is thus very different from that which pertains to the evaluation of new vaccines against capsulated bacteria or viruses, such as rotavirus, which are based on technologies that have been shown previously to be very safe in children.

Malaria vaccines currently being evaluated include those based on DNA, modified vaccinia virus and modified fowlpox virus. Moreover, powerful new adjuvants, such as AS02, are being used, for which there are relatively few data in young children. There are therefore special concerns over the use of DNA vaccines and novel adjuvants in young children, as several of these new adjuvants have caused significant side-effects in adults. Evaluation of many new malaria vaccines in children is likely to raise special safety issues.

Trial end-points

There are a number of potential end-points that can be used to measure the impact of a malaria vaccine. These follow the spectrum of malaria infection, which extends from infection to mild clinical illness to severe clinical illness to death. It is possible that some vaccines, especially blood stage vaccines, could reduce the risk of severe illness and/or death, but not infection. The converse could also be true. Trials to show this would need to be much larger (perhaps 10 000 subjects) than those that could show an effect against infection (500). Thus, investigators are faced with a dilemma. If a vaccine is shown to have a modest but statistically significant effect (e.g. 30% efficacy) against infection or mild disease in a trial powered only to detect these end-points, would it be ethical to progress to a randomized controlled trial of severe disease or death in the same community or a community where the epidemiology of the infection was similar?

¹ Prepared by Brian Greenwood, Peter Smith and Geoff Targett

It could be argued that it would not, on the presumption that an effect on severe disease would be highly likely, given established efficacy against mild disease. On the other hand, it could be argued that protection against infection or mild disease might not be carried through to severe disease, particularly if the protective efficacy was relatively low, and that it would be unethical to consider widespread use of a vaccine until a properly controlled trial had demonstrated an unequivocal effect against the end-points of major public health interest.

To avoid this dilemma, a case can be made for ensuring that initial trials are large enough to evaluate protection against severe end-points. However, this would involve exposing a large number of children to the potential safety risks of a new vaccine, before these had been evaluated comprehensively in a smaller number of children. A possible approach to this situation is an integrated trial in which intensive observations are made on the first few hundred children in the trial which, provided that the safety observations are satisfactory, is then allowed to continue to reach a sample size large enough to assess protection against severe disease and/or mortality end-point.

Age de-escalation

Marked variations are seen from area to area in the age group most at risk from severe malaria. In low transmission areas, all ages are at risk; while in very high transmission areas, most severe disease is seen in children under the age of one year. This has led to discussions as to whether the classical de-escalation approach used in vaccine evaluation, namely moving from adults to older children to toddlers to infants, is appropriate in high transmission areas.

It has been argued that it is not justifiable to put older children at risk from a new vaccine when they are not at risk of severe malaria; and that after trials in adults, who are able to give genuine informed consent and to understand the potential risks and benefits to themselves, have established vaccine safety, trials should immediately involve young children who are the group most at risk of severe disease or death. However, as indicated above, there are concerns about the safety of vaccinating very young children with novel constructs without background information on safety in older participants. A compromise, especially for blood-stage vaccines that are designed to reduce clinical illness rather than to prevent infection, may be to progress rapidly from safety studies in adults to studies in children in the age range of 1 – 5 years, who are at risk of severe malaria, before progressing to infants.

Transmission-blocking vaccines

Experimentally, it is possible to induce antibodies that block the development of the malaria parasites in a mosquito, and good progress is being made in the development of transmission-blocking vaccines, which are now entering the first phase of clinical trials. It has been argued that such vaccines are “altruistic”, as they do not protect the vaccine recipient from infection or its consequence, but only from infecting someone else.

However, provided that a high proportion of a community is vaccinated, then each vaccinated individual will obtain some personal benefit, as they are less likely to be bitten by an infected mosquito. As a substantial amount of malaria transmission takes place at a micro-epidemiological level, this probably applies at the household as well as at the community level. It is likely that, if all children in a compound are vaccinated with a highly effective transmission-blocking vaccine, each will achieve some protection from infection derived from their siblings, although they will still be at risk outside the household. Thus,

there is a potential for some individual benefit as well as risk, meeting the ethical requirement of equipoise.

Efficacy versus safety

An intriguing issue has arisen in two malaria vaccine trials in children over the issue of efficacy versus safety. In two studies undertaken in the Gambia, collection of safety data required the investigation of children who became ill during the period of observation after the vaccine had been delivered and, as a component of routine investigation of these children, blood films were obtained. Thus, information was obtained on the incidence of clinical malaria in vaccinated and control children, although the trial was powered only to detect safety and immunogenicity, and not efficacy.

In one case, review of the safety data suggested an adverse effect of the malaria vaccine on malaria incidence and, in the other, the reverse. How this information should be handled if a significant result is obtained raises difficult questions. Is it permissible to continue with a placebo-controlled evaluation of the vaccine in that community if a statistically significant level of efficacy is obtained in a trial that was not designed to evaluate this end-point? It probably is, provided that the trial was not of a sufficient size to detect an efficacy effect with any degree of reliability and that it is stated clearly in the study protocol that efficacy is not a trial end-point.

Annex 4:

Some ethical considerations regarding pneumococcus vaccine trials¹

Introduction

Pneumococcal vaccination may be one of the most important new developments in immunization in the coming decade, but the complex nature of pneumococcal disease presents special technical and ethical problems. The most common manifestation of pneumococcal disease is pneumonia. But the burden of pneumococcal pneumonia is difficult to quantify, as the bacteriological cause cannot be determined in most cases of pneumonia. In addition to pneumonia, the pneumococcus causes a variety of other conditions ranging from meningitis to benign febrile bacteraemia and otitis media. While recognition of pneumococcal meningitis is relatively straightforward, the more common but less serious manifestations are difficult to identify as pneumococcal in origin, and as a result, the epidemiology of these conditions in developing countries is poorly understood.

To make matters more complex, there are at least 90 different serotypes of pneumococcus, which vary in their pathogenic potential. Existing vaccines are serotype-specific, covering the most important seven to eleven serotypes (in the case of conjugate vaccines) or 23 serotypes (in the case of polysaccharide vaccines). Uncertainty as to the true burden of vaccine-preventable disease is likely to become a major obstacle to the introduction of pneumococcal vaccines and may lead to future trials being set up to demonstrate the vaccine-preventable burden of disease, rather than the efficacy of the vaccine.

At present there are three types of pneumococcal vaccine, either available or under development:

1. **Pneumococcal polysaccharide vaccines.** These vaccines have been available for 20 years and cover the most important 23 serotypes. They are inexpensive, are only used at present for high-risk individuals and the elderly in industrialized countries, are poorly immunogenic in young children, and have unclear value for children in developing countries.
2. **Pneumococcal conjugate vaccines.** These vaccines have been designed to overcome the poor immunogenicity of the polysaccharide vaccine in young infants. One conjugate vaccine is licensed (7-valent Pnc-CRM, Prevenar, Wyeth Vaccines), but lacks two important serotypes for developing countries (types 1 and 5) and is expensive (currently \$US 50 per dose for four doses). New pneumococcal conjugate vaccines under development cover 9 or 11 serotypes, potentially preventing a larger proportion of pneumococcal disease in developing countries, and one new product may also prevent disease due to non-typable *Haemophilus influenzae*, another important cause of pneumonia, and otitis media.

¹ Prepared by Dr Kim Mulholland

3. **Pneumococcal common protein vaccines.** This new class of vaccines, which is currently under development, aims to prevent pneumococcal disease by raising antibodies against the capsular proteins. These vaccines would not have the problem of serotype specificity, as these proteins are represented on all serotypes. Furthermore, they could be produced relatively simply in large volumes at low cost. At an individual level, the degree of protection offered by these vaccines is likely to be less than for the conjugate vaccines, but their public health impact may be greater.

General ethical considerations

The most profitable market for pneumococcal vaccines, i.e. the market in industrialized countries, is where they are needed least. This fact increases the potential for serious ethical concerns in any attempt to achieve two possibly conflicting goals: (a) to make profits in the industrialized world, and (b) to make vaccines available in developing countries. Most would consider it unethical to evaluate a pneumococcal vaccine in a developing country with the aim of licensure and distribution in the industrialized world. However, it is essential that these vaccines *be* evaluated in developing countries to establish their public health value in those settings. Indeed, the demonstration of efficacy in such settings may provide important moral and political pressures to find ways to make the vaccines available at affordable cost. This complex ethical environment requires that there should be substantial public sector involvement in any pneumococcal vaccine trial conducted by industry in a developing country. This is particularly the case where industry draws together groups of relatively inexperienced investigators into large multi-centre studies.

Furthermore, pneumococcal vaccine trials in developing countries are usually reviewed by multiple ethical committees. Ethical review in the country hosting the trial is essential. Although it is generally the case that any one ethics committee has the power to veto the conduct of a trial, it is important to find ways of ensuring effective dialogue among different ethics committees so that their respective positions can be mutually appreciated and compromise positions can be sought, where possible. In some areas, it is appropriate for the committee(s) in developing countries to have the major input, such as the form and process of obtaining informed consent and the level of care to be provided to trial participants, including the choice of the comparator in trials of new vaccines.

Some specific ethical problems

The existence of an “effective” vaccine

It has been argued that the existence of an effective vaccine precludes the conduct of a controlled trial unless the trial is a comparison with the existing vaccine (see Helsinki Declaration, paragraph 29). In the case of pneumococcal vaccination, the issue is unclear, as different vaccines may be more or less effective under different conditions. The 7-valent conjugate vaccine, the only pneumococcal conjugate vaccine currently licensed, may be highly effective in the United States but less so in Africa, where patterns of disease and the range of responsible serotypes is wider. With regard to pneumococcal polysaccharide vaccine in children, there are doubts about its effectiveness, though it may be argued that it is effective based on data from Papua New Guinea. There have been no calls for the use of this vaccine in control groups for pneumococcal conjugate vaccine trials in the United States or elsewhere. Had such vaccines been used in the US trials, some of the results would have been very difficult to interpret, as the efficacy of the polysaccharide vaccine is unknown.

On the other hand, the 7-valent conjugate vaccine has been proven effective in the United States. This means that future improved conjugate vaccines (with 11 or more serotypes) cannot be tested against placebo in the United States, as this would deny the placebo recipients a vaccine to which they are entitled. The FDA has suggested that improved vaccines can be licensed based on immunogenicity. However, despite its immunogenicity appearing to be adequate, the serotype 19F component of Prevenar may have relatively poor efficacy compared to other serotypes. At present, producers of new pneumococcal conjugate vaccines are planning trials in developing countries. This strategy may be motivated in part as a means of bypassing the problem of evaluation in the United States, and therefore could raise difficult ethical issues.

In the Gambia, which may be typical of many countries in sub-Saharan Africa, rates of pneumococcal disease, pneumonia and mortality are high. In response to this, a trial with the 9-valent vaccine has been designed to yield vital information for the use of pneumococcal vaccines in the Gambia, the results of which will have relevance elsewhere in Africa. Can such a trial be conducted with a placebo as the comparator? If the trial was conducted with Prevenar as the control vaccine, the pneumonia impact would be difficult to interpret, and a huge trial would be needed to measure an impact on bacteriological outcomes, as only the impact on disease caused by serotypes 1 and 5 could be measured. Under such circumstances, the trial would never be done. The Gambian Ethical Committee considered that the conduct of a trial with an unvaccinated control group was ethically justified because: (a) Prevenar is unavailable in the country and (b) a demonstration of high efficacy in the trial would facilitate the introduction of pneumococcal vaccination into the country and into other countries in Africa.

Ethical considerations would be even more complex if the vaccine were available in the private sector of the country. In the case of Prevenar, it could be used in the private sector, justified on the basis of prevention of invasive disease. But from the point of view of the Gambian Government, it is seeking a pneumococcal vaccine that can be used in the general community and will have its primary impact on pneumonia. Prevenar is not considered ideal or suitable for the country on the grounds of its limited serotype coverage, and its unknown value for the prevention of pneumonia. Any trial designed to measure impact on pneumonia, in which it was proposed to use Prevenar as a control vaccine, is likely to be difficult to interpret, and would not be conducted – with the unsatisfactory result that the county/region would not obtain the information necessary to facilitate pneumococcal vaccination.

In the case of the common protein vaccine, which will be entering large field trials in the coming years, the situation would be similar, but may be made more complex by the existence of a conjugate vaccine formulation more suitable than Prevenar for use in developing countries. All these situations need to be considered on their merits, applying ethical principles in a way that protects individuals and communities from exploitation, but does not obstruct processes that will lead to the use of the vaccine in developing countries.

Availability of the vaccine after the trial

An important issue is the access of the community and/or the country that hosted the trial to the vaccine after the completion of the trial. The aim is to ensure that those participating communities and countries benefit from hosting a trial and have first call on the interventions that result from the trial. Vaccine availability after the trial is a desirable principle, but the nature and extent of the obligation on trial sponsors, those conducting the trial and the local public health service is not clear, and the situation may depend on the product and the country concerned. Mechanisms for ensuring provision of the vaccine to the

community after a trial can take a number of forms. In all cases, sustainability should be the goal.

The minimalist approach is simply to provide the vaccine for the control group. This approach is popular with companies and funding agencies as it seems to fulfil their responsibility to the community, but it may have drawbacks (see below). Another approach is to provide the vaccine for a fixed period to the community or geographical area that supported the trial, either for free or at a greatly reduced price. If this is done, it should be for sufficient time to allow other funding sources for sustained provision to be found. It should also deal with issues of equity within the country. (In the Gambia, the Government has insisted that the vaccine be donated for at least five years in order to give the Government time to find other sources to fund vaccine purchase.) A more extreme view holds that the community that supports a vaccine trial that results in the licensing of a profitable vaccine owns some part of the intellectual property of that product and should be rewarded accordingly.

Vaccination of the control group/duration of follow-up

Children and families in developing countries who participate in vaccine trials should benefit from the experience, apart from the known probability of receiving an active vaccine. In many settings, the improved health care that is necessary for the conduct of the trial provides a significant benefit. In some settings, a control vaccine is provided in place of a placebo.

There is also the obligation to provide the candidate vaccine to the control group, should it prove effective (see Declaration of Helsinki, paragraph 30). However, vaccination of the control group at the end of the trial may be questionable in the case of pneumococcal vaccines. For the individual children who were in the control group, there may be some benefit, but it would be limited, as they would be well past the age of highest risk by the time such a decision could be made.

The main disadvantage of provision of the vaccine to the control group is the loss of follow-up information, both for long-term efficacy and for safety. The risk of pneumococcal disease falls to low levels after the age of three years in many developing countries, but the duration of effectiveness up to this time will be an important issue influencing whether or not pneumococcal vaccines are introduced into vaccination programmes. At most sites, passive follow-up for invasive cases could be achieved with relatively little input, and the detection of even a small number of late cases may be enough to provide insight into the duration of protection achieved from the vaccine.

Perhaps of greater importance is the potential safety value of continued follow-up. The anti-vaccine lobby has rightly criticized trials for paying insufficient attention to long-term follow-up for unexpected serious adverse events. Administration of the study vaccine to the control group naturalizes the most effective tool available for detecting unexpected late serious adverse events.

Future issues

It is clear that more pneumococcal vaccine trials are needed. If the trials are to be “equivalence trials” in which a new product is compared with an existing product, they are likely to be large and expensive. Such trials can only be conducted validly if the effectiveness of the existing product against the end-points of primary public health interest (radiological pneumonia and mortality) is known. At present, for the currently available

conjugate vaccine, neither of these is known with any certainty. However, this will eventually be possible, as further studies to determine the effectiveness of existing vaccines will be required.

Even if the efficacy of the vaccines is established, doubts about the vaccine-preventable disease burden may persist and stand as a barrier to the introduction of the vaccines, as it is today with Hib vaccine, particularly in Asia. Randomized trials designed to determine the burden of disease (sometimes called “vaccine probe” studies) are already being conducted in Asia for Hib vaccine. Provided they have full support of the governments and communities concerned, such studies are ethical where the vaccine would not be otherwise available for the community. In the future, it is likely that a number of such trials will be conducted with pneumococcal vaccines (conjugate vaccines, polysaccharide vaccines or combined regimens). All will add to the understanding of pneumococcal disease and its prevention by vaccination, but their interpretation will be tempered by the knowledge that the epidemiology of pneumonia and pneumococcal disease varies greatly among communities, and so will the potential impact of a vaccine.

At this time in the development of pneumococcal vaccination, there is an urgent need for more high quality research in developing countries. Ethical considerations must always include consideration of the wider public health benefits that will accrue from trials. Every attempt should be made to conduct such research with appropriate ethical review and appropriate partnership among industry, developing country governments, and national and international public health groups.

Annex 5:

Some ethical considerations regarding rotavirus vaccine trials in developing countries¹

Rotavirus epidemiology

Rotavirus is the leading cause of severe diarrhoea in infants and young children worldwide, accounting for approximately one third of cases of severe diarrhoea requiring hospitalization. Although rotavirus causes relatively few deaths in industrialized countries, it results in approximately 400 000–600 000 deaths per year among children in developing countries. Thus, although the need for a rotavirus vaccine exists in both settings, the potential life-saving benefits of vaccination will be substantially greater in developing countries.

The experience with Rotashield

In 1998, the first rotavirus vaccine, Rotashield, was evaluated in a phase III trial. It was then licensed in the United States and was recommended for universal immunization of all American children. However, less than one year after its licensure, the use of Rotashield was suspended following reports of intussusception at a rate estimated to be 1 case per 2 500 to 11 000 vaccinated infants. Though some subsequent estimates put the risk substantially lower than this, the manufacturer voluntarily withdrew the vaccine from the market. It remains licensed.

Because insufficient data existed at the time to make a recommendation for use of Rotashield in developing countries, these events presented several ethical quandaries to the international community: (a) Should randomized controlled trials of Rotashield, which have already been started, continue in developing countries? (b) Could a vaccine that had been withdrawn from the US market be tested in developing countries? (c) Would it be unethical to stop trials that were evaluating a vaccine that could potentially save the lives of hundreds of thousands of children?

Proponents of continuing trials of Rotashield in developing countries argued that the potential benefits far exceeded the risks posed by the vaccine. It was estimated that widespread global use of Rotashield could result in 4 000 to 6 000 deaths per year due to intussusception, which is 100-fold less than the global mortality from rotavirus. In addition, it would not be known until large trials with future vaccines are conducted whether intussusception is a side-effect specific to the rhesus rotavirus vaccine or could occur with other vaccines.

At the same time, however, concerns were raised that it would be morally and politically unacceptable to test a vaccine in developing countries that had been withdrawn from the US market. Others counter-argued that making the standard of care in the United States the universal standard of care would only perpetuate the unjust distribution of healthcare resources globally.

¹ Prepared by Dr Umesh Parashar

Although a complete consensus was not obtained, it was recommended that it would be ethical to continue testing of Rotashield in developing countries, provided vaccine would be available for use if it were found acceptable in clinical trials and provided the children in the trial were adequately covered to the detection and management of intussusception. However, following the manufacturer's decision to stop the production of Rotashield, this vaccine was not tested further and is no longer available today. The Rotashield experience highlights the need to anticipate and address as early as possible key ethical issues related to testing of future rotavirus vaccines.

Ethical issues in trials of future rotavirus vaccines

Simultaneous testing of rotavirus vaccines in developing and developed countries

The experience with Rotashield has demonstrated that simultaneous testing of rotavirus vaccines in industrialized and developing countries should be encouraged so that the risk-benefit ratio of the vaccine can be evaluated in each setting. While few would argue against simultaneous testing, proposing such testing is easier than implementing it. Besides issues of availability and economics, concerns regarding vaccine safety may discourage vaccine manufacturers from testing vaccines in settings where the higher background rate of morbidity and mortality could "tarnish" the vaccine file submitted for licensure in developed countries.

Use of a rotavirus vaccine in control groups in clinical trials once a licensed product is available

Two leading candidate rotavirus vaccines are currently in phase III clinical trials. As no rotavirus vaccine is currently available, it is ethical to use a placebo in the control group of ongoing vaccine trials. Once data demonstrating reasonable vaccine safety and efficacy are obtained for one or more of these products and they are licensed, issues will arise with respect to the appropriate control arm in the evaluation of subsequent candidate vaccines. In particular, consideration will have to be given to the ethical acceptability of using a placebo or one of the licensed vaccines in the control group. Several factors might need to be considered, including the local standards on use of rotavirus vaccine, the need to conduct a local trial in a given country to ensure adoption of the vaccine by the national immunization programme, and other factors, such as vaccine price and local availability, that might influence the acceptability of the vaccine by the host country.

The impact of the withdrawal of Rotashield on future rotavirus vaccine trials

Vaccine manufacturers undertaking trials of newer rotavirus vaccines are now faced with two compounding obstacles. First, enrolment in trials is hampered by the fact that a significant adverse event was associated with a previous rotavirus vaccine. At the same time, to meet regulatory requirements in industrialized countries, large clinical trials involving more than 50,000 children are being conducted to evaluate the association of these vaccines with an uncommon adverse event such as intussusception. The large size of trials will not only prolong their duration and delay the availability of the next rotavirus vaccine, but will require substantial investment, which in turn would likely increase the price of the licensed vaccine. The ethical issue is whether the regulatory hurdle that needs to be overcome is operating in the best interests of society, particularly, in the interest of children in developing countries, who are in urgent need of an affordable and effective rotavirus vaccine. In addition, it raises the question whether clinical trials of this size will become the norm for all future rotavirus vaccines, including those that are developed and produced specifically for developing country markets.

Availability of vaccine after completion of trials

Perhaps one of the most challenging ethical issues concerns the availability of a proven rotavirus vaccine after completion of clinical trials. Specifically, what are the roles or responsibilities of researchers and trial sponsors to work with vaccine manufacturers, international and national health organizations, and economic development agencies to ensure vaccine supply and availability? Most would agree that trial participants who receive placebo should be offered vaccine after it has been shown to be safe and efficacious, if they are still at an age when they are at risk for severe rotavirus disease. Once it is licensed, should the vaccine also be offered to other at-risk populations in the host country? How about similar populations in other developing countries? Discussions surrounding these complex issues should begin early in planning of the trial so that data that would be relevant to decision-making (e.g. economic data) could be collected during the trial.

In summary, an urgent global need exists for safe and effective vaccines against rotavirus. Ethical issues related to the development and testing of these vaccines should be identified early so that they can be resolved through dialogue among the involved parties under the leadership of international health organizations and ethical bodies.