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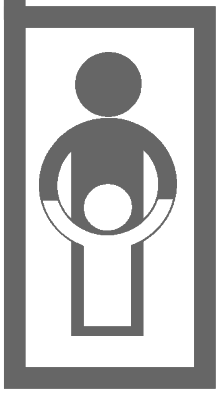
Report of the meeting on future directions for rotavirus vaccine research in developing countries

Geneva, 9–11 February 2000



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Copies may be requested from:
World Health Organization
Department of Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* + 41 22 791 4192 • *E-mail:* vaccines@who.int •

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Abbreviations

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
AIIMS	All Indian Institute of Medical Science
CDC	Centers for Disease Control and Prevention (USA)
CIOMS	Council for International Organizations of Medical Sciences
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration (USA)
GMP	good manufacturing practice
Hib	*Haemophilus influenzae*
HMOs	health maintenance organizations
IOM	the United States Institute of Medicine
IRR	intussusception relative risk
IVI	International Vaccine Initiative
LLR	rotavirus lamb strain
LPS	lipopolysaccharide
MMWR	Morbidity and Mortality Weekly Report
NIH	National Institutes of Health (USA)
NIP	CDC's National Immunization Program
NRA	national regulatory authorities
OPV	oral polio vaccine
ORT	oral rehydration therapy
RR	relative risk

RRV-TV	Rhesus rotavirus vaccine-tetra valent
UCLA	University of California Los Angeles
VAERS	Vaccine Adverse Event Report System
VAPP	vaccine-associated paralytic polio

1. Introduction

A meeting was convened in Geneva during 9–11 February 2000 to discuss issues related to future rotavirus vaccine research in developing countries. It was attended by members of international agencies and ministries of health, university-based scientists, industry representatives, public health officials and others. The aim of the meeting was to review the recommendations made in 1997 in light of the recent developments regarding the safety of currently licensed rotavirus vaccine, and to produce an agenda for future activities. A summary of the meeting is provided below.

We wish to acknowledge the generous support of the Children's Vaccine Program of the Bill and Melinda Gates Foundation for this meeting.

2. Background

Rotavirus is the most common cause of severe, dehydrating gastroenteritis among children worldwide, resulting in approximately 600 000 deaths each year. Most of these deaths occur in developing countries where access to rehydration therapy and other medical care may be limited.

Because of the dramatic disease burden associated with rotavirus and the fact that rotavirus is not likely to be prevented by improvements in hygiene and sanitation, efforts to develop vaccines against rotavirus have been under way since the early 1980s. With the impending licensure of the first rotavirus vaccine, WHO, together with Children's Vaccine Initiative and the Centers for Disease Control and Prevention, hosted a consensus workshop on rotavirus vaccines for developing countries in January 1997.

The goal of the meeting was to develop a list of activities to expedite the introduction of rotavirus vaccines into developing countries. From that meeting, four groups of activities were proposed, including: establishing studies to define rotavirus-associated disease burden and strain prevalence; conducting trials to address remaining issues related to the immunogenicity and effectiveness of rotavirus vaccine in developing countries; establishing plans to address issues related to inclusion of vaccines into the Expanded Programme on Immunization (EPI); and taking steps to address regulatory and supply issues related to introduction of new vaccines in these settings. Several of these activities have been carried out or are ongoing. In August 1998, the first rotavirus vaccine to be approved was licensed in the United States and was recommended for all United States infants as part of their routine immunization schedule. However, these recommendations were suspended in July 1999 and withdrawn in October 1999 following the discovery of an association between receipt of the vaccine and the development of intussusception. The withdrawal of the only licensed rotavirus vaccine has led to the need to reassess the priority activities derived at the previous meeting.

3. Minutes and summary of the meeting

3.1 Opening of the meeting

Dr Michael Scholtz opened the meeting with a welcome to participants. He said that the discussions in the next three days would be built on the idea that rotavirus vaccines are of value in both developed and developing countries. He reminded the group that a meeting at WHO in 1997 resulted in recommendations for further studies to determine the disease burden associated with rotavirus, to conduct efficacy trials in Asia and Africa, and to design surveillance that could be used to evaluate vaccines once introduced. There are 650 000 estimated deaths from rotavirus each year in the world, or one every minute. Because of this, there is an urgent need to develop rotavirus vaccines for less-developed countries, and this will require some risk taking on the part of industry. He remarked that the importance of this subject was reflected by the fact that this meeting, originally scheduled for 35 people, was being attended by 120 people. He gave thanks to the meeting organizers and sponsors.

Dr Mark LaForce also welcomed the group and outlined the format and agenda of the meeting. He introduced the five working groups that would create recommendations for their respective areas.

3.2 Overview of the issues

Dr Bernard Ivanoff then provided an overview of the main issues that the participants would be asked to address. He reviewed the history of rotavirus vaccine, noting that the efficacy of Rotashield, the only currently licensed vaccine, was 85–90% against severe disease and about 55% against all rotavirus gastroenteritis. The vaccine was licensed in August 1998, but recommendations for its use were withdrawn by the Advisory Committee on Immunization Practices (ACIP) in October 1999 following the identification of the association between the vaccine and intussusception. Despite the withdrawal of the vaccine, an urgent need exists for an effective vaccine in developing countries, where 650 000 children die each year from rotavirus gastroenteritis. Data are needed on the incidence and risk factors for intussusception in developing countries, as well as the attributable risk of intussusception with the current vaccine. In addition, a need exists to address the question whether intussusception will be associated with all rotavirus vaccines, and whether alternative vaccine schedules might be used to minimize or negate the risk.

Epidemiological issues that need to be addressed include the addition of surveillance for intussusception into any new vaccine trials and rotavirus disease burden studies. The answers to many of the epidemiological questions concerning rotavirus and intussusception will influence future trial design and directions for disease burden studies. Important regulatory and supply issues include the question of who will make

vaccines for developing countries, and whether local production can be used to expedite vaccine introduction. Finally, ethical questions will be addressed at this conference including whether a vaccine withdrawn by United States authorities and by the manufacturer can be used in developing countries. Alternatively, is it ethical not to use a vaccine in developing countries that we think is likely to be effective in reducing rotavirus-associated mortality? Dr Ivanoff reminded participants that 70 children die every hour in the developing world from rotavirus diarrhoea, and these data should be included in any risk-benefit analyses of rotavirus vaccination.

Dr Ivanoff reviewed the WHO-sponsored activities designed to expedite decisions regarding rotavirus vaccines for developing countries. These included several surveillance studies and surveillance networks, including those in Africa and Asia. WHO has also sponsored several vaccine evaluations, including trials in Bangladesh, Guinea-Bissau and India. Many of these studies have been delayed pending more information on intussusception.

4. Background information

4.1 Background on rotavirus and rotavirus vaccines

Dr Roger Glass provided a review of the disease burden associated with rotavirus and the history of vaccine development. He stated that rotavirus is the most common cause of severe gastroenteritis in the world, causing about one-fourth of all deaths among children from diarrhoeal diseases. Both in developed and developing countries, rotavirus also causes one-third of all hospitalizations for acute gastroenteritis. Rotavirus infects all children in the world by the age of five, indicating that disease transmission will not be limited by improvements in sanitation and hygiene, but that vaccines offer the best hope of disease reduction. He reviewed new global estimates of disease. In India alone, 140 000 children die annually, or about one child in every 200. Overall, approximately 111–135 million cases of rotavirus infection occur each year, leading to 650 000 deaths (or about 1 in 225 children). Most deaths occur in the Indian subcontinent and sub-Saharan Africa and, to a lesser extent, South America.

He reviewed a timeline of important events in rotavirus. In 1979, WHO's former Programme for Control of Diarrhoeal Diseases (WHO/CDD) listed for the first time the prevention of rotavirus disease as one of its goals. Six years later, in 1985, the United States Institute of Medicine (IOM) wrote that rotavirus vaccine development is a high priority for developing countries. In the same year, Feachem and DeZoysa published a paper outlining the disease burden associated with rotavirus. The estimates for mortality from this study were used for the next decade. In 1996, rotavirus was listed as a "best buy" for developing countries in a report for WHO and other agencies chaired by Dr Tore Godal.

However, even though the international community was convinced that rotavirus is an important problem for children in developing countries, support for prevention of rotavirus in developed countries was not significant. The same year (1996), the IOM issued a report claiming that rotavirus was not a high priority for prevention in the United States. This report was based on a dearth of good epidemiological data, and highlighted the need for disease burden research in the United States. Because of this, Dr Glass' group at the Centers for Disease Control and Prevention (CDC) and other United States investigators, conducted a series of investigations between the mid-1980s and late 1990s to better define the disease burden associated with rotavirus. CDC used the epidemiological pattern of rotavirus, the known age distribution and the wintertime seasonal peaks to convert national hospital and mortality data into rotavirus-specific disease estimates. Using these methods, they found that rotavirus accounts for 65 000–70 000 of the 175 000 hospitalizations for acute gastroenteritis in the United States. And although the deaths associated with rotavirus (20–40 each year) have decreased dramatically during the last two decades, hospitalizations have remained quite stable. These methods have been duplicated in other developed countries to show that rotavirus

is an important cause of childhood hospitalizations worldwide; however, data from Europe indicate that rotavirus hospitalization rates are about twice those in the United States presumably because of differences in health-care delivery. CDC has also conducted cost-effectiveness analyses of a vaccine programme in the USA which demonstrated that rotavirus results in more than US$ 1 billion in total societal costs each year, and that a vaccination programme would result in an overall cost savings.

Rotavirus vaccine is expected to prevent rotavirus disease similar to the protection induced by natural infection. A Mexican study has demonstrated that a child may have as many as five infections with rotavirus during the first two years of life, but that each infection confers greater protection. After the first infection, 88% of children are protected against severe gastroenteritis, and less against any rotavirus diarrhoea. Following the second infection, virtually all children are protected against severe disease and most are protected against any rotavirus disease. So, a good vaccine should mimic a natural infection.

The first vaccine to be tested was RIT 4237, a monovalent bovine strain, which was given as a single dose to 86 children in Finland by Dr Timo Vesikari. The vaccine was 50% protective against any rotavirus disease and 88% protective against diarrhoea lasting more than 24 hours. This early trial illustrated important lessons that would be used in later vaccines. First, even though the vaccine was poorly immunogenic, efficacy was good. Second, protection could be heterotypic – a bovine rotavirus strain could induce protection against a human strain. Finally, efficacy was greater against severe disease than against milder disease. However, this vaccine was found to be poorly efficacious when tested in less-developed countries and further development was halted. In retrospect, many of the studies of RIT 4237 in developing countries may have had design flaws that prevented a true evaluation of their efficacy, including not evaluating protection against severe disease, poor disease surveillance, and vaccination of children who had already been naturally infected.

One of the next vaccines tested was RRV, a serotype-3 rhesus strain. It was tested in several settings, but fared best in a study in Venezuela during which serotype 3 viruses were circulating. This led to the hypothesis that serotype-specific immunity may be important for protection, and resulted in the development of human-animal reassortant vaccines.

Reassortant strains were produced containing VP7 and VP4 proteins that represent the four common circulating strains. Recently, reassortants for G9 strains have been produced as well, since these have become the third or fourth most common strains identified in the USA. A trial in Finland with a tetravalent RRV-TV human-rhesus reassortant vaccine demonstrated an efficacy of 68% against any diarrhoea, 91% against severe diarrhoea, and 100% against hospitalizations. Importantly, the vaccine was also efficacious when tested in Venezuela. So, the vaccine efficacy was consistently efficacious in trials in both developed and developing countries. The main adverse event reported in pre-licensure trials was fever, which was self-limited. As a result, based on data from several trials, RRV-TV (Rotashield) was licensed in the USA by the Food and Drug Administration (FDA) in August 1998, and introduced into the routine schedule of immunizations by ACIP and the American Academy of Pediatrics (AAP).

Dr Glass pointed out differences in the epidemiology of rotavirus between developed and less-developed countries that make evaluation of vaccines in both settings necessary. Children in developing countries become infected much earlier in life (possibly necessitating earlier vaccination), they more commonly have mixed infections, and

they are more likely to have infections with uncommon serotypes. So study designs of vaccine trials in developing countries must keep these differences in mind.

Dr Glass reviewed the recommendations of the WHO-sponsored meeting on Future Priorities in Rotavirus Research in 1997. Following that meeting, WHO recommended: 1) developing surveillance activities to establish disease burden in developing countries that could be used, in part, to educate decision-makers; 2) confirming vaccine efficacy in Asia and Africa, where mortality from rotavirus is highest; 3) optimizing vaccine-delivery issues; and 4) establishing effectiveness in developing countries where the vaccine is given as part of an EPI programme. Data to address several issues related to introduction of new vaccines were lacking at the time of this meeting, and are still needed. These include whether vaccines would be equally effective in developed and developing country settings, whether they would work against a variety of serotypes uncommon in developed countries, and whether alternative schedules would be required to optimize effectiveness in developing countries.

A WHO agenda of activities included: vaccine trials in Bangladesh, Guinea-Bissau and Malawi; a study to evaluate the immunogenicity and safety of neonatal administration of vaccine in India; a study of an Indian strain vaccine in India; and a study of whether zinc supplementation might enhance immune response to vaccine in Bangladesh. These studies commenced but have been put on hold because of the investigation into the association between RRV-TV and intussusception.

Dr Glass reviewed the timeline of important events regarding the recognition and investigation of RRV-TV and intussusception. He first noted that the causes of intussusception are very poorly understood and include infections, anatomic factors, and altered motility. Before licensure, cases of intussusception were recognized among vaccine recipients; however, only two persons received the licensed formulation of the vaccine. The reasons that the vaccine might be associated with such an adverse event are unknown. One might expect that the phenomenon is an effect of a rotavirus infection. However, in review of sparse data on the possible association between natural rotavirus and intussusception, no such association is obvious. Three case series have been conducted which found that 8–37% of intussusception cases have some evidence of acute rotavirus infection. However, no study reported rates among comparison populations. In addition, ecological studies revealed that no seasonality exists for intussusception in the United States , whereas rotavirus has distinct wintertime peaks.

One other potential problem with studies of vaccine and intussusception is the variability in incidence of background intussusception in the United States. Dr Glass' group reviewed data from six surveys that found rates among US infants ranged from 37–74 per 100 000 per year. And data from the Indian Health Services demonstrate that rates are changing over time, with dramatic decreases in rates in this population over the past 20 years. So, in developing countries, patterns of intussusception may be quite variable and different from developed countries. Mortality associated with intussusception is quite low in the USA, probably because of better access to care. Deaths that do occur in the USA are associated with indicators of low socioeconomic status.

The age distribution of intussusception shows a peak between four and eight months. Cases in children under three months of age are uncommon, possibly because of the protective effects of maternal antibody, the capacity for development of lymphoid hypertrophy or decreased exposure to infectious agents. Perhaps we can use this age distribution to design a vaccine schedule for rotavirus that minimizes the risk of intussusception. Factors that might alter the risk of vaccine-associated intussusception

in developing countries include increased exposure to enteric infections, malnutrition, feeding habits, altered bowel wall thickness caused by malnutrition, and differences in gastrointestinal motility.

Dr Glass pointed out that a live, oral rotavirus vaccine might be more safely administered as part of a vaccination programme if we could give the first vaccine earlier in life when the baseline risk of intussusception is lower. In addition, we might educate physicians about the symptoms of intussusception and about seeking earlier intervention. Alternative vaccine approaches, such as the development of strains that result in less viral replication or use inactivated vaccines might be considered. Since many of the candidate vaccines are live oral vaccines, a need exists to learn more about the mechanisms of RRV-TV-associated intussusception.

Dr Glass finished with a possible timeline of candidate vaccines that indicated that newer live oral vaccine (such as 89-12 and bovine-human reassortants) will not be available to developing countries for four to seven years, and other candidates for possibly longer than seven years. Because of this, participants of this meeting should consider the risks and benefits of the current vaccine for use in developing countries, as the rotavirus disease burden in developing countries will still be present in this long interim.

Discussion of the presentation

Significant discussion was addressed to the question of whether multivalent vaccines were needed for protection, and if so which strains should be included. A reference to the emergence of serotype 9 strains was made. The issue is obviously controversial, exemplified by the presence of both monovalent and polyvalent vaccine candidates. Several participants reported data to support the need for multivalent vaccines, citing both results of trials in which multivalent and monovalent vaccines were tested as well as data demonstrating the importance of serotype-specific immunity in protection.

Some discussion followed on whether non-vaccine approaches might be pursued to decrease diarrhoeal disease mortality in place of vaccines. It was noted that despite introduction of oral rehydration therapy (ORT) programmes more than 20 years ago, significant mortality from diarrhoea remains. This point was echoed by investigators from developing countries.

Finally, a question was raised about whether earlier rotavirus vaccination might be problematic in the presence of high maternal antibody level that would interfere with vaccine take. Evidence from previous trials was cited to point out that immune responses in neonates were relatively low compared to older infants, but that protection was good. Also noted was the experience of Dr Ruth Bishop in Australia, who demonstrated that infection with a neonatal strain conferred protection in infants in Melbourne.

4.2 Mortality from rotavirus disease in developing countries and policy evaluation of rotavirus vaccines

Dr Mark Miller reviewed a study that he has recently completed on worldwide mortality associated with rotavirus. He used modelling to estimate mortality associated with rotavirus because of the lack of quality, direct data. The model incorporates country-specific data where available, and uses these data to estimate disease burden in countries with similar socioeconomic status. He used hospital-based data to establish the

proportion of severe disease associated with rotavirus, then combined these data with mortality rates associated with diarrhoeal disease from a collection of 52 studies to arrive at rotavirus-specific mortality.

He stratified countries by income level in all analyses presented. The proportion of hospitalizations associated with rotavirus were:

- 19% – low-income countries (< US$ 600/year)
- 22% – low-middle-income countries (US$ 600–1700/year)
- 23% – upper-middle-income countries (US$ 1700–8000/year)
- 22% – upper income countries (>US$ 8000/year)

Overall, he estimated that 418 000 to 520 000 deaths from rotavirus occur each year in the world among young children, and that these deaths are concentrated in low-income and low/middle-income countries, particularly China, India and sub-Saharan Africa. All estimates are conservative, and the model is intentionally biased to minimize disease burden.

In modelling the effectiveness of a potential vaccine programme, Dr Miller used data from published RRV-TV vaccine trials to estimate vaccine effectiveness, together with data on distribution of severe rotavirus disease and vaccine coverage from published surveys. Vaccine efficacy varied between 30% in low-income countries to 75% in high-income countries. Similarly, published reports were used to estimate case-fatality rates associated with intussusception, and ranged from 20% in low and 0% in high-income countries. Risks of vaccine-associated intussusception were taken from preliminary United States investigation results. The results of his study include the data in Table 1.

Table 1: Effectiveness of a potential vaccine programme indicated by death rates with and without vaccination

Country type	Annual RV-assoc. deaths	Prevented RV-assoc. deaths	Vaccine-associated intussusception deaths
Low income	347 000	80 000	3 200
Low–middle	60 000	15 000	500
Upper–middle	10 000	5 000	0
High	0	0	0
Total	417 000	100 000	3 700

Dr Miller reminded the meeting that the model incorporated data designed to provide the most conservative estimates of vaccine benefit. Better data were needed for many of the variables, including vaccine efficacy in developing country settings, comparison of the cost of vaccination versus other interventions designed to prevent diarrhoeal mortality (including improved water and sanitation, micronutrient supplementation and standard dehydration treatment protocols), and a timetable for implementing new vaccine programmes. Data that will be important for policy considerations include whether the vaccines are effective in diverse populations, definition of the appropriate

outcomes to be measured in trials, the ethical considerations surrounding the issues of commission versus omission of an intervention, and the economics of rotavirus vaccination.

Discussion following the presentation

Significant discussion following Dr Miller's presentation concerned the assumptions made in the model. It was noted that the data on risks of intussusception in the model arise from United States data, and that determination of the rates of intussusception in developing countries should be a research priority. Similarly, further explanation of the methods used to calculate the rotavirus-associated mortality served to highlight Dr Miller's point that better disease-burden data should be collected. This is particularly true in light of data indicating a decreasing diarrhoeal mortality in some areas of the world. Even so, it was discussed that the model was most sensitive to estimates of vaccine efficacy. Other ideas for data that might be included in future models included cost of disease and treatment of intussusception and the effect of natural rotavirus on intussusception. Several participants noted that the main risk factor for rotavirus deaths was lack of access to care in developing countries.

4.3 Review of data on intussusception and RRV-TV

Dr John Livengood reviewed preliminary data from CDC's investigation of the association between RRV-TV and intussusception in American children.

He first noted that following licensure of vaccines, the National Immunization Program (NIP) at CDC assumes the responsibility of implementing new vaccine programmes. He reviewed the components of the Vaccine Adverse Event Report System (VAERS), one of the primary methods used by CDC and FDA to survey for adverse events. Intussusception was added to VAERS as a coded term in 1998, and review of past data indicated that only three intussusception cases had been reported prior to licensure of rotavirus vaccine. Following licensure, a small number of reports prompted a review of the cases, but following the Morbidity and Mortality Weekly Report (MMWR) in July 1999 on the possible association, a dramatic increase in reports occurred. The impressive features of the intussusception cases reported to VAERS were that the cases generally occurred three to seven days following vaccine and were clustered following the first dose of vaccine. All reports were confirmed by medical record review and were only counted if they occurred within six weeks of vaccine suspension. So far, 114 cases have been reported; 99 of these are confirmed cases, 14 are unconfirmed and one did not receive vaccine. Sixty of the cases occurred within seven days of a vaccination and 49 occurred following the first dose of vaccine. One fatal case was reported, and 39 case-patients underwent surgery with seven having bowel resections. Eighty-six of the cases received other vaccines along with rotavirus vaccine.

Preliminary results from a multi-state case-control study were reported. The objective of the study was to estimate the relative risk of intussusception among infants who received vaccine compared to those who did not receive the vaccine. Cases in children less than 12 months old were diagnosed with intussusception between 1 November 1998 and 30 June 1999 and identified from hospital records in participating states. Four community-based controls were matched to each case by age (plus or minus one week). Rotavirus vaccine status was assessed through provider records and parents. Overall, 2046 subjects from 19 states have been enrolled including 427 cases and 1619

controls. Some 18% of cases have received rotavirus vaccine compared to 12% of controls. Cases were 1.8 times more likely to have received rotavirus vaccine at any time than controls. Dr Livengood presented the data divided by risk windows, which demonstrated an elevated RR (relative risk) of 3–7 days (RR=24.8) and 8–14 days (RR=7) following dose 1, and following dose 2 at 3–7 days (RR=13.4). There was no increased risk before 3 days nor more than 14 days following any dose, and no increased risk following the third dose. He showed that stratification of the data by age of subject revealed no differences in risk by age of vaccination.

Dr Livengood then presented data from the case-series study and compared it with data from the case-control study. He noted that the estimates of RR defined by the different studies are quite similar.

Table 2: Comparison of data from a case-series study and a case-control study

Risk period	Case series RR	Case-control RR
Ever	1.6	1.8
3–7 days post dose 1	18.9	24.8
8–14 days post dose 1	3.6	7.1
3–7 days post dose 2	5.8	13.4

He also presented data from the case series to indicate that no definable difference in RR by age was present. CDC still plans to analyse data according to several variables that may modify the risks seen, including age, gender, socioeconomic status and others.

Finally, Dr Livengood presented preliminary data from a cohort study among children enrolled in four large health maintenance organizations (HMOs) in the United States that comprise 2% of the population. NIP has expanded this cohort to include additional HMOs to better address the study objectives. This study has three stages. Stage 1 involved the post-licensure study from a single HMO that was funded by the manufacturer. In stage 2, data from six HMOs were analysed. Stage 3 includes plans to expand this network to 10 HMOs. In the cohort studies, intussusception cases were identified by ICD-coded hospitalizations for intussusception and procedures consistent with intussusception cases. Charts were reviewed to verify cases. Data from Stage 1 indicated an elevated risk of intussusception among vaccines within 1 week of a dose, but included a small number of cases. Stage 2 included six HMOs who had received at least 1000 doses of vaccine and in which access to medical records could be assured. In this larger cohort, 62 cases of intussusception have been identified in the vaccinated and never-vaccinated groups. When the data were analysed by risk windows following receipt of any dose of vaccine, the age-adjusted intussusception relative risk (IRR) was elevated in the 3–7 days following vaccination, compared to unexposed children. Only one site contributed data for a longer follow-up period, which indicated no compensatory decrease in vaccinated children following the period of higher risk (although with very little data).

In conclusion, Dr Livengood stated that rotavirus vaccine was associated with the occurrence of intussusception in children, and the risk was highest 3–7 days following vaccination. He said that the expansion of the HMO network will be a helpful tool in

this outbreak and could be used in subsequent studies when appropriate. NIP has further plans to continue follow-up of the HMO cohort for 12 months, and will work to determine background rates of intussusception and risk factors for intussusception in the United States. He concluded that given the magnitude and consistency of the risks defined, the association appeared causal. He concluded with calculations for the number of attributable cases. NIP estimates that an excess of 888 cases of intussusception would have occurred if an entire birth cohort of American children would have been vaccinated, and mostly in the three to five-month age group.

4.4 Pathogenesis of intussusception associated with RRV-TV

Dr Paul Offit then addressed the potential pathogenesis of intussusception related to RRV-TV. First, the risk of intussusception is clearly elevated during the first 3–7 days after vaccination. This finding suggests that intussusception is related to viral replication, which would be expected at about the same time. Second, risk predominantly follows the first dose, and does not vary according to age of the infant at vaccination. This suggests that passively acquired maternal antibodies do not play a role in protection from intussusception in this population, for if they were protective, one should see an increasing RR by age of infant. Alternatively, if natural rotavirus were a cause of intussusception, one might see a decreasing RR associated with vaccine by age. These assume no effect of breastfeeding on risk. So the findings from these studies suggest that natural infection is not a cause of intussusception. Third, the decreasing risk following the second and third vaccinations suggests that RRV-TV receipt protects against intussusception caused by RRV-TV. In summary, these findings indicate that vaccine-associated intussusception is likely to be a strain-specific phenomenon, and not a more general product of enteric infection with rotavirus. Features of RRV that might make it more likely to cause intussusception include the finding that RRV grows in the absence of trypsin, can cause diarrhoea across species, and can cause hepatitis in immune-suppressed mice. All indicate that RRV may not be fully attenuated. Dr Offit also noted that following infection with RRV-TV, RRV is predominantly shed following dose 1, whereas G2 is more likely to be shed following doses 2 and 3.

These hypotheses bring up the corollary questions of whether other rotavirus vaccines will cause intussusception. There are two candidates in advanced development – a bovine-human reassortant and a human strain vaccine. If intussusception is unique to RRV, neither vaccine should be associated with a risk. If intussusception is caused by any non-human rotavirus strain, the bovine-based vaccine might be associated as well. If intussusception is due solely to viral replication, the human strain, which appears to replicate well, might carry an elevated risk compared to the bovine strain, which replicates poorly.

Discussion following the presentations

Discussion focused on the pathogenesis of intussusception among those vaccinated. Regarding Dr Offit's hypothesis that the phenomenon is RRV-specific, it was noted that the bovine rotavirus or bovine rotavirus-based vaccines have been associated with three cases of intussusception in trials, two in China and one in Finland. However, higher background rates in Asia were cited as reasons that these cases were likely to be sporadic. It was noted that the lack of an evident association between natural rotavirus and intussusception supports the hypothesis that infection with a heterologous strain might be the risk factor. The data for and against the association of natural rotavirus

and intussusception were reviewed to determine whether a seasonality of intussusception might be missed given the low incidence. However, CDC data from six separate data sets did not reveal a consistent seasonality. Other possibilities raised included the hypothesis that the risk may be based on receipt of other vaccines concurrently with RRV-TV, related to co-infection with other gut flora or infections, or related to the dose of viral challenge. It was noted that the relatively low risk of intussusception defined in pre-licensure trials occurred in settings where other vaccines were often not given at the same time as RRV-TV.

There was considerable discussion about these analyses presented by Dr Livengood. One participant remarked that CDC data do not differentiate between cases of intussusception that might have been caused by vaccine and those that were triggered by vaccine (that is, those that would have occurred anyway given more time). To do this, additional follow-up time of the cohort studies is needed. It was noted that since few children were vaccinated past six months of age, we can not be assured that no risk exists for these children. Little data are available to define the risks among children by race and ethnicity that might apply to children in developing countries.

The timing of viral shedding following vaccination was discussed. Participants pointed out that viral shedding following RRV-TV administration occurs primarily following the first dose, but that seroconversions occur following each of the three doses. Other participants asserted that shedding of vaccine virus after dose 1 was equal to shedding after dose 3.

The possibility that some of the questions about pathogenesis of intussusception might be addressed with an animal model was raised. A brief summary of the National Institute of Health (NIH) working group on pathogenesis found no clear evidence for a good animal model to mimic rotavirus-induced intussusception. Even if one existed, the rarity of the association would make this work very difficult. CDC is currently examining tissue samples obtained from children with intussusception, but results are not yet available. It was noted that the identification of a surrogate marker for intussusception risk for use in animal models was discussed at the NIH meeting, but that no such marker is known.

Future trials of vaccines would need to demonstrate safety of the vaccine with respect to intussusception. Although one might get a signal from a study of 16 000–20 000 children, how large a trial must be to assure FDA that a vaccine is sufficiently safe was discussed. However, several participants asserted that sample size depended on the endpoints of the study. In addressing the question of intussusception in vaccine trials in less-developed countries, it was pointed out that children are exposed to many different agents early in life in these settings and this might affect rates of intussusception. In addition, the high prevalence of malnutrition in these settings may affect the rates, and thus, the sample size of trials.

Dr LaForce remarked, in summary, that we know very little about the pathogenesis of intussusception, and that this fact is surprising and needs to be remedied.

5. Intussusception among children in developing countries

5.1 Epidemiology of intussusception

Venezuela

Dr Irene Perez-Schael reviewed data from Venezuela on intussusception. In Carabobo, of 50 000 hospitalizations among children, 21 cases of intussusception were identified for a rate of 24/100 000/year among children under 12 months of age. Of these, 81% of the cases were male and 62% were in children among the middle or middle–low class. Importantly, 38% were among children of low or marginal classes, while these children make up 80% of the population. The mean age of the cases was 8 months (range 3–60 months), but 81% were between 3–6 months. No seasonal trends were noted. The rate of intussusception in the population compares to the rate of rotavirus hospitalization of 3 738/100 000/year in the same age group. Thus, rotavirus hospitalization is 158 times greater than that for intussusception. A total of 83% of the children were diagnosed within 24 hours of onset, and 94% underwent surgery for correction (only 1 treated with barium enema). 82% had ileocolic intussusception. Of the 18 patients for whom data were available, all presented with bloody stools, and 72% had vomiting at presentation. There were no deaths.

Dr Perez-Schael then presented data from a three-country rotavirus surveillance project in which she participates. Overall, 33–35% of emergency room visits and 39–50% of hospitalizations for diarrhoea are for rotavirus in Argentina, Chile and Venezuela. She pointed out epidemiological differences in two separate populations, which she hypothesized were related to the density of the populations in each site. While there is a marked seasonality in Caracas, no seasonality is present in Valencia. Additionally, in the densely populated Caracas area, 85% of children are infected with rotavirus by 12 months of age, while only 67% are infected in Valencia, which has a lower population density.

In conclusion, Dr Perez-Schael said that intussusception is rare in Caracas, but occurs in infants three to six months old and has no distinct seasonality. The epidemiology of intussusception in Venezuela appears similar to that in the United States.

Peru

Dr Claudio Lanata reviewed data on the epidemiology of intussusception in Peru. First, he reviewed data from his studies in Lima on the rates of rotavirus and diarrhoeal disease. Overall, the rate of all rotavirus diarrhoea is 13/100 child-years, and 5/100 child-years, 2/100 child-years and 0.3/100 child-years for outpatient visits, hospitalization and deaths, respectively. He reviewed data from all hospitals in Lima

that admit children and have the capacity to do surgery on children. He found 18 cases of intussusception in 1999 (compared to an expected number of 15–111 based on rates from United States data).

He placed these data in the context of potential rotavirus vaccination. He reminded the group that RRV-TV was safer when tested in Peru compared to developed countries, demonstrated by lower rates of fever following vaccination. In addition, the background rates of intussusception are lower in Peru. RRV-TV might induce a diminished inflammatory response in Peruvian children, and so may result in lower risk for intussusception following vaccination. He provided data from a cost-benefit study he has completed for Peru, which showed that vaccine would prevent 1440 deaths, 23 000 hospitalizations, and 29 000 outpatient visits in Peru. This is compared to an estimated 78 cases of intussusception that might be caused by vaccine. He concluded that rotavirus was an important cause of hospitalizations in Peru, and that RRV-TV has been found to be safe and effective in Peruvian trials. Because the risk of intussusception might be lower in Peru, the vaccine offers a potential for great benefit in this population. He has discussed these findings with decision-makers in Peru, who agree with this conclusion.

Brazil

Dr Alexandre Linhares then reviewed cases of intussusception from national data sources in Brazil and used 1996 census data to calculate rates. He looked at 1997–98 data for children under 1 year using ICD-9 and ICD-10 codes for intussusception. He found 203 cases of hospitalizations for intussusception, compared to 450 000 hospitalizations for infections of the intestine. While there was some indication of seasonal peaks in intussusception, there was no correlation between the curves of intussusception and either diarrhoeal disease or oral polio vaccine receipt. The peak age of intussusception is 4–6 months. The rate calculated for children in Brazil was 3.5/100 000/year among infants and lower in the northern tropical region and higher in the central, western regions of Brazil. He thought that these differences were attributable to reporting differences.

He remarked that there was a single case in the trials of RRV-TV in Belem. It occurred in a two-year old who had received three doses of placebo. This case-patient was rotavirus antigen negative during the episode. In conclusion, Dr Linhares stated that rates of intussusception were quite low in Brazil, and that no distinct seasonality was noted. There were no associations between diarrhoeal disease and intussusception peaks, nor for OPV receipt. The highest rates were among children aged four to six months, and regional differences were probably a result of surveillance artifacts. Finally, he concluded that the risk of intussusception seems to be much lower than the benefit of vaccine.

India

Dr M. K. Bhan reviewed data from three hospitals in Delhi, India. At the All Indian Institute of Medical Science (AIIMS), in 1993–1997, 17 cases of intussusception were found among the 22 000 admissions. The mean age was 6 months (3–36 months). No patients were found with malnutrition (<2 Z score) compared with 10% in the referral population. Most were well-nourished. There was some association with the dry, hot months of the year, and perhaps with peaks in diarrhoeal diseases. However,

diarrhoea was not a preceding illness in most cases. The presenting symptoms of the patients were similar to previously reported cases. There were no deaths among the children and 50% underwent surgery.

At the Postgraduate Institute of Medical Education, 61 cases of intussusception were found in 4 595 admissions between 1968 and 1978; 90% were males. Mortality was 26%, associated with longer times between onset and treatment. All patients received surgery and 62% had resection of part of the bowel. The third hospital, also in Delhi, reported 24% mortality as well, but only 32% of children underwent surgery.

He wondered why children less than two months were protected from intussusception, but hypothesized that vaccination of neonates may therefore increase the safety of vaccination. He remarked that the incidence of intussusception appeared to be very low in Delhi compared to developed countries.

Africa

Dr Duncan Steele reviewed data on intussusception from Africa, concentrating on studies from South Africa and Nigeria. He noted that the numbers are quite low in all African studies. Early reports of intussusception in tropical regions tended to reflect an older age distribution, a higher proportion of colo-colic intussusception, later presentation, an association with parasitic infections, and a very low incidence of primary bowel lesions. This has changed in recent reports to reflect the epidemiology seen in developed countries. Most patients are males, and most are less than one year of age (median age 3–9 months). The clinical symptoms are similar to reports from developed countries, except that children present to the hospital later in the course of their illness, and often face a delay in diagnosis once they reach the hospital. There appears to be a seasonal peak in intussusception (March/April in South Africa and December in Nigeria). Most cases are ileo-colic. Surgical correction is routine and 20–60% of children need bowel resection. Mortality is between 3–11% in South Africa and 9% in Nigerian studies. Diagnosis is primarily made by surgery, and less often by plain radiographs and ultrasound. Diarrhoea may be a contributing factor, and intussusception may be confused by dysentery, delaying treatment.

Discussion of the presentations

Most of the discussion concerned the reported rates of intussusception in developing countries and hypotheses for the reason for differences between developed and developing countries. All of the presentations seemed to indicate the rates of intussusception appeared to be of the order of 20/100 000/year in developing countries, and lower in developing countries than in developed countries. Several participants thought that the most likely reason for this was incomplete reporting of cases. However, researchers involved in the surveillance felt comfortable that all cases were detected and that the rates in these countries were truly lower than those reported in the United States. One possibility is that fatal cases are reported as being due to dysentery. It was noted that rates of intussusception may vary according to socioeconomic status.

There was general agreement as to the value of good studies to estimate the background rates of intussusception in developing countries, particularly in settings where vaccine trials might be conducted.

Some participants were concerned that any intussusception caused by vaccination in some settings will be fatal; however, this point of view was countered by others who reported self-reducing intussusception in infants and in animal models.

The data from Africa that seemed to indicate a comparable seasonality for rotavirus and intussusception were mentioned, but Dr Steele remarked that these data are not reliable enough to make this conclusion. Generally, it was agreed that the data to associate rotavirus infection and intussusception are very poor.

Pathogenesis theories were further discussed, particularly, the association between immunogenicity and reactinogenicity of a vaccine strain and its predilection for leading to intussusception were debated. However, the implications of this possible association for vaccine selection was doubted. The point was made that despite the presence of new infection (RRV) in humans, it does not follow that the strain is necessarily the cause of intussusception. The histology of infections with viruses from various species in animal models is not different.

5.2 Views from developing countries

Bangladesh

Dr David Sack pointed out that rotavirus was first detected in 1978 in Bangladesh, and since then has been a well-recognized cause of acute, severe gastroenteritis among children less than two years old. At the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), 50% of hospitalized patients have rotavirus infection. In 1998, there were 27 400 admissions for rotavirus gastroenteritis. In estimating the relative risks and benefits of rotavirus vaccination, he estimated 20 000 deaths each year because of rotavirus from a birth cohort of 7.5 million in Bangladesh. If we assume an 80% efficacy against rotavirus-associated death, a vaccination programme would prevent 13 000 deaths each year and another 240 000 cases of severe diarrhoea. Vaccination would lead to 650 cases of intussusception.

Dr Sack pointed out that risks of intussusception following vaccination might be lower if maternal antibodies protected against intussusception, if the shorter villi or interference with vaccine take one would expect in Bangladeshi children were to be protective, or if breastfeeding were protective. Alternatively, risk might be increased if malnourished children had higher risks, or if rotavirus vaccine infection was synergistic with other enteric infections in causing intussusception. It is clear that if vaccine did cause intussusception, fatalities would occur as a result. Apart from the reluctance to adopt any new vaccine programme, additional resistance would be present for this vaccine since it has been withdrawn from the United States market.

Dr Sack reported on a meeting of physicians and public health officials on 22 January 2000, to discuss problems with this vaccine and intussusception in general. The physicians reported about 70 cases of intussusception each year from two hospitals in Dhaka. Cases were usually between 5 and 12 months of age, and were rarely reported among children younger than 4 months. A distinct wintertime seasonality exists, and cases are predominant among males (eight males per every one female) and among well-nourished infants. Few patients are found to have lymphoid enlargement. Only one death has been reported during the past two years. Diagnosis is generally by ultrasound, and all patients are treated with surgery. The group concluded that rotavirus vaccine development should be encouraged, but that good safety monitoring needed to be

included in any trials or programmes. The physicians were eager to participate in studies, and felt that the risk of intussusception is minimal when compared to the risk of severe disease. Dr Sack thought that this discussion with physicians was quite helpful in deciding what studies might be conducted, and how.

The view of ICDDR,B is that vaccine development is important, but that further studies with RRV-TV will be difficult. Other vaccines would be acceptable, as long as close monitoring is provided. ICDDR,B has a field site that would be appropriate for Phase II and III field trials. Since the true intent of rotavirus vaccines will be to prevent deaths in the poorest countries, vaccines should be tested in countries that will benefit most. Regulatory approval in developed countries is reassuring but not a prerequisite for acceptance in developing countries.

Viet Nam

Professor Dang Duc Trach reported data from Viet Nam. He conducted a hospital-based study in 1995–99 in Hanoi, Hue and Ho Chi Minh City. Between 472 and 722 cases of intussusception were found each year among children under 12 months of age. These represented 5–8% of all hospitalizations. Most cases occurred among children three to eight months of age, 65% were male and a slight increased incidence during December and February was noted. The case fatality rate has decreased from 9% in 1997 to zero in 1999. Air enemas are routinely used for treatment. He concluded that there existed a need for rotavirus vaccination in developing countries, and that intussusception could be followed in Viet Nam in the setting of a vaccination programme.

China

Dr Zhi-Sheng Bai reviewed data from Lanzhou and Beijing, which demonstrated that rotavirus disease accounted for 38% and 28% of diarrhoeal hospitalizations, respectively. Each city reports a wintertime seasonality and G1-3 are the most common types, but G9 viruses have recently been identified. He could collect no data on intussusception yet, but was attempting to conduct studies.

The rotavirus lamb strain (LLR) was isolated in 1985. The strain has undergone 10 passages in lamb and 32 passages in primary calf kidney (CK) cells. In practice, frozen CK cells are often used at the second passage. The vaccine is a liquid that can be kept at +2°C to +8°C and remains stable for one year. The vaccine contains sucrose and lactose as stabilizer. For administration, the cork of the vial is open and the contents poured out. For older children the contents have been poured on a cake and fed to the children. LLR is of G10 serotype. This vaccine was approved by the Ministry of Public Health. This IND approval has been granted on the basis of phase I study only. The IND allows production of experimental batches of LLR vaccine for safety and efficacy studies (clinical phase III trial) which have to be conducted within the coming two years. Lanzhou Institute estimated that LLR vaccine might be sold at US$ 1–2 for use at anti epidemic stations, at US$ 2–2.5 for the free market in China and US$ 3.5–5 for the international market.

This vaccine, given in one oral dose, was evaluated in 800 children, aged from 6 months to 24 months, in phase I clinical studies conducted for 8 years. It showed itself to be safe and immunogenic in the studied target age. However, no data exists on safety and

immunogenicity in infants less than 6 months of age nor in relation to the impact of one, two or three doses. No study was conducted on the potential interference with OPV.

A G3 reassortant vaccine was prepared and evaluated, at a concentration of 10^5 pfu, for safety and immunogenicity in children from 6 to 24 months of age. The first results showed that the vaccine is safe and immunogenic. The antibody levels were not different from those obtained with the simple LLR vaccine. The Institute is working on G1, G2 and G4 reassortants to prepare a tetravalent vaccine. The price of such a vaccine might be twice that of LLR.

Discussion following the presentations

Most of the discussion concerned the difficulty in getting developing countries to accept new vaccines without approval and support from the USA. Many participants felt that the regulatory decisions made in the USA have made use of RRV-TV impossible. Many felt that testing of this vaccine would be unacceptable to participants and to the ethical reviewers in their countries. Instead, a new vaccine was the most acceptable solution. The acceptance of a vaccine is both a political and scientific decision. Since, new vaccines compete for scarce resources, a vaccine not burdened with the perception of serious adverse events will be needed. It was noted that in the future, trials in developing countries should proceed concurrently with trials in developed countries, and that licensure of vaccines in developing countries could be independent of United States decisions.

Some participants suggested that the low risk of intussusception in very young children suggests that vaccination in neonates may limit the risk of intussusception.

5.3 Monitoring intussusception in field trials

Dr Bhan outlined features of field trials that would be necessary to monitor the occurrence of intussusception. The first criterion is that sites be in areas where access to diagnosis and treatment is assured and rapid. The objectives of trials, whether to merely monitor for intussusception or to assess vaccine as a risk factor for intussusception, would determine the sample size needed. He estimated that a trial of 64 000 children per group might be enough to assess the effect of vaccine both on intussusception and rotavirus-associated mortality. He asserted that any vaccination programme could not be sustained if the risks of the vaccine are unknown, so that the answer to the intussusception question should come early, either with trials or quickly in the post-licensure period. Finally, a full consent must be used to tell patients of the potential risks of vaccination. During any trial, patients should be monitored following each vaccination, perhaps daily for the first two weeks then twice each week for at least three months. Monitoring should be done by physicians trained to diagnose cases of intussusception. Families should be educated on the signs of intussusception and provided a method to seek diagnosis and treatment appropriately. Monitoring for specific symptoms might include vomiting, bloody stools, abdominal pain and other symptoms based on local disease patterns. An algorithm could be made for decision-making based on specific groups of symptoms. Suspected intussusception cases should be referred to a hospital capable of treating patients.

Discussion following the presentation

The discussion first centred on how trials might be conducted to evaluate safety of new vaccines and how large the studies have to be. It was agreed that cases of intussusception were likely to occur in any trial, so the size of the trial would be dependent on the level of assurance required. Several participants called for guidelines for the size of such studies and a delineation of what acceptable outcomes might be. It was noted that sample size might be reduced for trials of neonatal vaccination, since the background rates of intussusception are so low that any increase would be easy to detect. In addition, any trial large enough to detect intussusception cases would be large enough to assess efficacy against rotavirus-associated mortality. The group generally agreed that a highly organized medical system that can effectively treat intussusception be a requirement for any trial, and that standard surveillance and treatment guidelines be developed in advance of future trials. In addition, inclusion of collection and evaluation of clinical specimens (stools, serum and tissue) should be made a part of any protocols.

Some discussion of the sequence of trials included the reminder from several participants that, before a large safety trial is conducted, evaluation of the efficacy of the vaccine should be the first goal. In addition, support for testing RRV-TV was voiced to avoid a long delay until a vaccine is ready for testing in developing countries.

The group concurred that the relative risks and benefits of vaccination in the USA will be quite different from that in developing countries. So, any decisions by the FDA or CDC are specific to the USA and should not adversely affect discussions in developing countries. The group was reminded that the ACIP statement on withdrawal of the vaccine specifically stated that the decisions are only to be applied to the USA and may not be applicable to other settings.

Several participants asked whether RRV-TV would be available to developing countries should they be interested. Dr Peter Paradiso said that a decision had not yet been made, but will be made on the basis of the expected desire for the product. However, he doubted that demand for the product would be great. Several indicated that since no data were available in developing countries, no final decisions on any vaccine should be made yet. Some participants recommended that WHO issue a statement in strong support of a study with RRV-TV in a developing country so that some of the reluctance to test this vaccine might be overcome.

5.4 Can vaccine-associated intussusception be avoided?

Dr Timo Vesikari first asked the question of whether vaccine-associated intussusception could be avoided. The first possible answer is through the development of new vaccines or new routes of administration. He outlined several alternatives including: 1) non-oral vaccines, either vaccine-like particles administered intranasally or inactivated vaccines; 2) nasal administration of live vaccines; 3) live vaccine other than rhesus-based vaccines, including bovine or human-based vaccines; and 4) altered rhesus vaccines, such as low-titer vaccines.

He then discussed the possibility of administering vaccines in the neonatal period. Support for this idea includes the finding that natural intussusception is rare in this age-group and rhesus and bovine rotavirus vaccines have been found to be safely administered in this age group (maternal antibodies may suppress reactions). Even

though immunogenicity of vaccines has been found to be lower in this age group, vaccine take might be good. A single dose of bovine vaccine (RIT 4237) administered within the first week of life protected against severe rotavirus disease, if given *shortly before* the rotavirus season. Such a dose was less effective if given several months before the season. He presented data from a phase II study conducted in Israel using a low-dose RRV-TV vaccine that demonstrated low rates of adverse events among those vaccinated, while 70% of the children demonstrated an immune response to vaccine. In a Finnish trial with RRV-TV, three vaccine schedules were tested – three doses of vaccine given at either 0/2/4 months, 0/4/6 months or 2/4/6 months. Febrile reactions were absent among children given the vaccine in the neonatal period compared to 18% following the two-month dose. Immunoglobulin A responses were seen in 90–100% in all groups studied.

In conclusion, Dr Vesikari addressed the question of whether intussusception might be avoided using a schedule for vaccination that includes a neonatal dose. He noted that one dose may be partly protective but that children may require a booster dose. He also noted that RRV-TV seems to protect against RRV-TV-associated intussusception, but only after 2 doses. He concluded that a schedule of 0, 6, and 10 weeks might be safe but may not provide optimal protection. He recommended that future studies should be based on a schedule consistent with the EPI programme. If RRV-TV were further tested, a lower dose might be considered.

Discussion following the presentations

Participants discussed the duration of viral excretion following vaccination with respect to the safety of neonatal vaccination. Data indicate that the average duration of excretion is five days following vaccination, but that children in Melbourne infected with a human strain were protected from subsequent illness and excreted virus for a prolonged period. Mouse studies indicate that newborn mice are as immune competent with respect to response to gut infections as older mice. Similarly, in humans, newborns had good immune responses to natural infection by nursery strains. However, it was noted that there was no difference in risk of intussusception among those vaccinated by age group, so that there was no reason to believe that neonatal vaccination would diminish the risk.

6. Second day of the workshop: opening and review

6.1 Opening of the meeting

Following a welcome from Dr LaForce, Dr Kapikian addressed the meeting on the opening of the second day about some issues concerning the data presented by CDC. He opened with the reminder that we know much more about RRV-TV than about any other rotavirus vaccine. As we wait for new vaccines, children in developing countries will continue to die of rotavirus diarrhoea.

Prior to licensure, Rotashield or related formulations of this product were given to more than 10 000 children, five of whom developed intussusception. The rates of intussusception among those vaccinated and placebo recipients were 5/10 054 and 1/4633, respectively. For Rotashield, during the pre-licensure period, 2/8 240 developed intussusception, and these cases occurred on day 51, post-dose two, and day 7, post-dose three. He said that the rate of intussusception among those vaccinated in the Northern California cohort study was about 30/100 000, which was less than the background rate in the United States. Similarly, the rate in the Minnesota study, where over 50 000 doses had been administered, was consistent with what would be expected without vaccine. Finally, he reviewed the data from the United States HMO study noted that the incidence of 14 cases among 50 000 vaccinated was hardly different from the incidence among unvaccinated children – 48 cases reported among the 142 000 that were not vaccinated. He acknowledged that further follow-up would be required to finally assess the true risk, but that the final determination of an increased risk has still not been made. Finally, he said that the 102 VAERS cases per 1 million of those vaccinated results in a rate of only ~10/100 000/year and that Southern California Kaiser Permanente has reported that none of their almost 6 000 persons vaccinated have had intussusception.

In conclusion, he said that the cluster of cases following the first dose and in the first week indicated a significant problem. However, additional analyses are required to establish the attributable rate of intussusception among vaccines. These are the data that are most needed to make decisions for using this vaccine in developing countries. To calculate the attributable risk, additional follow-up of the cohorts is required. He recommended analysing cohorts with comparable periods of observation among vaccinated and non-vaccinated groups, rather than making conclusions based on the markedly unequal person-year denominators in the current analyses, which magnify the risk of vaccine-associated intussusception.

Discussion of the presentation

Additional CDC data were presented showing that if person-time were included in analysis of the HMO study, the risk in the three- to seven-day time period would still be elevated 15-fold. It was also noted that the Southern California Kaiser data was included in the analyses presented the day before and that use of person-time is a standard method to analyse such data. In cases where the follow-up periods of exposed and unexposed populations are different person-time is used to allow comparisons. One participant noted that 20 intussusception deaths might be expected for every 5 000 deaths averted with use of RRV-TV – a similar ratio to the risk-benefit of OPV and vaccine-associated paralytic polio (VAPP) in the UK.

6.2 Report of a workshop held at NIH on future directions for research on the relationship between intussusception, viral infection and vaccines

Dr Michael Gerber presented the results of a meeting held at NIH on 21 January 2000. The objectives of the meeting were to review the epidemiology, pathology and pathogenesis of intussusception associated with rotavirus vaccine and to establish a research agenda to prevent the future occurrence of intussusception associated with vaccines. The National Vaccine Program Office established three working groups to evaluate research priorities related to epidemiology, pathology and pathophysiology of the RRV-TV/intussusception investigation. The Epidemiology Working Group reported the findings of the CDC studies, including VAERS data, case-control study data, and the data from the case-series and cohort studies. Researchers from the University of California Los Angeles (UCLA) reported on a study that found no association between natural rotavirus infection and intussusception in their population.

Dr Gerber summarized a proposed study from researchers from the Children's Hospital Medical Center to conduct a prospective case-control study to define risk factors for intussusception in the USA, including rotavirus infection. The Pathology Working Group reported on plans for the evaluation of tissue specimens collected as a part of the CDC investigation. Intestinal tissue from cases of intussusception associated with vaccine will be compared to tissues from cases of intussusception not associated with vaccine and other control tissues with respect to the histologic findings, viruses detected, and perhaps characteristics of the immune response. Methods, including immunohistochemical staining, *in situ* hybridization and polymerase chain reaction, are being developed by CDC to detect rotaviruses, enteroviruses and adenoviruses.

The Pathogenesis Working Group reviewed discussion on the development of animal models for intussusception that might be used to evaluate the mechanism of RRV-TV-associated intussusception. The conclusions of this working group included the finding that while animals do get intussusception, no reliable animal model for vaccine-induced intussusception is likely to be found. Perhaps some surrogates of intussusception, such as lymphoid hypertrophy, may be worth pursuing. Presentations of ultrasonography and a review of intussusception were provided. Dr Mary Estes stated that there were animal models for rotavirus infection but that they differ from humans in several important ways. Animals only become infected with homologous rotavirus strains and gain lifetime immunity following infection. Mice would be a difficult model to use for intussusception studies as their intestines are small and hard to work with. Rabbits

may be easier because of size, but they are expensive. Instead, she presented data on a suckling rat model that may be more representative of a human, and that would provide a larger intestine. Dr Hanani presented data on a mouse model in which intussusception could be induced by lipopolysaccharide (LPS) administered intraperitoneally. LPS-induced intussusception is mediated by changes in motility, not through pathologic or inflammatory changes of the gut. He hypothesized that inflammatory mediators resulting from a rotavirus vaccine infection might cause a change in the gut motility, and the intussusception. Therefore, if one could block prostaglandin production, intussusception might be prevented.

Dr Atreya presented data on NSP4 enterotoxin, which could be associated with intussusception in human guts. A discussion of the risks and benefits of vaccination of children in developing countries was led by Dr Ivanoff, with presentations by Drs Miller and Lanata. Dr Livengood provided the United States perspective and presented data on the cost-effectiveness of vaccine. Finally, industry representatives reviewed their own plan for developing rotavirus vaccines. A draft research agenda was created, and a report of the meeting will be published by NIH.

Discussion of the presentation

The participants were reminded of the language from the ACIP statement on rotavirus vaccines that specifically indicated that United States decisions should not apply to settings with different disease burdens. Even so, some participants doubted that such a vaccine would be acceptable in developing countries. India was mentioned as an example.

The discussions that occurred at CDC preceding the withdrawal of the vaccine were reviewed. The intention of CDC was to make decisions based on United States data, and only for American children. A need still exists to evaluate the vaccine for developing countries, and it would be unfortunate for a US decision to translate directly into decisions by other countries. Each country should consider the decision in its own setting. Many agreed with this, saying that decisions in the USA may have been much different if the US rotavirus-associated mortality was high. WHO could use its influence to help the process of evaluating this vaccine in developing countries.

There was a sentiment among some at the meeting that the long experience with trying to introduce hepatitis B vaccine and other new vaccines into developing countries indicates that a vaccine such as RRV-TV will face many hurdles. In addition, RRV-TV faces the added problem of the potential risk of a serious adverse event (and withdrawal by the USA). The ultimate decision about vaccine introduction is not one of ethics, but of politics. In that light, efforts should be directed towards newer vaccines that have a better chance of acceptance. This was countered with the position that the way the ethical arguments are stated might affect the politics of the vaccine. The perception of a double standard will be important to avoid. WHO could educate decision-makers that a single standard of risk-benefit ratios should be used in evaluating this vaccine.

The assertion was made that a few underlying themes had been identified at this meeting. First that the US situation was completely separate from developing countries, where mortality associated with rotavirus is common. However, a complication associated with a vaccine is visible, while the deaths prevented by a vaccine are invisible. Because of this, political will has to be developed before promoting a vaccination programme. As there is still a great need for an effective rotavirus vaccine, a strong recommendation

from WHO could boost that political will. Finally, while CDC and Wyeth have withdrawn recommendation and the product, respectively, FDA has not yet withdrawn the licence of the product. So it is still possible that a developing country could use this vaccine.

7. Rotavirus vaccines

7.1 Industry perspectives: regulatory perspectives and expectation; liability issues at home and abroad; impact of domestic decisions on vaccine decisions abroad

Dr Philip Minor reviewed the components of vaccine regulation, particularly as they relate to safety, to give the meeting a framework to consider the discussion. He said that there are three aspects of regulation of products: safety, efficacy and quality. Each is important, but safety is foremost for vaccines.

Components of safety include the safety of the recipient and of the environment. To monitor the safety of the recipient, adverse events are reported and assessed. These can either be obviously related to the agent (e.g. diarrhoea) or other events that seem to be related to the product (e.g. intussusception). These events are placed in the context of a risk-benefit analysis. The issues of safety of the environment include the potential of the vaccine strains to revert to virulent form, to make reassortants, or to create mutants or non-target effects. Efficacy is related to dosage and protection. Questions asked include those about interference from other agents, the dose required, the balance of components, and whether trial data are likely to be a good approximation of what really happens. Finally, quality evaluation is to determine whether a product can be reliably and consistently produced. The relevant production parameters, process control and final product tests are reviewed. So, a number of factors are included in the regulatory process, and these processes should be under the control of each country.

Discussion of the presentation

Some discussion of the similarities between the experience with rotavirus vaccine and intussusception and adverse events associated with other vaccines was undertaken. The examples of OPV and DTP were produced to make the point that vaccines that are no longer used in the USA are still used in developing countries. These examples have established the precedent that countries can have different recommendations, based on varying risk-benefit ratios. It was noted, however, that each of these vaccines is or has been used in developed countries.

There was concern about whether a company would accept the liability of such a vaccine for use in developing countries. One problem is that in settings where treatment for intussusception is available, diarrhoeal mortality is likely to be low, making the need for a vaccine less pressing. While local production of this vaccine might be an answer, it is unclear whether willing countries will have access to the technology. Although little doubt exists that a rotavirus vaccine is needed, the cost of production and evaluation has been significantly increased as a result of the intussusception issue. Development

of new vaccines should be promoted by international organizations, and countries should make it clear to industry that the vaccines will be used.

Some participants supported the notion that vaccines should be evaluated based on their risk-benefit in each setting, and thought that standards for these calculations should be delineated. This argument should be made soon to avoid a long delay in vaccine development, and the resulting accumulation of potentially preventable deaths. Participants noted that a child's death that occurs proximate to a vaccine is more apparent than the prevention of a death through vaccination. So the risk-benefit models should not be viewed in purely abstract terms. In addition, since developing countries are not homogenous, a single risk-benefit evaluation will not be true of everyone in a country. One solution to foster use of RRV-TV might be to define a population most in need. A trial could then be done in that population first. This is still problematic because of legal and acceptance issues, however one participant remarked that one problem with future trials is that vaccine-induced intussusception is not a unique syndrome, so that any case of intussusception will be associated with vaccine in public perception. In addition, these rare events are unlikely to be detected pre-licensure, so better post-licensure surveillance is needed.

7.2 Ethical issues: is it ethical to make different vaccines for different markets? Risks and benefits issues

Dr Charles Weijer reviewed some of the basic disease-burden numbers and milestones in rotavirus vaccine licensure and withdrawal. The main question to answer, he said, was whether vaccine trials with this vaccine continue in less-developed countries. He reviewed three principles of research ethics: 1) respect for persons – that choices of people are taken seriously, and that non-autonomous persons are protected; 2) beneficence – that benefits be maximized and risks be minimized for participants; and 3) justice – that there is an equitable distribution of the risks and benefits to participants.

The guidelines for research ethics are provided in either the Declaration of Helsinki (1996) or the International Ethical Guidelines for Biomedical Research involving human subjects of the Council for International Organizations of Medical Sciences' (CIOMS) (1993). CIOMS states that research should be responsive to the health needs and practices of the community in which the research is conducted. In addition, the products of the research should be available to the study subjects. In illustrating limitations of the last sentence, he pointed out that the context of the research is crucial in evaluating the ethics of the research. He used the perinatal trials of AZT in Africa as an example. He noted that these studies and future studies of RRV-TV are different, but that they may be compared. Instead, the requirement for the "the best proven therapeutic method" being available to study participants has been considered the local standard of care. He described the requirement for clinical equipoise, as it serves as the basis for randomized, controlled trials. It provides that there must be general uncertainty as to the preferred treatment and that the purpose of the trial is to resolve this uncertainty.

He posited that trials of RRV-TV fulfill the requirement for "clinical equipoise". While there are data that the vaccine is effective, there is uncertainty as to whether it will be effective in developing countries. He then countered the argument that omission is ethically more acceptable than commission. He claimed that there is no morally relevant distinction between action and inaction. In this case, the failure to act may lead to

480 000 deaths. Dr Weijer recommended that trials with RRV-TV be conducted, and that they include methods to reduce the potential risk to participants and to improve care for intussusception should it occur. He also recommended that the ethical argument for these trials be made in medical and lay journals.

Discussion of the presentation

The major theme of the discussion following this presentation was whether or under what conditions RRV-TV could be studied further. The general issue of whether to pursue studies with the vaccine or not was controversial. Several participants supported continued trials, claiming that a vaccine exists, ready for trials in developing countries, as well as several vaccine candidates that are years away from availability. By waiting for the next generation of vaccines, hundreds of thousands of children who could be saved will die. We should evaluate RRV-TV in developing countries now, and the new vaccines when they are ready. Several investigators from developing countries reiterated that trials of a vaccine withdrawn from the US market would face major obstacles in their countries. The difficulties lie in the perception that there are two standards for vaccine safety – one for the United States and one for developing countries. Not only are there problems with possible serious adverse reactions, but also the cost of the vaccine and the perceived need for it are still troublesome issues in many countries.

In addition, the availability of the vaccine is in doubt, even if trials were to find that it is safe and effective. For practical reasons, this group advocated using resources to develop and test new vaccines that may be more acceptable. This was countered with the idea that it is a researcher's role to educate decision-makers, and that the group should first decide what is ethical to do, then figure out how to create the political will to do it.

Even so, many participants voiced optimism that RRV-TV might be acceptable under certain circumstances. For instance, a change in the schedule might make a trial more acceptable, if there were a reason to think that the change would enhance safety. Additionally, a strong WHO recommendation for use of the vaccine might be important in swaying some review boards.

Dr John Clemens reviewed past decisions regarding other vaccines based on their relative risks and benefits to remind participants that this situation is not unique, and that past decisions may provide some guidance. Several examples were discussed including smallpox vaccine and post-vaccine encephalopathy, measles vaccine and encephalitis, high titer measles vaccine and increased mortality of females, complications of rabies vaccine, and OPV and VAPP. All diseases had a heavy disease burden and all vaccines had known, serious side-effects that were known at the time of introduction. This history highlights the fact that vaccines have been introduced with known serious adverse events, and that the higher the disease burden was, the more willing the population was to accept the complications. However, the diseases were different from rotavirus as there was no available treatment for them, and a different social climate with respect to vaccine safety now exists.

7.3. Characteristics and status of rotavirus vaccine development

Neonatal strain vaccine

Dr Ruth Bishop opened this session with a review of a vaccine candidate developed in her lab. The strain is a human strain (G3, P6) isolated from an infant and attenuated through multiple passages. In epidemiological studies, infants who were naturally infected with the strain were protected from rotavirus infection during the first two years of life. It represents the only neonatal strain currently under development. A placebo-controlled trial involving 60 children has been completed. Twenty children each received either placebo, vaccine, or vaccine and soy milk. The outcome measures in the study were immune responses measured as IgA or neutralizing antibody titer rises. Children were vaccinated at three, five and seven months of age with 6×10^5 infectious units per dose. Overall, 10/20 placebo recipients, 10/20 vaccine recipients, and 5/20 vaccine-plus-soy recipients developed rotavirus disease during the study. Vaccinees who became ill were found not to have had a seroresponse to vaccine. Some 40% of children responded to vaccine, while 55% of the vaccine-plus-soy group demonstrated an immune response. Dr Bishop concluded that if an immune response is triggered by the vaccine, the child is protected; where there is no evidence of immune response, protection is poor. The vaccine can induce heterotypic protection against G1 strains.

Merck Research Laboratories

Dr Penny Adcock reviewed Merck's position on rotavirus vaccines. She said that favourable attributes of Merck's vaccine candidate, a WC-based bovine-human reassortant, is that it induces good protection against any rotavirus disease (~70%) and better protection against severe disease (95–100%). It is generally well tolerated, causing no excess fever and a low rate of shedding. Because it is non-reactinogenic, it may have less potential for causing intussusception. The challenges of future research include establishing baseline rates of intussusception in populations, conducting large field trials to establish safety, and providing close monitoring of safety during trials. Even though the pathogenesis of intussusception associated with RRV-TV may take years to elucidate, trials with new vaccines should continue. Merck plans a large field trial with its candidate next year.

SmithKline Beecham Pharmaceutical

Dr Georges Thiry outlined the rotavirus vaccine plans of SmithKline Beecham Pharmaceutical (SKB). The objective of SKB's programme is to develop an oral vaccine to protect children against rotavirus disease worldwide. Their candidate, 89-12, was isolated from a 15-month-old child with gastroenteritis in December 1988, and is a G1P[8] strain. During 1997–98, the strain was passaged and attenuated. A phase IIb trial was conducted by the Virus Research Institute (now Avant Immunotherapeutics Inc.) in which 215 children were randomized to receive two doses of 10^5 pfus of vaccine or placebo at two and four months of age. One hundred per cent protection against physician visits was observed, and of the 20 cases of rotavirus diarrhoea, 18 occurred among placebo recipients compared to 2 among those vaccinated. SmithKline licensed

the vaccine from Avant, and the results of studies have been published in two papers. The vaccine candidate is a monovalent, live, attenuated human rotavirus strain with G1P8 specificity. It is developed for use worldwide and will be administered along with an antacid. It is stable at room temperature, and will be given at two and four months of age in a dose of 10^5 pfus. SKB has a plan to develop the vaccine for developed and developing countries along parallel tracks.

Wyeth Lederle Vaccines

Dr Paradiso stated that Wyeth believes that RRV-TV is important and needed. Even so, this company is developing other vaccine candidates to improve safety and expand coverage for additional serotypes. Currently, Wyeth has a human–bovine reassortant vaccine candidate and in the future may use its virus-like particle vaccine programme to develop rotavirus vaccines. The company may investigate alternative ways to deliver the vaccine, such as neonatal schedules or formulation changes. Dr Paradiso stressed that Wyeth sees a need to fully understand the Rotashield problem and, while it is unsure of the future of the vaccine, has no current plans to abandon it.

Lanzhou Institute of Biomedical Products

Dr Bai reviewed the development of a lamb strain vaccine, LLR, by the Lanzhou Institute of Biomedical Products in Lanzhou, China. LLR is an orally administered, live, monovalent rotavirus vaccine. The virus is a group A, subgroup I rotavirus, with G10,P[12] specificity and a long electropherotype. It underwent 37 passages and received IND approval for phase I and phase II trials by the Chinese government. Data from these studies, in 1992–96, indicated fever rates among those vaccinated of 6% (mild), 1% (moderate) and 0% (severe) compared to placebo recipients (7%, 1%, and 0%, respectively). Some 61% of 103 vaccinees compared to 3% of 105 placebo recipients developed neutralizing antibody (NA) responses to LLR. A dosing study was conducted comparing three doses of vaccine, 10^4, 10^5, and 10^6. In 1998, Dr Bai received approval to conduct a phase III trial. The study began in October of 1999, and thus far 500 children under six months of age have been enrolled and randomized. Preliminary data indicate a lack of fever after vaccination and no cases of intussusception. Efficacy has not yet been evaluated. WHO has made three site visits to examine production facilities and help design trials. The International Vaccine Initiative (IVI) has been a partner in the studies. The next step is to complete the trial and perhaps further develop a reassortant vaccine.

8. Presentation of the Working Group discussions

8.1 Rotavirus Epidemiology Working Group

Chairs: Drs Robert Black and Alexandre Linhares

Dr Black summarized the discussions and consensus of the working group. Two types of data are needed to assess the rotavirus disease burden.

International/regional data

In a small number of select countries, in-depth studies of disease burden and cost might be undertaken. These should perhaps be the countries in which trials are planned. One of the most important objectives will be to estimate rotavirus-associated mortality. This need is evident based on the conversations of this meeting in which discussions of risk and benefits of vaccination are frequently phrased in terms of mortality. In addition, few data on rotavirus mortality exist, and quality data will be required in outlining the benefits of vaccinations with policy-makers. These data might be collected by using surveys or through ICD-coded data in some countries. Choosing countries with a defined rotavirus seasonality may make estimation of rotavirus-specific mortality possible. In settings with low mortality, assessment of the severe disease requiring hospitalization will be most useful.

A standardized, common protocol for conduct of these large studies will be helpful to ensure comparability and generalizability of the resulting data. One such protocol already exists and can be modified to include current recommendations.

National data needs

Any country that wishes to test or implement rotavirus vaccines will need some local data on burden and cost of disease. The generic protocol noted above will be useful for this purpose. Assessment of the cost-effectiveness of prospective vaccines will be increasingly important, both in discussions with country or local decision-makers and with international funding agencies. The group favours a simple assessment of the costs associated with disease (from hospitalizations for rotavirus, for example).

The group recognized the need to consider the heterogeneity within and between countries. Because of this, the risk-benefit, cost-effectiveness and need/feasibility equations may be different in different populations within a country. These should be considered, particularly in the selection of sites and design of the large intensive studies listed above.

The group recommends that laboratory surveillance be continued and linked with disease-burden studies. While studies of strain distribution are needed, these data are most important in the context of a vaccine study or programme. The group encouraged the development of regional laboratory surveillance systems to share expertise and resources.

The group agreed that more data are needed on intussusception, especially on baseline rates and risk factors in developing countries. A standard protocol to conduct surveillance, diagnosis and treatment of intussusception is needed to support vaccine trials. Following vaccine introduction, sentinel surveillance for intussusception might be organized for monitoring.

Discussion following the presentation

Two themes emerged from the discussions following the presentation. First, several participants asserted that a strong need exists for continued laboratory and strain surveillance, even outside of the context of a disease-burden or vaccine study. Knowledge of strains in various settings is important in evaluating which vaccines to develop, to associate strains with clinical symptoms, to track the changing distribution of strains and to learn about the basic virology of rotavirus.

A second group of comments surrounded issues of the timetable and order of vaccine evaluation. One group asserted that the safety profile of any vaccine must be determined prior to its inclusion of the vaccine in a country's vaccine programme. A second group countered that assurance of safety *vis-à-vis* intussusception will be impossible prior to licensure and widespread use, so that final determinations of safety must be in the post-licensure and introduction phase. It was pointed out that each country may not need its own data to licence a vaccine. This point was illustrated by the example of Peru's licensure of *Haemophilus influenzae* (Hib) vaccine based on data collected in Uruguay.

Finally, a case was made for a standard protocol for disease surveillance developed by WHO along the lines of previous protocols developed for Hib and RSV surveillance. The group was reminded that CDC and WHO had created such a protocol; it was being used in Viet Nam and is planned to be used in a multi-country study in Asia.

8.2 Epidemiology of Intussusception Working Group

Chairs: Drs John Clemens and Irene Perez-Schael

The working group addressed five issues.

Studies should be conducted to determine the incidence of intussusception in a variety of settings. A clear need exists for the development of core data on rates of intussusception. To accomplish this, case definitions for surveillance should be accepted. Retrospective studies of existing data may yet help to define the problem and the epidemiology of intussusception in developing countries and should be encouraged. Prospective studies should begin in populations targeted for vaccine trials. Impediments to these studies include the large sample size needed (at least 20 000 children), the availability of appropriate care, and the development of consensus diagnostic criteria. Algorithms and standard protocols should be developed for these studies. It was noted that the added cost and potential iatrogenic complications be considered in settings conducting these studies.

Studies to better define the risk factors of intussusception should be conducted. No data exist specifically regarding the differences between risk factors for intussusception in developed and developing countries. Case-control studies should be designed. These might be nested studies in a large prospective surveillance study and, more efficiently, retrospective studies based on hospitalized cases. In a retrospective design, cases could easily be enrolled in multiple sites. The first priority for these studies is to determine if rotavirus infection is associated with intussusception, and the design of such studies should include appropriate specimen collection. It is clear that the current ecological data are inadequate.

It was also clear to the group that differences in the epidemiology of intussusception may differ between developed and developing countries, but that there were no guarantees that the risk of vaccine-associated intussusception would be different. Careful studies to determine this will be necessary.

Could vaccine programmes be designed to minimize the potential risks of vaccine-associated intussusception? The answer to this is unclear. And while diagnosis and access to care might be improved as a way to limit morbidity and mortality associated with adverse events, children who most need rotavirus vaccines will be those with the poorest access to these services. Changing vaccine schedules to minimize risks was discussed by the Vaccine Trial Group.

To accomplish surveillance for intussusception in the context of a vaccine programme, the group agreed that efforts to establish large linked databases should be encouraged where possible. Although these will be too expensive and programmatically difficult for many settings, they might be available to some. The benefit of these is clear in surveying for vaccine-associated adverse events.

Discussion following the presentation

Most of the discussion related to the issue of the timing, design and size of a trial that would evaluate the safety of any vaccine with respect to intussusception. As with the previous discussion, participants were split on the need for a full evaluation of the intussusception potential of a vaccine before its introduction. Much of this discussion was based on the perceived size requirements of safety trials. Some participants thought that the size of trials need not be too large because one could use the known risk windows following vaccination to decrease the size needed. Others, however, felt that the features of the association between RRV-TV and intussusception do not offer assurance that new vaccines may also be associated but with a distinctly different pattern. For this reason, researchers are obligated to survey for intussusception during a longer period than one to two weeks following each vaccination, as was proposed by some participants.

Discussion about the size of trials led to some comments about the feasibility of evaluating the reduction in rotavirus-specific mortality as one outcome in a large trial. It was pointed out that no trial has been large enough to demonstrate differences in mortality among participants. The design of large trials to evaluate safety may offer a chance to do this, and they should be designed appropriately. Several participants were sceptical of this plan, asserting that the requirement of good access to medical care as a condition for the safety trial necessitates that the study be conducted in a population with a low diarrhoeal mortality.

Finally, several participants voiced a request that this group or some appropriate group make recommendations about the level of demonstrated safety to which a vaccine should be held. Since a zero risk is impossible to prove, the acceptance of risk will be determined by risk-benefit calculations. If these could be done before the trial design, it would benefit researchers and industry. Some participants thought that it would be impossible to create these guidelines since safety is a relative concept between countries.

8.3 Vaccine Trial Issues Working Group

Chairs: Drs Bhan and Vesikari

Dr Vesikari reviewed the Working Group's discussions related to several questions.

If available, should RRV-TV be used in further trials in developing countries? Following a somewhat controversial discussion, a consensus was reached to "keep the door open" for potential evaluation of Rotashield vaccine in developing countries, since no data were yet available for Africa and Asia.

However, three concerns were raised. First, the availability of the vaccine is uncertain, even if trials carried out in the future were promising with regard to the efficacy and risk of intussusception. Second, investigators at sites available for trials thought that it would be difficult to obtain clearances from local authorities to test the vaccine in their countries because of the risk of intussusception in the USA. Finally, the future availability of new vaccines for trials would make these vaccines a higher priority.

Dr Vesikari pointed out that the priority for RRV-TV testing should be reconsidered, if any of the three reasons were to change. He relayed that the group wished to keep the option for future use of the vaccine open, pending further developments. Long expected delay in preparation for the next generation of vaccines, the proven efficacy of RRV-TV and the lack of data on the association with intussusception in developing countries were cited as reasons for continued support.

Should existing sites test other vaccines? The group felt that sites that are ready to test RRV-TV vaccine should also be considered for trials of new vaccines. The change in the protocols would be minimal, and the delay in preparation for the trials would be diminished. The group recognized that all protocols should be comparable, and that the studies be designed in such a way that the data could be compared to existing data on rotavirus vaccines. The group cited four vaccine candidates as promising for future efficacy evaluation in developing countries: 1) bovine rotavirus reassortant vaccines based on the WC3 strain – developed by Merck and undergoing phase II and III trials; 2) bovine rotavirus reassortant vaccines based on UK strain – developed by NIH and licensed to Wyeth Lederle; no clinical studies are currently under way; 3) human rotavirus vaccine strain 89-12 – developed by SmithKline Beecham and undergoing phase II trials; and 4) ovine rotavirus strain LLR – developed at Lanzhou Institute in China and undergoing phase III trials.

Should neonatal vaccination be tested? The group regarded neonatal vaccination as an attractive option for several reasons. First, the low background risk early in life would make the association with this schedule and intussusception relatively easy to identify. Second, take of vaccine might be increased in the neonatal gut before the colonization with microbial flora. Preliminary data from India support this hypothesis. Third, early vaccination might be necessary to provide protection before the earlier exposure to

natural infection in developing countries. Fourth, neonates are accessible in many developing country settings through EPI programmes that give BCG and OPV as a neonatal dose. It was noted that this recommendation is not universally followed however, and that even where neonatal vaccination is practiced doses are often given late. Finally, a single dose of vaccine in the neonatal period might be effective, and if so would result in cost savings in the rotavirus vaccine programme. The group recommended that neonatal schedules be studied, both with a single dose and with a later booster dose. Other schedules, such as a one-month vaccination, might also be studied. The group noted, however, that evaluating new vaccines in a schedule consistent with EPI programmes will be most important.

The group further recommended that all trials have close monitoring for intussusception. Prospective trial sites would be encouraged to have a proven record of quality surveillance for and treatment of intussusception.

It was also clear to the group that the study sizes of existing vaccine evaluation protocols are too small to assess the possible association of intussusception with vaccine. The group recognized that the first large-scale trial to assess any new vaccine's potential to cause intussusception should be tested in developed countries, where complications can be diagnosed and treated readily. However, efficacy trials in developed countries should proceed concurrently with large safety trials in developed countries.

Discussion following the presentation

Several themes emerged from the discussion following the working group's presentation. One was the commitment to keeping the options for use of RRV-TV open, pending 1) either a country's or investigator's interest in testing the vaccine, or 2) changes in the three criteria cited by the working group to delay further testing. Specifically, if the risk of intussusception is found to be much lower than the preliminary data from CDC might suggest, the recommendation should be reconsidered. In addition, participants pointed out that, programmatically and ethically, trials with RRV-TV should be undertaken only if the supply of the vaccine following a successful trial is assured. Several participants noted that no data support the idea that candidate vaccines are less associated with intussusception than RRV-TV, and that the risk of intussusception associated with RRV-TV in developing country settings is unknown.

Several participants voiced the opinion that trials be conducted in developed and developing countries in parallel and concurrently. The paradigm used for RRV-TV of conducting trials and introducing the vaccine in developed countries before developing countries is not in the best interest of the countries that need the vaccines most. Not only is there an urgent need to expedite testing and introduction of these vaccines in developing countries but also concerns over the safety of RRV-TV in developing countries might have been minimized if there had been data from large trials in these settings at the time of United States introduction.

Finally, a strong consensus was voiced for planning future studies of vaccine to include active, reliable detection and care for children who might have intussusception in the trials. It was mentioned that this does not necessarily imply that the studies cannot be conducted in developing countries, but may limit the early trials to large, urban areas with appropriate facilities. There was no consensus as to what appropriate treatment means in this context, but a general feeling was voiced that criteria for diagnosis and treatment of intussusception be developed before design of trials. In addition, informed consent should discuss fully the possible risks, and community agreement should be

sought for trials.

8.4 Working Group on Regulatory and Supply Issues

Moderators: Drs Homma and Chaloner-Larsson

Dr Gillian Chaloner-Larsson opened the discussion with the statement that each country that is interested in licensing a vaccine is responsible for its own decision and evaluation of the data, and each must have a protocol developed to facilitate these decisions. Countries will have to have some of the below components, depending on whether they are producing vaccine or merely importing vaccine. 1) They must be able to assess clinical trial protocols and data. They will be involved in the review, approval, and monitoring of studies. 2) They will be responsible for licensing and lot release decisions. This will entail a review of licensing documents, evaluation of technical data, evaluation of data from clinical trials, and the review and release of vaccine lots. 3) They must assess initially and periodically review production facilities to assure Good Manufacturing Practices (GMP). Countries that only plan on importing vaccine will need only licensing and lot release functions, and will need to conduct field surveillance and access production laboratories when necessary.

Dr Chaloner-Larsson outlined six critical functions regarding regulation of vaccines: licensing, surveillance, lot release, laboratory access, GMP inspections, and clinical evaluations. How many of these functions a country accepts depends on the source of the vaccine it uses. If procured from a United Nations (UN) agency, the country needs only to oversee licensure and surveillance for disease and adverse events. If the country procures vaccine independently of a UN agency, the additional tasks of releasing lots of vaccine for use and accessing laboratories will be necessary. Finally, if a country produces vaccine, all six functions are required.

Dr Chaloner-Larsson related comments of the group, but cautioned that they did not represent group consensus. She divided the comments into general observations, regulatory comments and supply-issue comments. In general, she reminded the group that RRV-TV is still licensed in the USA and the European Union. Although vaccine recommendations have been withdrawn, licensure is still intact. She also reminded the group that the FDA makes regulatory decisions only for the USA, and only for products sold in the United States. If a trial of RRV-TV were conducted outside of the USA, the FDA would not necessarily have to approve it. She stated that the technology for RRV-TV regulation takes time to develop, so that alerting regulatory authorities in countries well in advance of proposed licensure is advised. Licensure is not absolute. For example in India, licensure for new products can be given for one year, during which additional data on the safety and efficacy are expected to be collected. If the data are acceptable, the license can be extended.

Regulatory comments

Participants thought that phase III trials should focus on efficacy determinations and leave safety issues to be tested in phase IV trials. However, industry may prefer not to take a risk on the usual paradigm and will want safety determination before licensure. It is clear that all trials with any vaccine must evaluate the possibility that the vaccine causes intussusception. The group recommended parallel conduct of trials in developed and developing countries to speed the process of introduction. Baseline rates of intussusception should be known before the start of any trial.

WHO'S role in regulatory affairs should include: 1) assessment, training and support of national regulatory authorities; 2) assessment and support of developing country manufacturers; 3) assessment of product for export; and 4) promotion and support of research and development of rotavirus vaccines. An example of this is the support WHO is providing to China in developing local rotavirus vaccines.

Supply issues

Currently no vaccine is available for licensure in developing countries. A few countries have the capacity and infrastructure to locally produce rotavirus vaccines. These efforts may require technology transfer, development of local vaccine strains, development of a GMP facility, conduct of local clinical trials and the capability to carry out the regulatory functions listed above. The group wondered if enough manufacturing capacity would be available if there were demand for a rotavirus vaccine. Local production in one or two countries may not be sufficient to satisfy supply. She noted that there were mechanisms to finance essential vaccines for very poor countries. Finally, she stated that in training provided by WHO to local regulatory authorities, local and international manufacturers should be held to the same criteria.

Discussion following the presentation

Much of the discussion again revolved around the notion that a level of safety required of vaccines be outlined in anticipation of trials. Several participants noted that the acceptable level of risk is a setting-specific condition, so the level must be adjusted to the context of each setting. It was pointed out that until you know the benefit of the vaccine (i.e. efficacy), definitions of the acceptable risk are premature. One possible solution to the confusion about the order of trials is to design a large trial to examine safety, but have defined periods of interim analyses to examine efficacy. In this way, one could evaluate the risk-benefit questions in an ongoing and more timely manner. Some participants pointed out that large safety trials are likely to be conducted in developed countries first, regardless of the recommendations of this group, so that some safety data will be known prior to design of trials in developing countries.

It was noted that some of the reluctance on the part of manufacturers is the real or perceived problem of data from developing country trials damaging the safety profile of a vaccine. That is, if a child in Bangladesh were to die during a trial, the death would have to be listed as a complication in the package insert. Participants thought that manufacturers could work with the FDA to minimize this risk and relieve this obstacle to initiating studies in developing countries. Some participants noted that this has not been a problem with several other vaccines.

8.5 Ethical Issues Working Group

Chairs: Drs Chokevivat, Weijer, and Snider

Dr Dixie Snider presented the first part of the working group's summary. He reminded the group that the summary only takes into account the ethical considerations of whether to continue trials, and does not account for social, political, pragmatic, economic and other issues. The first question to be answered was whether a vaccine withdrawn in the USA could be used in developing countries. The group agreed that it was ethical to proceed with trials of such a vaccine, provided that it be used only in clinical trials, that

informed consent be obtained and that it be used only where the benefit is likely to outweigh the potential risks. The group also agreed that one can test a vaccine with known adverse events that are likely to be serious or fatal. This is acceptable when the expected risks of the vaccine is small in relation to the expected benefits. Several examples of experience with other vaccines were given to illustrate this point, including measles vaccine, OPV, smallpox vaccine and others. The group advocated that the community be involved in decision-making about vaccine trials, and that trials in developed and developing countries be conducted concurrently and in parallel.

Dr Charles Weijer divided his summary into three parts – ethics, safeguards and availability. First, he reviewed the finding of the group that inaction was not a morally neutral choice. The distinction between action and inaction is often a post-hoc rationalization. The determinants of the ethics of an action should be based on the finding of a public health problem and the presence of a favourable balance between risks and benefits of an intervention (from the viewpoint of study participants). Failure to proceed with further trials of RRV-TV, he said, would further any existing inequities in health between developed and developing countries. Safeguards that should be in place in the setting of a trial include: 1) a favourable risk-benefit based on evidence; 2) informed consent that is sensitive to local cultures; 3) community involvement in the development of consent and in the definition of appropriate risks and benefits of the intervention; and 4) the monitoring of adverse events during the trial. Finally, the requirement for the availability of an intervention to participants after the completion of a trial is important but not always necessary.

Dr Weijer concluded by asserting that the data developed for RRV-TV far exceed the data available on other vaccines. Inaction, waiting for comparable data on other vaccines, is not morally neutral, since the disease burden cannot be ignored in the interim. He concluded that it would be immoral not to proceed with trials of RRV-TV in developing countries.

Discussion following the presentation

Much of the discussion was of the central theme of whether RRV-TV should be used in trials or not. While the participants had few comments about the ethical issues in making this decision, several were concerned about future availability of the vaccine. They asserted that if no vaccine were available following trials, the data are not useful and resources have been wasted. The group agreed that if it were clear that no vaccine was available, the ethical argument might change as well. Another worry was that the ethical arguments were based on the perceived risk-benefits, for which few quality data were available. Certainly, some said, more children die of rotavirus than will of vaccine-associated intussusception, but the ratio is not defined. These data need to be collected before decisions are made. Several participants agreed with the recommendations of the group and reminded other participants of the continuing disease burden and the risk of a delay in progress towards introduction of rotavirus vaccines. They felt that a strong statement from WHO in support of further testing of the vaccine would provide industry the incentive to continue interest and ensure availability of the vaccine.

Dr Kim Mulholland summarized some concerns he had about this recommendation. He noted that existing EPI vaccines are generally against severe or fatal diseases for which no treatment is available and so the risk of disability or death from these diseases is fairly uniform within a developing country. This is not the case with rotavirus vaccines, and the risk of severe disease with fatal outcome is quite variable within a country.

Because of this, the risks and benefits of the vaccine are likely to be unevenly spread within a population. The implications for a vaccine trial are that any site that can conduct good surveillance for intussusception and provide appropriate treatment will enrol children at a low or almost zero risk of death, although this may not have been the case prior to the study in the same community. Under such conditions, the risks and benefits need to be viewed at the individual level and at the level of the trial community, as well as at the level of the country as a whole. It is important that the ethical aspects are carefully thought through before embarking on future studies with RRV-TV vaccine or other rotavirus vaccines in developing countries.

9. Recommendations

1. The group strongly encouraged the rapid development of new rotavirus vaccine candidates. Any trials of new rotavirus vaccines must assess the potential risk of intussusception with the use of the vaccine. The group strongly encouraged parallel testing of new rotavirus vaccine candidates in developed and developing countries.

   The group also recommended that a rotavirus vaccine schedule mirror, as much as possible, the current country-specific calendar of immunizations. Rotavirus vaccines are to be given at the same time as other EPI antigens. Serologic studies should confirm a lack of effect on EPI antigens. National control authorities should be intimately involved in protocol design.

2. The group agreed that further studies of the current rotavirus vaccine (RRV-TV) in developing countries were ethical, given the higher disease burden and potential higher benefit/risk ratio in a developing country. The group was careful, however, in insisting that further testing of RRV-TV not occur without the assurance that the vaccine would be available for general use should the results of the trial prove to be positive. In addition, RRV trials would have to ensure access to proper management for cases of intussusception, should they occur.

3. The group recommended that the current WHO rotavirus disease burden protocol be used to conduct disease burden studies in selected developing countries.

4. The group strongly recommended that WHO encourage research activities on the pathogenesis and epidemiology of intussusception. Case definitions and baseline incidence studies in countries likely to be interested in testing new rotavirus vaccines were strongly encouraged.

5. The group recommended that WHO provide continuing support to the national regulatory authorities (NRA) of developing countries to reach international standards for vaccine regulation. Particular to this workshop, it was recommended that WHO aid NRAs in countries where rotavirus clinical trials are proposed, or where local production of rotavirus vaccine exists or is contemplated, in their evaluation of clinical safety and efficacy protocols and the quality of clinical trial product.

6. Laboratory surveillance of rotavirus strains should be continued, particularly in Africa and Asia.

Annex 1: Agenda

Wednesday, 9 February

09:00-09:05	Opening	M. Scholtz
09:05-09:10	Adoption of agenda	M. La Force
09:05-09:15	Overview of the issues	B. Ivanoff
I. Background information		
09:15-09:45	Background on rotavirus and rotavirus vaccines	R. I. Glass
09:45-10:00	Discussion	
10:00-10:30	Mortality of rotavirus diseases in developing countries	M. Miller
	Policy evaluation of rotavirus vaccine	
10:30-10:45	Discussion	
10:45-11:15	*Coffee break*	
11:15-11:45	Review of data on intussusception and RRV-TV	J. Livengood
11:45-12:30	Discussion	
12:30-13:45	*Lunch*	
II. Intussusception among children in developing countries		
13:45-14:45	1. Epidemiology	
	Peru	C. Lanata
	Venezuela	I. Perez-Schael
	Brazil	A. Linhares
	India	M.K. Bhan
	South Africa	A.D. Steele
14:45-15:00	Discussion	

15:00-15:20	2. Pathogenesis, treatment and outcomes of intussusception in industrialized countries	P. Offit
15:20-16:00	*Coffee*	
16:00-16:50	Views from developing countries	
	India	M.K. Bhan
	Bangladesh	D. Sack
	Viet Nam	D.D. Trach
	China	Z.S. Bai
16:50-17:10	Discussion	
17:10-17:30	3. Monitoring intussusception in field trials	M.K. Bhan
17:30-17:45	Discussion	
17:45-18:00	4. Can vaccine associated intussusception be avoided?	
	Neonatal immunization	T. Vesikari
18:00-18:20	Discussion (other strains, route of immunization, new vaccine: VLPs)	
18:30	*End of the session*	

Thursday, 10 February

09:00-09:20	5. Report of a workshop held at NIH on future direction for research on the relationship between intussusception, viral infection and vaccines	M. Gerber
09:00-09:30	Discussion	

III. Rotavirus vaccines

09:30-10:00	1. Industry perspectives:	
	Regulatory perspectives and expectation	P. Minor
	Liability issues at home and abroad. How will domestic decisions effect decisions for vaccine use abroad?	Industry
10:00-10:20	Discussion	
10:20-10:45	*Coffee*	

10:45-11:10	2. Ethical issues	
	Is it ethical to make different vaccines for different markets? Risks and benefits issues	C. Weijer
	Some risks and benefits issues related to childhood vaccines	J. Clements
11:10-11:30	Discussion	
11:30-12:10	3. Characteristics and status of rotavirus vaccine development	
	RRV-TV/Bovine	Wyeth
	WC3	Merck
	89-12	SmithKline
	LLR	Lanzhou
12:10-12:30	Discussion	
12:30-14:00	*Lunch*	
14:00-16:00	Working groups	
16:00 -16:15	*Coffee break*	
16:15-17:15	Presentation of the Working Groups and discussion (Summary report written)	
17:30	End of the session	
18:00	*Cocktail*	

Friday, 11 February

9:00-12:00	Presentation of the Working Groups and discussion	
10:30	*Coffee break*	
10:45	Presentations continued	
12:30	*Lunch*	
14:00-16:00	Presentation of the Working Groups and discussion	
15:15	*Coffee break*	
16:30-17:30	Recommendation	M. La Force
17:30	Closure	B. Melgaard

Annex 2: Working Groups

I. Epidemiological surveillance and disease burden

A. Linhares, B. Black

Many countries have little knowledge of the role played by rotavirus as a cause of diarrhoeal disease or child mortality. What data will be required for countries to consider the future introduction of rotavirus vaccines? How can countries simply and economically assess their own burden of rotavirus-associated mortality and morbidity and provide regional data on disease patterns? What role will economic data play in the decision-making process? *This group will attempt to arrive at some simple strategies and directions to address issues of epidemiological surveillance and disease-burden assessment that could facilitate future decision- making concerning the introduction of rotavirus vaccines.*

II. Epidemiology of intussusception in developing countries

I. Perez-Schael, J.Clemens

Children in developing countries are exposed to a myriad of enteric pathogens every day. How do these effect their baseline rates of intussusception and what risk factors can be identified that could explain why some children get intussusception while others do not? Are children in developing countries protected against intussusception in the first few months of life when rotavirus vaccines might be added to the current schedule of neonatal or EPI immunizations (0, 6, 10, 14 weeks)? How do the rates of intussusception vary according to time, place and person? Many questions need to be addressed in considering the problem of intussusception among children in developing countries that would influence our thinking about rotavirus vaccines. *This group will address and define the types of studies that will need to be conducted.*

III. Clinical trial issues

M.K. Bhan, T. Vesikari

Two priorities for testing the live oral rotavirus vaccines have been to ascertain whether they are efficacious for children in developing countries of Africa and Asia, and to determine whether neonatal immunization would be a preferred strategy for vaccination. Studies to address these questions with RRV-TV were cut short because of the problem of intussusception and remain to be addressed. Should these questions be readdressed and trials continued with the Rhesus or other candidate vaccines? Would RRV-TV or

other candidate vaccines be available for further trials? What safeguards need to be incorporated into future trials to ensure that episodes of intussusception could be identified in timely fashion and these children triaged to proper care? Should large-scale safety trials be conducted in developing countries and what level of safety would be required given the relative morbidity and mortality of the disease?

IV. Regulatory and supply issues

A. Homma, G. Chaloner-Larsson

Who will provide vaccines for developing countries? Should studies be pursued with RRV-TV vaccine? If so, what are the hurdles to address for its use? Should WHO encourage local production in China, Viet Nam, India, Brazil, Indonesia and other countries? Should the donor community support the testing of new candidate vaccines in developing countries at the same time they are being tested in developed countries, or should these trials be conducted in sequence? Should the international community support the development and testing of locally prepared rotavirus vaccines that have been cleared for testing by the local regulatory control authorities? Should the international community help manufacturers in developing countries work to improve the quality of locally prepared vaccines? What laboratory support is needed by WHO to ensure the potency, quality, safety of rotavirus vaccines under development?

V. Ethical issues

V. Chokevivat, C. Weijer, D. Snider

Can a vaccine withdrawn from the US market be used in developing countries? Can we support testing a vaccine with known adverse risks that can be fatal? What safeguards will be required? Would it be ethical to not use a vaccine that could prevent against a large burden of fatal disease? Should new candidate vaccines being developed by industry be tested simultaneously in developed and developing countries or in sequence? This group needs to address difficult ethical issues for a vaccine aimed at a disease which is commonly fatal in developing countries but rarely fatal in the developed world.

Annex 3: List of participants

Dr Penny Adcock, Merck Research Laboratories, Cellular and Molecular Biology, P.O Box 4, Att: BL3 3, West Point, PA 19486-0004, USA
Tel: +1 610 397 2615; Fax: +1 610 397 7679
E-mail: penny_adcock@merck.com

Dr Jeffrey Almond, Aventis Pasteur, Pasteur-Mérieux Connaught , 1541 Avenue Marcel Mérieux, 69280 Marcy l'Etoile, France
Tel: +33 437 37 9453; Fax: +33 437 37 9157
E-mail: jalmond@f.pmc-vacc.com

Dr Jacques Armand, Aventis Pasteur SA, 2, avenue Pont Pasteur, 69280 Marcy L'etoile, France
Tel: +33 4 37 37 35 61; Fax: +33 4 37 37 39 50
E-mail: jarmand@fr.pmc-vacc.com

Dr Shams, El Arifeen, ICDDR,B, Public Health Services Division , Child Health Programme, Mohkhali, Dhaka, Bangladesh
Tel: +880 2 871751; Fax: +880 2 886050
E-mail: shams@icddrb.org

Dr Zhi-Sheng Bai, Lanzhou Institute of Biomedical Products, 118, Yan Chang Road , Lanzhou 730046, China
Tel: +86 931 888 83 11; Fax: +86 931 836 7199
E-mail: baizs@public.iz.gs.cn

Dr David I. Bernstein, Children's Hospital Medical Center, Division of Infectious Diseases, CH 1331, 3333 Burnet Avenue, Cincinatti, OH 45229, USA
Tel: +1 513 636 7625; Fax: +1 513 636 7682
E-mail: dib@chmcc.org

Dr Natth Bhamarapravati, Mahidol University at Salaya, Center for Vaccine Development, Institute of Sciences & Technology for Development, 22/25 Phutthamonthon 4, Nakhonpathom 73170, Thailand
Tel: +66 2 441 9744; Fax: +66 2 441 9744
E-mail: stnbm@mucc.mahidol.ac.th

Dr M.K. Bhan, All India Institute of Medical Sciences, Department of Pediatrics, Ansari Nagar, New Delhi 110029, India
Tel: +91 11 649 3883; Fax: +91 11 686 2663
E-mail: community.research@cih.uib.no

Professor Ruth F. Bishop, Royal Children's Hospital, Department of Gastroenterology, Flemington Road, Parkville, Victoria 3052, Australia
Tel: +61 3 9345 5062; Fax: +61 3 9345 6240
E-mail: bishopr@cryptic.rch.unimelb.edu.au

Dr Robert Black, Department of International Health, Johns Hopkins University, 615 North Wolfe Street, Room 5039, Baltimore, MD 21205-2179, USA
Tel: +1 410 955 3934; Fax: +1 410 955 7159
E-mail: rblack@jhsph.edu

Dr Michael D. Blum, Global Safety Surveillance and Epidemiolgy, Wyeth-Ayerst Research, 240 North Radnor-Chester Road, St. Davids, PA 19087, USA
Tel: +1 610 902 2982; Fax: +1 610 989 5551
E-mail: blumm@labs.wyeth.com

Dr Robert F. Breiman, National Vaccine Program Office, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Mailstop A11, Atlanta, GA 30333, USA
Tel: +1 404 687 6672; Fax: +1 404 687 6687
E-mail: rfb2@cdc.gov

Dr Joseph S. Bresee, Centers for Disease Control and Prevention, Division of Viral and Rickettsial Diseases, 1600 Clifton Road, N.E., Atlanta, GA 30333, USA
Tel: +1 404 639 4651; Fax: +1 404 639 3866
E-mail: jsb6@ciddvd1.em.cdc.gov

Mr Alan Brooks, Bill & Melinda Gates Children's Vaccine Program, PATH, 4 Nickerson Street, Suite 300, Seattle, WA 98109, USA
Tel: +1 206 285 3500; Fax: +1 206 285 6619
E-mail: abrooks@path.org

Dr Kathryn Carbone, FDA/CBER HFM 445, 1401 Rockville Pike, Rockville, MD 20852, USA
Tel: +1 301 827 1973; Fax: +1 301 496 1810

Dr Gillian Chaloner-Larsson, GCL Bioconsult, 130 Lewis Street, Ottawa, Ontario, Canada K2P 0S7
Tel: +1 613 232 1600; Fax: +1 613 232 7018
E-mail: larsson@intranet.ca

Dr Vichai Chokevivat, Office of Inspector General, Building 2, 5th Floor, Office of Permanent Secretary, Ministry of Public Health, Nonthaburi 11000, Thailand
Tel: +66 2 590 3022; Fax: +66 2 591 8397
E-mail: vichai@health.moph.th

Dr H. Fred Clark, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
Tel: +1 215 590 2044; Fax: +1 215 590 2025
E-mail: clarkf@email.chop.edu

Dr John Clemens, International Vaccine Institute, Kwanak P.O.Box 14 ,
Seoul 151-600, Republic of Korea
Tel: +82 2 872 2801; Fax: +82 2 872 2803
E-mail: jclemens@ivi.org

Dr Jean Cohen, INRA Virologie, 7832 Jouy-en Josas Cedex, France
Tel: +33 1 34 65 26 04; Fax: +33 1 34 65 26 21
E-mail: cohen@biotech.joy.inra.fr

Dr Margaret E. Conner, Baylor College of Medicine, Division of Molecular Virology, One Baylor Plaza; Texas Medical Center, Houston, TX 77030-3498, USA
Tel: +1 713 798 3590; Fax: +1 713 798 3586
E-mail: mconner@bcm.tmc.edu

Dr Philip E. Coyne, The World Bank, Africa Region Room S-8-029,
1818 H Street, NW, Washington, D.C. 20433, USA
Tel: +1 202 458 1511; Fax: +1 202 522 3157
E-mail: pcoyne@worldbank.org

Dr George T. Curlin, NIAID/NIH, Division of Microbiology and Infectious Diseases, National Institutes of Health, 6700-B Rockledge Drive - Room 3143, Bethesda, MD 20892, USA
Tel: +1 301 496.5893; Fax: +1 301 480 4528
E-mail: gc24a@nih.gov

Dr Thierry Darcis, SmithKline Beecham Biologicals, rue de l'Institut 89,
B-1330 Rixensart, Belgium

Dr Beatrice De Vos, SmithKline Beecham Biologicals, rue de l'Institut 89,
B-1330 Rixensart, Belgium
Tel: +32 2 6569122; Fax: +32 2 656 8133
E-mail: beatrice.de-vos@sbbio.be

Ms Andrée Delem, SmithKline Beecham Biologicals, rue de l'Institut 89,
B-1330 Rixensart, Belgium
Tel: +32 2 656 8353; Fax: +32 2 656 8133
E-mail: andree.delem@sbbio.be

Dr Ulrich Desselberger, Public Health and Clinical Microbiology Laboratory, Level 6, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QW,
United Kingdom
Tel: +44 1223 21 6816; Fax: +44 1223 242775
E-mail: ulrich.desselberger@msexc.addenbrookes.uk

Dr Roland Dobbelaer, Scientific Institute of Public Health Louis Pasteur, Biological Standardization Section, 14, Juliette Wytsmanstraat, B-1050 Brussels, Belgium
Tel: +32 2 642 50 50; Fax: +32 2 642 52 10
E-mail: roland.dobbelaer@iph.fgov.be

Dr Thomas Eckhardt, Wyeth Lederle Vaccines, North Middletown Road, Pearl River, NY 10965, USA
Tel: +1 914 732 4282; Fax: +1 914 732 2436
E-mail: eckhart@war.wyeth.com

Dr William Egan, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, USA
Tel: +1 301 827 0652; Fax: +1 301 827 0448
E-mail: egan@cber.fda.gov

Dr Jose G. Esparza, UNAIDS, CH-1211 Geneva 27, Switzerland
Tel: +41 22 791 4392; Fax: +41 22 791 4860
E-mail: esparzabrachoj@wholint

Ms Thea Fischer, Statens Seruminsitut, 5, Artillerivej, DK-23 Copenhagen S, Demark
Tel: +45 3268 3268; Fax: +45 3268 3165
E-mail: thea@dadlnet.dk

Dr Peter I. Folb, University of Cape Town, Department of Pharmacology, OMB, Groote Schur Hospital, Observatory 7925, Cape Town, South Africa
Tel: +27 21 406 6286; Fax: +27 21 448 6181
E-mail: pfolb@uctgsh1.uct.ac.za

Dr Ruth Frischer, U.S. Agency for International Development, G/PHN/CS, Ronald Reagan Building, Room 3.07, 3rd floor, 1300 Pennsylvania Avenue, Washington, D.C. 20523, USA
Tel: +1 202 712 0771; Fax: +1 202 216 3702
E-mail: rfrischer@usaid.gov

Dr Michael A. Gerber, National Institutes of Health, NIAID/DMID/CRAB, Room 3104, 6700-B Rockledge Drive, MSC 7630, Bethesda, MD 20892, USA
Tel: +1 301 402 8339; Fax: +1 301 402 0804
E-mail: mg289d@nih.gov

Dr Roger Glass, Centers for Disease Control and Prevention, Viral Gastroenteritis Unit (G04), 1600 Clifton Road, Atlanta, GA 30333, USA
Tel: +1 404 639 3577; Fax: +1 404 639 3645
E-mail: rig2@cdc.gov

Dr Tore Godal, Global Alliance for Vaccines and Immunization, UNICEF, Palais des Nations, CH-1211 Geneva 10, Switzerland
Tel: +41 22 909 5020; Fax: +41 22 909 5900
E-mail: tgodal@unicef.ch

Dr Jesse L. Goodman, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852, USA
Tel: +1 301 435 5680; Fax: +1 301 827 0440
E-mail: goodmanj@cber.fda.gov

Dr Leif Gothefors, University of Umea, Department of Pediatrics,
S-901 85 Umea, Sweden
Tel: +46 90 9852102; Fax: +46 90123728
E-mail: leif.gothefors.us@vll.se

Dr Harry B. Greenberg, Grant Professor of Medicine and , Microbiology and Immunology, Senior Associate Dean for Research, Stanford University School of Medicine, Dean's Office M 121, 300 Pasteur Drive, Stanford, CA 94305-5119, USA
Tel: +1 650 498 4379; Fax: +1 650 725 7368
E-mail: hbreen@stanford.edu

Dr Akira Homma, Oswaldo Cruz Foundation, Av. Brasil 4365 - Manquinhos,
Rio de Janeiro, CEP 21045 900, Brazil
Tel: +55 21 590 5114; Fax: +55 21 260 6707
E-mail: homma@netra.castelo.fiocruz.br

Dr Jacob Johns, 439 Civil Supplies Godown Lane, Kamalakshipuram,
Vellore TN 632 002, India
Tel: +91 416 262 603; Fax: +91 416 262 268
E-mail: tjjohn@md4.vsnl.net.in

Dr Mark Kane, PATH, 4 Nickerrson Street, Suite 300, Seattle, WA 98109, USA
Tel: +1 206 285 3500; Fax: +1 206 285 6619
E-mail: mkane@path.org

Dr Albert Z. Kapikian, NIH/NIAID, Laboratory of Infectious Diseases, National Institutes of Health, Building 7, Room 103, Bethesda, MD 20892, USA
Tel: +1 301 496 3371; Fax: +1 301 496 8312
E-mail: akapikian@niaid.nih.gov

Dr Paul Kilgore, International Vaccine Institute, Kwanak P.O.Box 14, Kwanak-Ku,
Seoul 151-600, Republic of Korea
Tel: +82 2 882 2964; Fax: +82 2 872 2803
E-mail: pkilgore@ivi.org

Dr Piotr Kramarz, CDC, MS-E61 Epidemiology & Surveillance, National Immunization Program, 1600 Clifton Road, Mailstop E 61, Atlanta 30333, USA
Tel: +1 404 639 8693; Fax: +1 404 639 8834
E-mail: pdk3@cdc.gov

Dr Ella Krishna, Bharat Biotech, 726 Road #3, Banjara Hills, Hyderabad 50034,
India
Tel: +91 40 3350794; Fax: +91 40 3350 344
E-mail: ellakrishna@yahoo.com

Professor F. Marc LaForce, BASICS II, Suite 300, 1600 Wilson Boulevard,
Arlington, VA 22209, USA
Tel: +1 703 312 6576; Fax: +1 703 312 6900
E-mail: mlaforce@basics.org

Dr Paul-Henri Lambert, University of Geneva, 1 rue Michel Servet, CH-1211 Geneva 4, Switzerland
Tel: +41 22 702 57 77; Fax: +41 22 702 58 01
E-mail: paul.lambert@medecine.unige.ch

Dr Claudio F. Lanata, Instituto de Investigación Nutritional, La Molina, Apartado Postal 18 0191, Miraflores, Lima 18, Peru
Tel: +51 1349 6023; Fax: +51 1349 6025
E-mail: clanata@ii.sld.pe

Dr Dennis Lang, NIAID/NIH, 6700B Rockledge Drive, Room 3110, Bethesda, MD 20892, USA
Tel: +1 301 496 7051; Fax: +1 301 402 1456
E-mail: dl73v@nih.gov

Professor Myron M. Levine, University of Maryland School of Medicine, HSF-Room 480 , 685 W. Baltimore Street, Baltimore, MD 21201, USA
Tel: +1 410 706 7588; Fax: + 1 410 706 6205
E-mail: mlevine@medicine.umaryland.edu

Dr Alexandre C. Linhares, Instituto Evandro Chagas, Virology Section, Av. Almirante Barroso, 492, 66.050 Belem, Para, Brazil
Tel: +55 91 211 4403; Fax: +55 91 2142005
E-mail: linhares@supridad.com.br

Dr John R Livengood, National Immunization Program, MS E61, Centers for Disease Control and Prevention, 1660 Clifton Road NE, Atlanta GA 30333, USA
Tel: +1 404 639 8254; Fax: +1 404 639 8616
E-mail: jrl1@cdc.gov

Dr Nguyen Van Man, National Institute of Hygiene and Epidemiology, 1 Yersin Street, Hanoi 10 000, Viet Nam
Tel: +84 48 266352; Fax: +84 48 210853
E-mail: nihe@netnam.org.vn

Dr David Matson, Center for Pediatric Research, 855 West Brambleton Avenue, Norfolk, VA 23510-1001, USA
Tel: +1 757 668 6400; Fax: +1 757 668 6475
E-mail: dmatson@chkd.com

Dr James Maynard, PATH, 4 Nickerson Street, Suite 300, Seattle, WA 98109, USA
Tel: +1 206 285 3500; Fax: +1 206 285 6619
E-mail: jmaynard@path.org

Dr René Mignolet, Wyeth Lederle Vaccines, Rue du Bosquet 15, B-1348 Louvain la Neuve, Belgium
Tel: +32 10494651; Fax: +32 10 494690
E-mail: mignolr@labs.wyeth.com

Dr Mark Miller, Fogarty International Center, National Institutes of Health, 31 Center Drive, Room B2C02 Bethesda, MD 20892-2220, USA
Tel: +1 301 496 1415; Fax: +1 301 402 2173
E-mail: millermark@nih.gov

Dr Philip Minor, National Institute of Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Herts. EN6 3QG, United Kingdom
Tel: +44 170 765 4753; Fax: +44 1707 646 730
E-mail: pminor@nibsc.ac.uk

Dr Kare Molbak, Statens Seruminsitut, 5, Artillerivej, DK-23 Copenhagen S, Denmark
Tel: +45 3268 3268; Fax: +45 3268 3165
E-mail: krm@ssi.dk

Dr Trudy Murphy, Centers for Disease Control and Prevention, Childhood & Vaccine Preventable Diseases, Epidemiology Section, 1600 Clifton Road, Mail Stop E-61, Atlanta, GA 30333, USA
Tel: +1 404 639 8845; Fax: +1 404 639 8616
E-mail: tkm4@cdc.gov

Dr Osamu Nakagomi, Akita University School of Medicine, Department of Microbiology, Hondo, Akita 010, Japan
Tel: +81 18 884 6079; Fax: +81 188 36 2607
E-mail: onakagom@ipc.akita-u.ac.jp

Dr Paul A. Offit, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
Tel: +1 215 590 2020; Fax: +1 215 590 2025
E-mail: offit@email.ch

Dr Peter R. Paradiso, Lederle Praxis Biologicals Division, 211 Bailey Road, West Henrietta, NY 14586 9728, USA
Tel: +1 716 273 7545/7759; Fax: +1 716 273 7677
E-mail: millerjl@war.wyeth.com

Dr Irene Perez-Schael, Instituto de Biomedicina, Apartado 4043 Carmelitas, Caracas 1010A, Venezuela
Tel: +58 2 814636; Fax: +58 2 861 1258
E-mail: iperez@reaccivn.ve

Dr Stanley A. Plotkin, Aventis Pasteur, 4650 Wismer Road, Doylestown, PA 18901, USA
Tel: +1 215 297 9321; Fax: +1 215 297 9323
E-mail: stanley.plotkin@aventis.com

Dr Regina Rabinovich, Malaria Vaccine Initiative at PATH, 6290 Montrose Avenue, Rockville MD 20852, USA
Tel: +1 301 770 5377; Fax: +1 301 770 5322
E-mail: nregina@aol.com

Dr Guillermo Ruiz-Palacios, Department of Infectious Diseases, Instituto Nacional de la Nutricion Salvador Zubiran, Calle Vasco de Quiroga 15, Delegacion Tlalpan 14000, Mexico City DF, Mexico
Tel: +525 655 9675; Fax: +525 513 0010
E-mail: gmrps@servidor.unam.mx

Dr Philip Russell, Strategic Advisory Council, CVP, 11909 Coldstream Drive, Potomac, MD 20854, USA
Tel: +1 301 299 7313; Fax: +1 809 301 299 7313
E-mail: pkrussell@aol.com

Dr David A. Sack, International Center for Diarrhoeal Disease Research, GPO Box 128 , Dhaka 1000, Bangladesh
Tel: +880 2 88 23 031; Fax: +880 2 88 31 16
E-mail: dsack@icddrb.org

Dr Jerald C. Sadoff, Merck Research Laboratories, Cellular and Molecular Biology, P.O. Box 4, Attn: BL3 3, West Point, PA 19486-0004, USA
Tel: +1 610 397 2615; Fax: +1 610 397 7679
E-mail: jerald_sadoff@merck.com

Dr David M. Salisbury, Department of Health, Immunisation and Communicable Diseases Branch, Wellington House, 133-155 Waterloo Road, London SE1 8UG, United Kingdom
Tel: +44 20 7972 4488; Fax: +44 20 7972 4468
E-mail: dsalisbu@doh.gov.uk

Prof. Philippe J. Sansonetti, Institut Pasteur, 25-28 rue du docteur Roux, F-75724 Paris Cedex 15, France
Tel: +33 1 40 61 30 95; Fax: +33 1 45 68 89 53
E-mail: psanson@pasteur.fr

Dr Florian Schodel, EVAX Technologies, , Fraunhofer str. 10, D-82152 Martinsried Germany
Tel: +49 8 989 967 433; Fax: +49 8 989 967 474
E-mail: f.schodel@evax.de

Dr Alan R. Shaw, Merck Research Laboratories, Cellular & Molecular Biology, WP 16 100, West Point, PA 19486, USA
Tel: +1 215 652 7400; Fax: +1 215 652 2142
E-mail: alan_shaw@merck.com

Dr Claire-Anne Siegrist, Centre Médical Universitaire, 1 rue Michel Servet, 1211 Geveva 4, Switzerland
Tel: +41 22 702 5778; Fax: +41 22 702 58 01
E-mail: siegrist@cmu.unige.ch

Dr Dixie E. Snider, Jnr, Centers for Disease Control and Prevention, 1600 Clifton Road, N.E., Atlanta, GA 30333, USA
Tel: +1 404 539 7240; Fax: +1 404 539 7341
E-mail: des1@cdc.gov

Prof. Bonita Stanton, West Virginia University, 4612 HSC N, Post Office Box 9214, Morgantown, WV 26506, USA
Tel: +1 410 293 4451; Fax: +1 410 706 0653
E-mail: bstanton@hsc.wvu.edu

Dr Duncan Steele, Medical University of South Africa (MEDUNSA), P.O. Box 173, Medunsa 0204, Pretoria, South Africa
Tel: +27 12 521 4117; Fax: +27 12 521 5938
E-mail: adsteele@sunshine.medunsa.ac.za

Dr Georges Thiry, Smithkline Beecham Pharmaceuticals, Clinical R&D, rue de l'Institu 89, B-1130 Rixensart, Belgium
Tel: +32 2 656 9138; Fax: +32 2 656 8133
E-mail: georges.thiry@sbbio.be

Dr Abdelhalim Trabelsi, CHU Farhat Hached, Laboratoire de Microbiologie, avenue Ibn El Jazzar, 4002 Sousse, Tunisia
Tel: +216 3221411; Fax: +216 3 226 702

Prof. Dang Duc Trach, National Institute of Hygiene and Epidemiology, 1 Yersin Street, Hanoi 10 000, Viet Nam
Tel: +84 4 972 2989; Fax: +84 4 8212 660
E-mail: dir@nihe.gov.vn

Dr Timo Vesikari, University of Tampere Medical School, Pediatric Infectious Disease, P.O. Box 607, FIN-33101 Tampere, Finland
Tel: +358 3 2156717; Fax: +358 3 2156170
E-mail: lltive@uta.fi

Dr Emmanuel Vidor, Aventis Pasteur, SA, B.P. 10, 3 avenue Pasteur, F-69348 Lyon Cedex 07, France
Tel: +33 1 47 95 80 50; Fax: +33 1 47 01 07 99
E-mail: evidor@fr.pmc-vacc.com

Dr Richard L. Ward, Division of Infectious Diseases, Children's Hospital Research Foundation, 3333 Burnet Avenue, Cincinnatti, OH 45229-3039, USA
Tel: +1 513 636 7628; Fax: +1 513 636 7632
E-mail: wardd0@chmcc.org

Dr Somsak Wattanasri, Ministry of Public Health, International Division, Office of the Permanent, Secretary, Tivanond Road, Nonthaburi 11000, Thailand
Tel: +66 2 5901969; Fax: +66 2 5901374
E-mail: does@health.mohph.go.th

Dr Charles Weijer, Dalhousie University, Department of Bioethics, 5849 University Avenue, Room C 105, Halifax, Nova Scotia B3 4H7, Canada
Tel: +1 902 494 3801; Fax: +1 902 494 3865
E-mail: cweijer@tupdean2.med.dal.ca

Dr Jolyon White, Medeva Pharma Limited, Gaskill road, Speke, Liverpool, L24 9GR, United Kingdom
Tel: +44 151 705 5057; Fax: +44 151 705 5080

Dr Zhi-yi Xu, International Vaccine Institute, Kwanak P.O.Box 14, Kwanak-Ku, Seoul 151-600, Republic of Korea
Tel: +82 2 872 2926; Fax: +82 2 872 2803
E-mail: xuzhiyi@ivi.org

Dr Mohammad Yunus, ICDDR,B , GPO Box 128, Dhaka 1000, Bangladesh
Tel: +880 2 871751; Fax: +880 2 883116
E-mail: myunus@icddrb.org

WHO Secretariat

Regional Offices

Dr Ottavio de Oliva, Division of Vaccine and Immunization, WHO Regional Office of the Americas/Pan American Sanitary Bureau, 525 23rd Street, N.W.
Washington, D.C. 20037-2895, USA
Tel: +1 202 974 3000; Fax: +1 202 974 3635
E-mail: olivaota@paho.org

Dr Abdulaziz A. Adish, WHO Regional Office for South-East Asia, World Health House, Indraprastha Estate, Mahatma Ghandi Road, New Delhi 110002, India
Tel: 91 11 331 7804; Fax: 91 11 332 7972
E-mail: aadish16@hotmail.com

WHO headquarters
Avenue Appia, 1211 Geneva 27, Switzerland

Dr M. Teresa Aguado, Coordinator, Vaccine Development, Department of Vaccines and Biologicals
Tel: +41 22 791 2644; Fax: +4122 791 4860
E-mail: aguadom@who.int

Ms Maureen Birmingham, Coordinator, Vaccine Assessment and Monitoring, Department of Vaccines and Biologicals
Tel: +41 22 791 4359; Fax: +41 22 7914210
E-mail: birminghamm@who.int

Dr John Clements, Expanded Programme on Immunization, Department of Vaccines and Biologicals
Tel: +41 22 791 4402; Fax: +41 22 791 4193
E-mail: clementc@who.int

Dr Nora Dellepiane, Access to Technologies, Department of Vaccines and Biologicals
Tel: +41 22 791 4711; Fax: +41 22 791 4384
E-mail: dellepianen@who.int

Dr Philippe Duclos, Vaccine Assessment and Monitoring, Department of Vaccines and Biologicals
Tel: +41 22 791 4527; Fax: +41 22 791 4210
E-mail: duclosp@who.int

Ms Maria Dweggah, Assisant to Dr B. Ivanoff, Vaccine Development, Department of Vaccines and Biologicals
Tel: +41 22 791 2350; Fax: 41 22 791 4860
E-mail: dweggahm@who.int

Ms Christine Encrenaz, Secretariat Committee on Research involving Human Subjects (SCRIHS)
Tel: +41 22 791 3663; Fax: +41 22 791 4860
E-mail: encrenazc@who.int

Dr Olivier Fontaine, Department of Child and Adolescent Health & Development
Tel: +41 22 791 2894; Fax: +41 22 791 4853
E-mail: fontaineo@who.int

Dr Bernard Ivanoff, Vaccine Development, Department of Vaccines and Biologicals
Tel: +41 22 791 2698; Fax: +41 22 791 4860
E-mail: ivanoffb@who.ch

Dr Luis Jodar, Vaccine Development, Department of Vaccines and Biologicals
Tel: +41 22 791 3744; Fax: +41 22 791 4860
E-mail: jodarl@who.int

Dr Bjorn Melgaard, Director, Department of Vaccines and Biologicals
Tel: +41 22 791 4408; Fax: +41 22 791 4227
E-mail: melgaard@who.int

Dr Julie Milstien, Coordinator a.i. Access to Technologies, Department of Vaccines and Biologicals
Tel: +41 22 791 4471; Fax: +41 22 791 4384
E-mail: milstienj@who.int

Dr Kim Mulholland, Vaccine Development, Department of Vaccines and Biologicals
Tel: +41 22 791 4760; Fax: +41 22 791 4860
E-mail: mulhollandkim@who.int

Dr Jean Marc Olivé, Coordinator a.i. Programme on Immunization, Department of Vaccines and Biologicals
Tel: +41 22 791 4409
E-mail: olivej@who.int

Dr Tikki Pang, Director, Department of Research Policy and Cooperation
Tel: +41 22 791 2786; Fax: +41 22 791 4169
E-mail: pangt@who.int

Dr Daniel Wikler, Department of Evidence for Healh Policy
Tel: +41 22 791 3043; Fax: +41 22 791 4860
E-mail: wiklerd@who.int