UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL

PRODUCTS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY, MAY 27, 1998

The meeting took place in Versailles rooms I and II, Holiday Inn, 8210 Wisconsin Avenue, Bethesda, Maryland, at 9:00 a.m., Patricia L. Ferrieri, M.D., Chair, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D.	Chair
NANCY CHERRY	Exec. Secy.
WILLIAM FREAS, Ph.D.	Substitute Exec. Sec.
MARY LOU CLEMENTS-MANN, M.D.	Member
REBECCA E. COLE	Member

ROBERT S. DAUM, M.D.	Member
KATHRYN M. EDWARDS, M.D.	Member
DIANNE M. FINKELSTEIN, Ph.D.	Member
HARRY B. GREENBERG, M.D.	Member
CAROLINE B. HALL, M.D.	Member
ALICE S. HUANG, Ph.D.	Member
KWANG SIK KIM, M.D.	Member
STEVE KOHL, M.D.	Member
GREGORY A. POLAND, M.D.	Member
DIXIE E. SNIDER, Jr., M.D.,MPH	Member
ROBERT BREIMAN, M.D.	FDA Consult.
THEODORE EICKHOFF, M.D.	FDA Consult.
THOMAS FLEMING, Ph.D.	FDA Consult.
RANDALL HOLMES, M.D.,Ph.D.	FDA Consult.
DAVID KARZON, M.D.	FDA Consult.
DR. STANLEY CRYZ, Jr.,	Sponsor Rep.
DR. JAMES KAPER	Sponsor Rep.
DR. KAREN KOTLOFF	Sponsor Rep.
DR. MYRON M. LEVINE	Sponsor Rep.
DR. CYRUS SIMANJUNTAK	Sponsor Rep.
DR. CAROL TACKET	Sponsor Rep.
DR. STEVEN WASSERMAN	Sponsor Rep.

FDA CONSULTANTS:

CHARLES CARPENTER, M.D.

DR. ERIC MINTZ

ALISON O'BRIEN, Ph.D.

NATHANIEL PIERCE, M.D.

SPEAKERS:

DR. MARGARET BASH

DR. SCOTT STIBITZ

ALSO PRESENT:

CAROLYN HARDEGREE, M.D.

CONTENTS

PROCEEDINGS

9:14 a.m.

CHAIR FERRIERI: We need to have an open public hearing. I'll just introduce myself first and then -- I'm Pat Ferrieri of the University of Minnesota and I chair the committee, and Nancy Cherry, our executive secretary will introduce the open public meeting.

MS. CHERRY: This is an opportunity for anyone who wishes to make a statement to the committee relative to the subject to be discussed at this session, you could come forward and speak. I've not been notified that anyone wishes to. No one showing any indication then, we will go on with the session.

CHAIR FERRIERI: Thank you, Nancy. Let's start with introductions of the committee then, starting with Dr. Poland. Please state your institution as well.

DR. POLAND: Greg Poland, Mayo Clinic, Rochester.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, Nashville.

DR. HUANG: Alice Huang, Cal Tech.

DR. SNIDER: Dixie Snider, Centers for Disease Control and Prevention.

DR. HALL: Caroline Hall, University of Rochester.

DR. GREENBERG: Harry Greenberg, Stanford.

DR. CLEMENTS-MANN: Mary Lou Clements-Mann, Johns Hopkins University.

DR. FINKELSTEIN: Dianne Finkelstein, Harvard.

DR. DAUM: Robert Daum, University of Chicago.

MS. COLE: Rebecca Cole, Consumer Representative, Chapel Hill, North Carolina.

DR. MINTZ: Eric Mintz, Centers for Disease Control and Prevention.

DR. KIM: I'm Kwang Sik Kim, Children's Hospital, Los Angeles.

CHAIR FERRIERI: Pat Ferrieri, University of Minnesota, Minneapolis.

DR. KARZON: David Karzon, Vanderbilt.

DR. KOHL: Steve Kohl, UCSF.

DR. FLEMING: Tom Fleming, University of Washington.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. BREIMAN: Rob Breiman, National Vaccine Program Office.

DR. O'BRIEN: Alison O'Brien, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

DR. HOLMES: Randy Holmes, University of Colorado, Denver.

DR. PIERCE: Nate Pierce, Johns Hopkins University.

CHAIR FERRIERI: Thank you. Before we start we'd just like to mention that we conduct business by raising hands and being recognized. Speak and then introducing yourselves so that we have everything for the transcriber. Everything you say today is transcribed so that might influence you in your thinking and speaking.

MS. CHERRY: And the transcripts appear on the Internet.

CHAIR FERRIERI: Thank you, Nancy. I did not know that, or I hadn't thought of that.

Well, this is Session 4 for us. It's open and it's dedicated to the Cholera vaccine, Live Oral CVD 103-HgR, from the Swiss Serum and Vaccine Institute. And I'll turn the meeting over now to Dr. Scott Stibitz from FDA who will introduce the subject and then he can introduce the other two speakers.

We will do everything we can to stay on time

or we will not make the agendas for the rest of the day. Dr. Stibitz.

DR. STIBITZ: Thank you. I'd like to thank the committee for the time this morning and the reason why we're here is to seek your input regarding data submitted in support of a product license application for CVD103-HgR, a live oral cholera vaccine. Trade name for this product is Mutacol Berna.

The sponsor for this product is the Swiss Serum Vaccine Institute of Berne, and the indication for this vaccine is for the prevention of cholera in travelers to cholera-affected areas. This PLA was submitted February of 1997.

This slide just gives the vaccine composition. The vaccine is packaged in a foil sachet containing two hermetically sealed compartments, each containing dry ingredients.

Compartment A contains between two and ten times 10^8 viable vaccine organisms of CVD103-HgR. It also contains approximately ten times as many non-viable organisms.

Compartment B contains a dry sodium bicarbonate ascorbic acid buffer and the vaccine is administered by mixing both compartments with 100 milliliters of water and consuming them.

This is just a brief outline of the construction of the CVD103-HgR vaccine strain. I think you'll hear more details about this during the sponsor's presentation. But this strain was created in two steps from the starting of Vibrio cholerae 569B strain.

This cholera strain is of the Classical biotype and the Inaba serotype. It is also non-shigatozin producing. In the first step which was introduced by genetic manipulation the gene for the A subunit of cholera toxin in both chromosoma loci and coding collar toxin was deleted.

This leaves the B subunit gene intact and this strain produces the B subunit in its native pentameric form.

In a second step that was performed primarily to mark this strain phenotypically for environmental studies and not for the purposes of further attenuation, a gene encoding mercury resistance was introduced at the hemolysin gene locus -- the resulting deletion of most of hemolysin gene.

Thus, the desired end phenotype of this strain is that it does not produce the A subunit of collar toxin -- notice it's non-toxigenic -- yet it produces the B subunit of allowing this to be

presented as an antigen to create anti-cholera toxin antibodies. It's also hemolysin-negative and mercury resistant.

Now, the point of this slide is to point out that during the rather lengthy process involved in the creation of this strain, apparently a second unknown or uncharacterized mutation was introduced. And the phenotype of this mutation is that it results in reduced colonization with this vaccine strain.

This reduced colonization can be demonstrated when one compares colonization of CVD103-HgR either to the parental CVD103 or to an analogous strain, CVD103-HgR2, which was created in a manner that involved far fewer passages in vitro.

So that in either a mouse or a rabbit model for colonization, CVD103-HgR is seen to colonize less than either of these two strains. In addition, in human volunteers, CVD103-HgR was shed from human volunteers significantly less than CVD103.

Okay. Now one of the primary reasons we're addressing the VRBPAC today is with questions regarding efficacy of this vaccine. And to put this in context it's necessary to go back about five years now to the VRBPAC meeting of January 1993.

And at this time a generic question was

addressed. That was the question of whether data from human challenge studies could be sufficient to demonstrate efficacy of cholera vaccines for use in travelers to endemic areas, or to cholera-affected areas.

And the reason for asking this question was that there appeared to be differences in the way different populations respond to cholera vaccines, such that travelers from more developed countries where field trials cannot really be performed respond to this vaccine different than residents in cholera-endemic areas where one could and have, performed field trials.

And these differences are revealed by the dose of vaccine which is needed to achieve comparable rates of seroconversion. Thus, in endemic areas approximately a tenfold higher dose of vaccine is needed to achieve the same rate of seroconversion.

In addition, immunogenicity in these populations tends to be less than in naive volunteers. And this has been attributed to two, non-exclusive possibilities.

One is that in endemic areas higher levels of pre-existing immunity to cholera limit the replication of the vaccine organisms, thus engendering

less of an immune response. And also that perhaps competing ileal microflora can also compete with this vaccine strain limiting its replication.

Now, the questions that we're bringing to the panel today are primarily directed at efficacy, and the data submitted to support efficacy in this application have primarily involved the volunteer challenge studies with live Vibrio cholerae.

Now, the degree of protection observed in these studies has varied depending upon the nature of the challenge strain. The highest protection was seen against challenge with the classical parental vaccine strain, 569B, and somewhat lower efficacy was seen with El Tor biotype strains.

In addition, we've just recently received results of a large scale field trial of CVD103-HgR in Indonesia, and this did not demonstrate efficacy against cholera. Possible causes for this -- and I'm sure the sponsors will elaborate on this -- would include that the timing of the disease peak incidence was not optimal relative to time of vaccination.

In addition, the requirement for protection against El Tor biotype of gamma serotype strains -- this is virtually all the disease that was seen was due to strains of this type -- and this represents a

heterologous challenge to this vaccine.

In light of what I've said, the questions for the VRBPAC are as follows. First question: In light of the recent results from the Indonesian field trail, does the panel consider that volunteer challenge studies with Vibrio cholerae can suffice to demonstrate the efficacy of CVD103-HgR in the prevention of cholera in U.S. travelers to cholera-affected areas?

The second question: If the panel considers that challenge studies can be adequate for demonstration of efficacy in travelers, are the data from the challenge studies presented for CVD103-HgR adequate in this regard?

This has four subparts: a) were the challenge studies designed and executed adequately?; b) are the data regarding heterologous biotype challenge (in other words, with El Tor strains) adequate in light of the prevalence of El Tor strains in endemic areas?; c) are the data sufficient to demonstrate protection from challenge for a period of time following vaccination that is sufficient for travelers?; and d) if the panel feels that the data regarding efficacy are not sufficient to support licensure, what additional studies would be needed to

address these issues?

The third question addresses the question of bridging data: Can immunogenicity studies be used to provide bridging data to the adult volunteer population to support administration of this vaccine to children?

And four, we would like the panel to comment on the adequacy of the data supporting safety in the target population -- in adults and in children.

That's all I have at this point. Any questions? If not, I will turn the podium over to Dr. Eric Mintz who will give us some background on the epidemiology of cholera.

CHAIR FERRIERI: Thank you, Dr. Stibitz.

DR. MINTZ: Good morning. It's a pleasure to be here this morning and I'd like to thank the committee for inviting me. Most of the slides I'll show are included on this handout. There are several copies I think, circulating, and there are also some additional references -- copies are also available.

Cholera has challenged humanity for centuries and yet despite our best efforts it is still a disease that remains very much in force today. This talk will focus on cholera epidemiology in the modern era, and I'll begin when cholera ventured forth in

pandemic fashion from its homeland on the Indian subcontinent to populations throughout the rest of the inhabited world.

According to Politzer, the first cholera pandemic began in 1817 and ended six years later in 1823. No isolates of Vibrio cholerae from that pandemic were serogrouped or biotyped; in fact, the bacterial cause of cholera would not be discovered until many years later.

Similarly, pandemics 2, 3, and 4 were caused by Vibrio cholerae of an unknown serogroup and biotype. We do know, however, that the fifth and sixth pandemics were both caused by Vibrio cholerae strains that were serogroup 0-1 and the Classical biotype.

Although other serogroups and biotypes of Vibrio cholerae were recognized causes of diarrheal disease, until the 1960s it was widely believed that only the 0-1 serogroup and the Classical biotype strains had the potential to cause epidemic disease.

The El Tor biotype was first isolated from the dead bodies of returning Pilgrims in Egypt in 1905, and was considered at that time a curiosity. It was not seen again until 1937 when it resurfaced in Egypt and it caused sporadic cases and small outbreaks

there over the next 20 years.

In 1958 the World Health assembly concluded that El Tor Vibrio lacked the capacity for epidemic spread; a decision that was soon overturned in the face of overwhelming evidence to the contrary provided by the 7th pandemic.

This ongoing pandemic that began in 1961, has reached more countries, caused more cases, and has lasted far longer than any of its predecessors. I'll say a bit more about it and the features that distinguish the El Tor from the Classical biotypes shortly.

In 1992 an epidemic of cholera emerged in Madras, India, thoroughly disproving the other tenet of traditional cholera scholarship. The strains from this epidemic did not agglutinate in O-1 antisera or in any of the other existing O-group antisera, and was designated serogroup O-139.

Molecular analyses have since demonstrated that the O-139 strains resemble serogroup O-1 biogroup El Tor strains, although infection with one does not confer immunity with infection to another.

After causing epidemics in a dozen countries on the Indian subcontinent and in Southeast Asia, the O-139 strain has all but disappeared, leading one to

question whether it will return to cause a much heralded 8th pandemic, or sink into public health obscurity.

This slide shows the distribution of cholera during the first six pandemics, from 1817 through 1950. And this slide shows the global spread of the 7th pandemic of cholera from 1961 through 1991 -- the first 30 years of the El Tor pandemic.

To bring this slide up-to-date we should really extend this red line that goes down the coast of South America, eastward along the Amazon River and both South and Northward along the coast of Brazil and the Guyanas.

Please also note this small, green circle marked 1977 in the riverine coastal areas of Queensland, Australia, and this small, yellow circle marked 1973, off the Gulf Coast of the United States. These two circles represent endemic, natural foci of Vibrio cholerae; distinct, toxigenic, Vibrio cholerae, serogroup O-1, biotype El Tor strains that differ from the pandemic strain.

The date represent the years in which the first cases of cholera due to these endemic strains were recognized. Since those years a handful of sporadic cases related to drinking or swimming in

contaminated waters in Australia, or even raw or undercooked shellfish from the Gulf Coast of the United States, have been documented.

However, neither of these strains has spread in epidemic fashion. Over the last decade or two the infamous agent of pandemics 5 and 6, the Classical biotype of V. cholerae O-1, has behaved just like this with a small, endemic focus responsible for a few sporadic cases in only one location in the world -- Bangladesh.

What are some of the clinically and epidemiologically relevant differences between the Classical and the El Tor biotypes? The El Tor strains survives longer in the environment and multiplies faster in foods than the Classical strain. These two pie charts illustrate the symptom profile of patients infected with either Classical or El Tor strains.

Asymptomatic cases, shown in green, represent 59 percent of Classical biotype infections and 75 percent of infections with the El Tor biotype. Severe cholera, shown in red, occurs in 11 percent of those patients infected with Classical strains, and only two percent of those infected with El Tor.

It may be that this apparent, reduced virulence confers a competitive advantage to El Tor

strains. Asymptomatic patients and those with mild or moderate disease may contribute more of the transmission overall than patients with severe cholera who may die soon after their illness begins. Severe illness is also associated with high dose exposure, low gastric acidity and blood group O.

Turning now to cholera surveillance, this histogram shows the number of cases reported to WHO by member nations from 1984 through 1996. Global surveillance for cholera has its problems. Fears of economic sanctions keep many nations from reporting, and even those countries that do report fail to identify many cases.

Nonetheless, we can see that worldwide, some 40- to 50,000 cases who reported annually in the late-1980s, rising to about 70,000 cases in 1990, and to nearly 600,000 cases in 1991 -- the year the 7th pandemic reached Latin America.

Since then, the reported world total has steadily dropped to 143,000 cases in 1996 - the most recent year for which data are available.

This is the same graph only the cases reported from the Americas are shown in yellow. The steady decline in reported cases from Latin America from nearly 400,000 cases in 1991 to less than 25,000

cases in 1996, is evident. Also apparent is the surge in cases in 1991, mostly due to activity in Africa, and another surge in 1993 and '94 related in part to the Asian spread of Vibrio cholerae O-139.

Data for the African, Asian, and American regions are shown more clearly here. Note that in 1996 Africa reported far more cases than any other region.

What about the situation in the U.S.? This graph shows cholera cases in the United States by year, from 1965 through 1997. Here too, one can see the dramatic impact of the Latin American epidemic in 1991, and the 1993/94 epidemic of O-139 in Asia.

These are essentially the cases that the United States reports to WHO each year, and cholera surveillance in the United States also has its problems. To meet the case definition of the CDC a person has to have a diarrheal illness and either a positive culture or a serologic test confirmed at CDC.

Therefore, all asymptomatic cases and all cases whose illness is not laboratory-confirmed, are missed. We try our best to confirm every suspected case of cholera reported to us but we miss cases who do not seek medical attention; those who seek medical attention but in whom cholera is not suspected; and

those who are treated without our being informed.

We don't have a very precise idea of how many cases that represents -- how many patients -- but it would include for example, cases among ex-patriots living overseas long-term.

What do we know about the reported cases in the U.S.? They numbered 333 over a 33-year period -- an average of ten cases per year. Four patients died, for a case mortality rate of 1.2 percent.

Two hundred and twenty-seven cases, or 68 percent, occurred in persons who reported foreign travel in the seven days before illness; compared with 58, or 17 percent of cases who reported eating Gulf Coast seafood in the seven days before illness, and from whom the Gulf Coast strain was isolated.

Eighteen cases, or five percent, were infected with Vibrio cholerae O-139. Although most cases were sporadic, several large outbreaks contributed to the total. An outbreak in 1994 among passengers on an Asian cruise, contributed 17 of the 18 total O-139 cases.

An outbreak in 1992 led to cholera in 75 airline passengers on a flight from Lima to Los Angeles. And the largest domestic outbreak occurred in 1981 when 16 workers on a Gulf Coast oil rig

developed cholera after sharing a common meal.

This graph shows the 58 cases of cholera associated with Gulf Coast seafood by year of onset. Apart from the occasional outbreak, few or no sporadic cases are reported each year. And here I should mention that in many areas cholera is a seasonal disease.

For example, cases associated with Gulf Coast seafood have always clustered in the late summer months when the waters are warm and consumption of raw oysters and steamed crab are at a peak. In Central America and other countries north of the equator, these same summer months tend to be the periods of most epidemic activity, whereas in Peru and in countries south of the equator, the most cases occur in their summer months -- from January through April.

Travel-associated cases in the U.S. don't show any particular seasonality, probably because they include a mix of many travelers to many different areas with overlapping and opposing seasonal patterns of cholera.

This graph shows the 227 travel-associated cases, not by season but by year, from 1965 through 1997. Again, the impact of the Latin American epidemic and the O-139 epidemic in Asia in the early

1990s is evident, with considerably fewer cases reported in the last two years.

Let's examine these travel-associated cases a little more closely. Two travelers died as a result of their infections for a case fatality rate of one percent. The number of cases reported rose from an average of 1.6 per year from 1965 through 1991, to 21 cases per year from 1992 through 1997.

However, there was a much less dramatic change in the rate of travel-associated cholera cases per 100,000 to overseas air travelers. From 1965 through 1991 this rate was estimated at 0.2 cases per 100,000 -- or approximately one case per million air travelers.

This rose to approximately .3 cases per 100,000 from 1992 through 1994. The rate has remained relatively stable in large part because of the enormous overall increase in international air travel in recent years.

When one looks at specific countries or regions one can find higher rates; for example, as high as 2.3 cases per 100,000 air travelers for India and Pakistan in 1992 through '94.

Who are the travelers who get cholera? From 1992 through '94 only 50 percent of them were U.S.

residents. Many of the non-U.S. residents who live overseas imported their cases of cholera with them on a visit to the U.S.

They are small numbers, but among the 40 U.S. residents with travel-associated cholera for whom the reason for travel was known, 31, or just over 75 percent were homeland visitors -- people who were born overseas and who acquired cholera during a trip home to visit family or friends -- while only a small number of cases occurred in traditional tourists or business travelers.

The large and heterogeneous group of homeland visitors also makes up the majority of cases of typhoid fever and malaria in the U.S., and they represent the difficult population to target with standard prevention measures such as health education, chemoprophylaxis, and immunizations.

To conclude, I threw this slide together and I hope it's not too controversial. It makes some rough comparisons between the epidemiology of cholera and that of typhoid fever.

I want everyone to understand that these diseases are different, that the surveillance systems operated out of CDC for these two diseases are quite different, the data available for comparison are from

different periods, and that different denominators were used to calculate rates per 100,000 travelers.

So if you bear all of that in mind we can go through this and see that there were 203 cases of cholera reported in 1992 through 1997, compared with 2,445 cases of typhoid fever reported from 1985 through 1994. This works out to an average of 34 cholera cases per year compared with about seven times that many, or 245 typhoid cases per year.

One death was attributed to cholera and ten deaths occurred due to typhoid fever. And 185, or 91 percent of the cholera cases occurred among travelers, compared with 1,687, or 72 percent of typhoid fever cases.

The one cholera death occurred in a traveler and five, or half of the typhoid fever deaths occurred in travelers. By coincidence, 57 percent of the travelers who acquired cholera were U.S. residents; the same percent of travelers who acquired typhoid fever were U.S. citizens.

Finally, despite the approximately 7-fold fewer cholera cases per year, the rates of cholera per 100,000 air travelers are approximately the same as the rates of typhoid fever per 100,000 travelers. This is in part due to the fact that for the typhoid

fever denominator, persons returning from Mexico and Canada over land or by sea were also included in the denominator.

And finally, travelers to India and Pakistan were at greatest risk for both cholera and typhoid fever for the periods studied: a rate of 2.3 cholera cases compared with the rate of 4.5 typhoid fever cases per 100,000 air travelers.

That concludes the presentation. If time permits I'd be happy to entertain questions.

CHAIR FERRIERI: Thank you, Dr. Mintz. Dr. Poland.

DR. POLAND: Are those U.S. civilian cases only? In other words, would military personnel be included in the numbers that you showed?

DR. MINTZ: I honestly don't know the answer to that question. I'm not aware of any military cases among personnel in the military reported to us in recent years. I think that would depend on whether or not we received a specimen -- we were notified and received a specimen for confirmation.

CHAIR FERRIERI: Dr. Edwards.

DR. EDWARDS: Could you comment on what countries require you to have cholera immunizations prior to entering, or are there any, currently?

DR. MINTZ: To the best of my knowledge -- and this is perhaps several years out of date -- no countries require cholera immunization. I was told in 1991 when the epidemic -- the 7th pandemic reached Latin America -- that the last country -- and I believe it was Pitcairn Islands -- abolished the requirement for a cholera vaccination for entry.

Now, that is what WHO is told and what actually occurs at the frontier of one country and another country during a cholera epidemic may be different from what WHO has on the record books.

CHAIR FERRIERI: Other questions? Dr. Greenberg.

DR. GREENBERG: Your data on the incidence of cholera in travelers, do you have any idea of what the duration of that travel was -- how that was defined? And specifically, the large number of cholera cases in homeland travelers, were those the typical 2-week to 2-month travelers, or could they be traveling for longer periods of time?

DR. MINTZ: We don't have that data, and regrettably. I think that would help inform recommendations and prevention measures. I think there's a range of -- and this is by anecdote -- of some patients who I'm aware had been overseas for a

short time, a week or two, and others who I think had been overseas for a good deal longer. But I can't give you any harder numbers.

CHAIR FERRIERI: Do you have any recent data, Dr. Mintz, on the prevalence of any specific biotypes of differences worldwide?

DR. MINTZ: Biotype El Tor and Classical? El Tor is predominant in every country in the world, and I believe the Classical biotype continues to cause relatively few sporadic cases in Bangladesh, but not elsewhere.

CHAIR FERRIERI: Thank you.

DR. MINTZ: Cholera has proven that it can surprise us and I can't predict what will happen, and I don't think anyone can.

CHAIR FERRIERI: Thank you very much. Oh, there is one other question. Yes please, Dr. Pierce?

DR. PIERCE: I take it from your data that if individuals traveling to other countries became ill in those countries, were treated and got better, that those episodes would not appear here. Is that right?

DR. MINTZ: Unless the person came back to the U.S. or their physician overseas reported the case to us, they would not be counted, that's correct.

CHAIR FERRIERI: Yes, Dr. Karzon.

DR. KARZON: Is your intelligence good enough so that a traveler can call you and say, I'm going to X country and will be there three weeks and I'm going to be doing thus and such work, for you to be able to say, what is there during that current period and what type it would be, and therefore whether a given vaccine is appropriate?

Essentially as is done with malaria where the sites are known and the resistant strain types are also known, and so one can tailor the response.

DR. MINTZ: No. I think it's partly a reflection of the surveillance problem. Many countries do not report cholera even though cases occur there, so we rely on other sources other than official sources.

In a sense, travelers are guinea pigs, our surveillance system, and we have information on every strain we isolate from a traveler in every country that traveler went to, and that's our most accurate source of this information. But it's not up-to-date.

CHAIR FERRIERI: Dr. Snider.

DR. SNIDER: Eric, I know it's almost a catch-22 since a lot of the places people would go if they got ill there with a diarrheal disease, may not have the facilities to really prove the diagnosis of

cholera.

But I was wondering about Peace Corps workers. If we've talked to those folks who do have access to -- if generally get very ill -- would have access to a good medical care, that might be evacuated. But do we know anything about cholera in that population?

DR. MINTZ: Again, in my time working with cholera surveillance at CDC about the last seven or eight years, no cases among Peace workers have been reported to us, and we have gotten on multiple occasions, notification or serologic specimens from Peace workers with suspected typhoid fever, for confirmation.

So I think the link between the Peace Corps and the Centers for Disease Control is close enough that we would hear if a case of cholera were diagnosed in a Peace Corps worker.

CHAIR FERRIERI: Dr. Breiman.

DR. BREIMAN: Eric, given the fact that we're going to be talking about challenge studies in a little while, do you have a -- in your epidemic studies -- do you have an idea of what the attack rate is given exposure? I'm sure it also has to do with the amount of exposure, but do you have a sense of --

is it one in 100 or one in ten?

DR. MINTZ: Well, the -- really from sporadic cases we can't get that information so it's only in the outbreaks such as the ones that I mentioned here. Attack rates there tend to be fairly high.

The 75 infected passengers on the airline flight I think made up more than half the total passengers on that flight; I don't recall the data exactly and I don't know that everyone on the flight ate the implicated food, either. But they tend to be fairly high, I would say, in the outbreaks that we've detected.

DR. BREIMAN: Okay. And one other thing. I'm sort of used to thinking about pandemics for another disease. Is the way you define a pandemic for cholera relevant in terms of how long the El Tor has lasted? Does your surveillance influence that? In other words --- well, maybe you could summarize how a pandemic is actually defined.

DR. MINTZ: I think it's based on isolating the same or a very similar strain from a predominant number of cases in a country or region or the world. And when one looks very closely at the seven pandemic strains one can see fine differences probably arising

from mutations. There are two strains circulating in Latin America. They are somewhat different from the strains in Africa. But overall it's a fairly homogeneous group of isolates. That's how we define them.

CHAIR FERRIERI: I'm afraid we have to close now in order to get on to the sponsor. Thank you very much, Dr. Mintz. That was very helpful.

Dr. Levine, will you be presenting? Please introduce yourself and then you can introduce other members of your team.

DR. CRYZ: Okay. My name is Stanley Cryz. I'm director of Research and the Serum and Vaccine Institute in Berne, Switzerland, and I'd like to first thank the committee and the special consultants for their time and effort spent in considering this massive amount of data you've been inundated with.

If I could have the first slide. What I'd briefly like to do is go through the topics that we will cover today, which we've divided into eight sections. I will briefly make some introductory comments followed by, again, a very brief overview on the indications for use.

I'll skip the manufacturing and concentrate on galenic formulation of the vaccine; then move on to

the rationale for why we developed the live, oral, attenuated vaccine for cholera -- specifically that versus an inactivated vaccine.

We'll then move on to a presentation on the construction and genetic characteristics of Vibrio cholerae CVD 103-HgR. And then, although we've heard an excellent presentation by Dr. Mintz on the epidemiology of cholera and the incidence in U.S. travelers and U.S. personnel, we'd also like to raise the question: Is vaccination warranted against cholera in the international traveler?

The next subject will be the safety and immunogenicity of the vaccine in subjects residing in cholera endemic and non-endemic regions; followed by the efficacy of the vaccine as determined in a volunteer challenge model.

And the final compartment will be the large-scale, double-blind, randomized, placebo-controlled field trails to demonstrate the effectiveness of Mutacol Berna vaccine in Jakarta, Indonesia.

Now, my introductory comments will focus on the current, existing vaccine that's licensed in the United States for use in preventing cholera among travelers. This is the armamentarium that we currently have. It's a venerable vaccine. Its method

of manufacturing and characteristics has remained unchanged, essentially, for the one century since it was first introduced.

It's comprised of phenol inactivated Vibrio cholerae whole cells of both the Inaba and the Ogawa serotype. Primary immunization consists of two doses given one to four weeks apart by either the intramuscular, interdermal, or subcutaneous route. The single booster dose is recommended every six months upon continued exposure to cholera.

As far as adverse reactions go, this is a direct quote from the package circular: local reactions manifested by erythema, induration, pain, and tenderness at the site of injection occur in most recipients, and such local reactions may persist for a few days. Recipients frequently develop malaise, headache, and mild to moderate temperature elevations which may persist for one or two days.

My own personal experience with this vaccine is that after receiving the first dose I experienced most if not all of these reactions, which did not motivate me to receive my second immunization as recommended.

Efficacy -- again, a direct quote: field studies carried out in endemic cholera areas have

shown cholera vaccines to be approximately 50 percent effective in reducing incidence of disease, and only for three to six months.

Now, some of what I'm to cover in the next three slides has already been addressed by Dr. Stibitz so I'll make it very brief. The vaccine, the strain is entitled CVD 103-HgR as a deletion in the A subunit of cholera toxin, and a cassette of genes encoding for mercury resistant was inserted into the hemolysin A loci.

A single, oral dose contains two to eight times 10^8 colony forming units of the vaccine organism, as mentioned. We envision the target population for this vaccine to be travelers greater than two years of age entering an area where cholera is either epidemic or endemic.

We'd like to emphasize immunization of high risk individuals -- and we believe we can target those -- and those with predisposing conditions which increase the risk of acquiring cholera. Dosing and administration, very straightforward. A single, oral dose of vaccine and buffer reconstituted in 100 mls of water taken on an empty stomach.

The galenic formulation of this vaccine is relatively unique and I'll spend a few moments on it.

The vaccine is presented in a double chambered, aluminum foil sachet.

Chamber A as Dr. Stibitz stated, contains sodium bicarbonate. Ascorbic acid buffer is necessary to neutralize the gastric acidity to maintain the viability of the vaccine organisms as they transit the gut.

The B chamber contains the lyophilized vaccine strain, together with excipients which are predominantly sugars.

Administration of the vaccine is relatively straightforward. You essentially -- let's go back to this slide -- you essentially fold along this perforation, you cut along the lines. The contents are emptied into 100 mls of water and they're ingested on an empty stomach.

And that is the extent of my introductory presentation. I'd like to save as much time as possible for the clinical aspects. If there are any questions I'll be happy to entertain them.

CHAIR FERRIERI: We'll be holding questions until afterwards. Thank you.

DR. LEVINE: Good morning, ladies and gentlemen. There are three populations that international advisory groups have targeted as

potential recipients that might benefit of new cholera vaccines.

These populations of the vaccines that could help such populations would have somewhat different characteristics. To prevent disease in endemic areas where there's a high incidence in toddlers and pre-school children, one would need a vaccine that could be administered within the expanded program on immunization because that is virtually the only infrastructure for delivering vaccines. And the vaccine would have to confer long-term protection, the vaccine would have to be extremely inexpensive to be used in that situation.

One of the characteristics epidemiologically of cholera, is that it tends to occur in relatively explosive or endemic areas, and in seasonal activity. And we've seen across the world in the past decade, certain populations such as refugees in sub-Sahara Africa and in Southeast Asia suffer cholera when they have gathered in refugee camps.

We've seen in the early days of cholera hitting Latin America, populations near areas of cholera activity at risk. And for those populations one would want a vaccine that ideally would work with a single dose, would have a very short period of time

between vaccination and the onset of protective activity.

And lastly, the group of travelers such as Dr. Mintz described, from industrialized countries who visit areas of the world where cholera is endemic or epidemic.

There is some degree of relationship between these groups. There's no country at present that uses cholera to prevent recurring, endemic disease. There is great interest on the part of the World Health Organization and other international agencies to perhaps stockpile vaccine for use in this type of situation.

And the use in vaccine in travelers creates the manufacturing commitment if you will, to make vaccine, and sales of vaccines to travelers form a subsidy that creates the potential for use of vaccine in other venues. We will be talking about a vaccine in the next minutes that we believe represents a step forward for the prevention of cholera in travelers.

The rationale for our approach of developing a live, oral cholera vaccine can be succinctly summarized in the followed bullet points. First, we and others found that an initial infection caused by a wild type Vibrio cholerae O-1 confers a high degree

of protection against subsequent cholera.

Cholera enterotoxin is a necessary prerequisite for the causation of cholera gravis -- the severe, rice water purging of voluminous stools. The fundamental, protective immunity against cholera as anti-bacterial which can work synergistically with antitoxic immunity, and serum vibriocidal antibody against Vibrio cholerae O-1 represents the best measure that we have, the best correlate of elicitation of anti-bacterial immunity.

Although about 84 percent of those vibriocidal antibodies are directed against the lipopolysaccharide O antigen, about 15 percent are directed against protein antigens, and there remains debate again, about what those antigens are.

Summarizing this then, we took the approach of trying to stimulate the same type of protection that wild type Vibrio stimulate by disarming Vibrio of their ability to produce cholera toxin, thereby of the ability to produce cholera gravis, leaving intact all the other surface antigens involved with protection.

I'd like to give a bit of background on some of these points. In 1976 the U.S. cholera panel of the National Institutes of Health asked the Center for Vaccine Development to establish an experimental

challenge model, a volunteer model of cholera, that would allow the evaluation of an oral toxoid vaccine, a glutaraldehyde cholera toxoid.

Such a model was set up as a cohort challenge model in healthy adult, community volunteers. The volunteers were students from Towson State University and other universities within the Baltimore Metropolitan area.

The challenge studies were carried out on a research isolation ward which at the time was a 22-bed ward. They were carried out under quarantine. When Vibrio cholerae O-1 organisms were given with buffer there was a high attack rate of diarrhea induced, and in a proportion of individuals, the diarrhea was quite copious with aggressive oral, and as necessary, intravenous rehydration and early antibiotic therapy.

There were no adverse consequences of the heavy purging, and those individuals who reached a total diarrheal stool volume purge of five liters were considered severe cholera in this model. Those who had a 3-liter purge or more were considered moderate cholera. There was precise quantitation by means of collecting all of the stools and measuring the stool volume.

We found that this oral toxoid vaccine did

not confer protection in those early studies, and the question arose as to whether this model was relevant; that is to say, would any vaccine, would anything protect in this model? We then began to explore whether an initial, experimental cholera infection could protect against subsequent cholera infection.

We found out that indeed, infection derived immunity was potent and could last up to three years if stimulated by Classical biotype. And we found over the years that certain vaccines were protective in this model.

Here we summarized the re-challenge studies by biotype. Within the classical biotype, whether a volunteer experienced an Inaba or an Ogawa serotype infection, he or she was completely protected clinically, against re-challenge with Classical biotype of either homologous or heterologous serotype.

Not only was there clinical protection but by direct coproculture we could not grow a Vibrio from the stool cultures, showing that Classical biotype stimulates a particularly potent protection.

Within the El Tor challenge model there was again, a high level of protection but there were occasional breakthroughs and the antibacterial immunity was less potent, and these data suggested

that El Tor in the volunteer model was somewhat less immunizing than Classical.

At the time that these studies were carried out the only data from the field at that time was one report that suggested that wild type cholera in the field, in the ancestral home of cholera in Bengal, did not protect.

However, consequent to the volunteer studies, two reports came out -- very nice epidemiologic studies, that in fact, corroborated the volunteer studies. The first was by Roger Glass who showed a high level of protection against subsequent cholera in the Maclabazar field area where a quarter of a million individuals are under long-term surveillance against cholera.

The most elegant study was carried out by John Clemens who had the opportunity to look at this question at a time when both Classical and El Tor infections were occurring in the Maclab community. What he found was that if an initial, clinical cholera infection was caused by the Classic biotype, that conferred complete protection against subsequent cholera, whether due to Classical or El To biotype.

In contrast, an initial, clinical, El Tor infection conferred only limited, long-term protection

-- about 29 percent protection -- against subsequent El Tor infections, and no protection against Classical. Taking these data, along with the volunteer data, if one wanted to make a vaccine against El Tor one would choose from these data, starting with a Classical biotype strain for the vaccine.

Although cholera is a non-invasive, intestinal, mucosal infection and many groups, ourselves included, have looked for intestinal or mucosal correlates of protection, the fact is that the best correlate of protection remains serum vibriocidal antibodies.

In endemic areas where infection is repeated, individuals develop serum IgG vibriocidal antibodies after repeated infections. In the experimental challenge model the vibriocidal response if exclusive IgM, it drops to baseline after a few months, but protection continues long thereafter.

And the serum vibriocidal assay has proved to be a very helpful assay for evaluating all vaccines in different populations, particularly in non-immune populations. It is less helpful in immunizing populations, or less helpful for assessing vaccines if there is a high degree of background immunity.

Dr. Jim Kaper now, will tell us about the construction of CVD 103-HgR.

DR. KAPER: Good morning. I'm Dr. James Kaper from the University of Maryland and I'll briefly discuss the genetic construction in CVD 103-HgR. This is the operon, the gene structure of cholera toxin, in which you have the A and the B subunits.

The A1 subunit is enzymatic -- the active portion of the toxin. That is the toxin portion that causes all the subsequent effects due to cholera toxin.

The B subunit is the binding portion antibody but is non-toxic to itself. Antibodies against the B subunit can protect against the effects of the whole toxin. There's a single promotor, a single transcript.

The mutation we introduced in the cholera toxin gene -- and there's two mutations that we deliberately introduced into the strain -- is the deletion of the A1 subunit -- and this is a particular restriction besides XbA1 CLA1 -- we deleted 94 percent of the A1 gene for cholera toxin.

This was then recombined into a wild type strain of cholera -- strain 569B -- representing the top line as the chromosome of the strain, with a

promotor A1B subunit. We first introduced a plasmid to the selectable tetracycline resistance marker by allelic exchange and mods recombination.

We had an intermediate strain that had the tetracycline in the middle of the cholera toxin operon, and then we took this intermediate strain and then added a plasmid that contained a deletion of the A1 gene and looked for tetracycline sensitive; that is, with allelic exchange, homologous recombination.

The loss of tetracycline resistance means that the wild type A1 genes had been replaced by the mutant, by the deletion of the A1 genes. And so the final strain -- we ended up with CVD 103 with the promotor A2B subunit, but not the toxic A1 subunit genes.

We then introduced a marker for the purposes of tracking the strain in the environment, and we used mercury resistance to avoid the use of any antibiotic resistance marker. We introduced this into a hemolysin gene of Vibrio cholerae, and we first made a deletion with the hemolysin gene, the single restriction enzyme site here, and we took a mercury resistance gene -- just the operon including mercury resistance; no other genes for transfer or trans-resistance or anything.

We introduced that mercury resistance into the middle of the hemolysin gene. This is all again, in plasmids and E. coli, and then we recombined -- we introduced this then, into the CVD 103 intermediate strain. We first of all had again, to use our tetracycline resistance marker in the hemolysin gene.

Homologous recombination starting with CVD 103 allowed introduction of the tetracycline gene into the hemolysin locus, to end up with another intermediate strain, JMK4. And finally, JMK4, the tetracycline resistance gene was then added -- the plasmid was added that has the mercury resistance gene and the hemolysin locus.

Again, homologous exchange replaced the tetracycline resistance gene with the mercury resistance gene. And so now we have this other strain, CVD 103-HgR, which has the deletion of the cholera toxin gene, the mercury resistance gene and hemolysin gene.

Another plasmid we used, selected this event resistance plasmid, a spontaneously cured derivative of this which lacked this resistance plasmid. So the final construction then, at the end of our manipulations was a CTXA deletion strain with a mercury resistance gene as a marker and hemolysin

locus.

As Dr. Stibitz mentioned along the way, along the various manipulations, another spontaneous mutation occurred which reduced somewhat the colonization ability of the strain in a mouse model and human volunteers, but the main mutations that prevent the strain from causing disease, from causing cholera, is deletion of the A1 subunit for the cholera toxin genes.

Thank you. Dr. Levine will now proceed with our presentation.

DR. LEVINE: Dr. Mintz from CDC gave a very broad-ranging, very comprehensive, excellent summary of the epidemiology of cholera including the risk for travelers. What I'd like to do now is complement and add to that a bit and try to add some practical suggestions.

Dr. Mintz pointed out that using purely passive surveillance, one of the difficulties in quantitating the magnitude of the problem of cholera in travelers is that one needs a confirmed case -- a case of not cholera unless there's confirmation -- which in most instances requires bacteriology, and bacteriology is not performed in most instances.

There have been two studies that are very

important because they represent a prospective, active look attempting to quantify the problem. They used good bacteriology and at least one of them had the advantage of a precise denominator which can answer one of the questions raised by Dr. Breiman.

The first of these two studies was carried out by Colonel Dave Taylor working in Peru. He set up surveillance at the U.S. Embassy where there was a health clinic. He arranged so that every individual with diarrhea had a good bacteriologic specimen with alkaline peptone water enrichment followed by TCBS medium, which is the preferred bacteriologic medium.

He carried out surveillance over three years, and what he found was that about one or two percent in these years of individuals with diarrhea attending this health clinic, grew Vibrio cholerae O-1. These tended to be the most severe of these traveler's diarrhea-type cases.

He was able to calculate an incidence per 1000 person years of exposure for the U.S. workers at the Embassy, and incredibly in this prospective surveillance, it turned out to be 5.3 per 1000. A bit later we'll see the incidence rate in the control group during one year in a famous field trial in Bangladesh, and the incidence was 5.3 per 1000. This

would be a right-good incidence -- a hot year in Maclabazar.

Another study was carried out by Swiss investigators in conjunction with Japanese investigators. Here they did not have precise denominators but they had very good bacteriology. And what they did was to give questionnaires to Japanese tourists coming back from Indonesia and Thailand on large, jumbo-jet group flights.

And they asked if anyone had had diarrhea within the past three days, and if they did, a culture was taken. They found that the incidence of cholera -- this is culture-proven cholera now -- despite the fact that many of these individuals had received antibiotic therapy, the incidence of confirmed cholera was 13 cases per 100,000 travelers for Japanese tourists going to Indonesia, and 2.9 per 100,000 for those going to Thailand.

They mention in this report that the average tour, the average stay, was seven days. If one takes ten days to add a bit of conservatism, and calculates an annual incidence based on these numbers, one gets an incidence very, very similar, virtually identical for Indonesia, to what Dave Taylor found in his prospective study for U.S. citizens in Peru.

Now, one can argue that Japanese tourists, because of food preferences for raw seafood, might be at particularly great risk. On the other hand, again, many of these individuals had already been treated with antibiotic.

To make this story short, these two prospective data suggests that the incidence of traveler's cholera is far higher than we had appreciated and in fact, is not only as high as traveler's typhoid, but is arguably even a 10-fold or even 100-fold higher if you do prospective surveillance.

Occasionally cholera can be very severe, and I want to present a famous example because it's in the literature, of someone who developed cholera in a sticky situation, and who had very early therapy, but nevertheless had a potentially life-threatening disease.

This was an epidemiologist who worked in East Bengal and woke up one morning in rural Bengal having a queasy feeling, diarrhea, and nausea. Within one hour because of the way he felt, a stool culture was taken, rehydration was begun, and antibiotics were initiated -- within one hour of onset of diarrhea.

Within three hours the diarrhea had become

what was called severe. He was developing muscle cramps and was receiving more rehydration. And it was decided to put him in a boat and to get him to a hospital.

In the boat with him was a physician, expert and experienced in the treatment of cholera, and three liters of IV fluids for a 5-hour boat ride. He began purging during the boat ride, rice water stools estimated to be at least one liter per hour.

He arrived at the hospital after five hours as a typical cholera patient with sunken eyes, poor skin turgor, dry mucous membranes, and a systolic pressure of 80. He went on to receive ten liters of IV fluids to replace the nine liters that he continued to lose over the next 21 hours.

This is an example of how severe cholera can be, and had this individual not had experts, clinical care and access to intravenous fluids, this potentially could have been a fatal case. We do not recommend cholera vaccine for all travelers, but we believe that there are subgroups of travelers at special risk, and if they're caught developing cholera, with bad luck and certain circumstances, their life could be in danger.

And so we recommend cholera vaccine in the

following situations. There are high risk countries and regions. Agreed, often we recognize these based on surveillance data of previous two or three years, but travel medicine is becoming fairly sophisticated and high risk areas are recognized.

These include parts of Latin America, Peru, Equador, Bolivia, and Guatemala, for example, parts of the Indian subcontinent, parts of Indonesia, much of Sub-Sahara Africa, and the Horn of Africa. In many of these areas there is a precise -- fairly precise cholera season and it's known -- for example, summertime in Peru.

We recommended in particular for travelers who will be somewhat off the beaten track -- that is to say, away from health care -- and it's away from health care not in terms of kilometers, but in terms of hours. And the reason that that's important is that in a previously healthy adult cholera can bring an individual to severe dehydration and near fatality within six or seven or eight hours.

And lastly, there are some sub-subpopulations of travelers who have host problems that put them at greater risk of the consequences of the fluid and electrolyte losses of cholera. These include individuals with cardiac chronic problems who

often are on medication, individuals who are achlorhydric or who are taking medications that make them hyperachlorhydric.

For such populations we believe that CVD 103-HdR represents an advance over the venerable killed cholera, or over the parenteral killed cholera vaccine, and for such populations they could and should be offered the possibility of protection.

I'd now like to pass the podium to Dr. Karen Kotloff who will begin to tell us about safety and immunogenicity in North American and European populations.

CHAIR FERRIERI: I'm sorry to remind the sponsors that your allotted time was 50 minutes. We started at 9:35 and so if all of you could keep that in mind. Theoretically we would be stopping now, but I realize that you still have much to do, but we'll try to be as concise as possible, please.

DR. KOTLOFF: During the initial Phase I studies a total of 226 volunteers participating in 16 separate studies received CVD 103-HgR in a dose of approximately 10^8 cfu. In these uncontrolled trials the vaccine was very well tolerated with mild diarrhea occurring in approximately four percent of subjects, and high immunogenic with a 4-fold rise in vibriocidal

antibody occurring in 94 percent of subjects.

The next step was to evaluate the safety and immunogenicity of the vaccine in a more rigorous trial using randomized, double-blind, placebo-controlled study design in a Phase II trial. Ninety-four healthy college students were randomized to receive a single, oral, 5 X 10^8 dose of either CVD 103-HgR or heat killed lyophilized E. coli K12 placebo.

In this crossover study design, eight days after the first inoculation the vaccine recipients received a dose of placebo and the placebo recipients received a dose of vaccine.

To evaluate safety of the vaccine, volunteers kept a diary for seven days after each dose, reporting any symptoms that they experienced. They recorded the consistency as looser formed of every stool that they passed, and took and recorded their evening oral temperature.

The immune response was measured by getting blood before vaccination and on days 8, 15, 21,and 28 after each dose. And vaccine excretion was measured using peri-rectal swabs on day-1, -3, and -7 after each dose.

The sample size was powered to detect a six percent difference between the vaccine and placebo

recipients in symptoms that were estimated to occur in one percent of placebo recipients.

These are the results of the clinical evaluation. In the first column here, these are symptoms that occurred in subjects after receiving the vaccine and after receiving the placebo. These symptoms occurred after receiving vaccine but not placebo, and these symptoms occurred after receiving placebo but not vaccine.

There was no statistically significant difference in the occurrence of any of these symptoms following vaccine versus placebo.

A 4-fold rise in vibriocidal antibody titer was observed in 97 percent of subjects -- 67 percent of whom developed a titer of greater or equal to one to 2,560. The geometric mean vibriocidal titer post-vaccination was 133 times higher than the titer pre-vaccination.

Seventy-two percent of subjects developed an antitoxin, antibody response, and 19 percent of subjects shed the vaccine for one day or longer.

I'd now like to introduce Dr. Carol Tacket who will give some more data on the safety and immunogenicity of the vaccine.

DR. TACKET: I'd like to describe a

moderately large, Phase I safety study of CVD 103-HgR in which 339 volunteers were randomized to received either CVD 103-HgR at 10^8 or at 10^9 cfu. This is 10-fold larger than the proposed dose for use in travelers or in an activated E. coli K12 placebo.

The volunteers kept a symptom diary for a few days after vaccination. Diarrhea in this outpatient study was defined as four loose stools in 24 hours.

Here are the results of that study. We accrued data on the symptoms that are listed in this column and these are the rates of these symptoms among placebo recipients -- the lower dose vaccine recipients and the higher dose vaccine recipients. And the P values are shown here.

The only one that reaches statistical significance is the incidence of nausea which is higher in the high dose vaccine recipients than among placebo recipients. However, among volunteers who received the proposed dose, the rate of nausea is lower than among placebo recipients.

DR. LEVINE: I'd now like to present some examples of immunogenicity and of safety studies in developing countries. You've seen that in North American volunteers the vaccine is well tolerated and

with a single dose of 8 logs one encounters vibriocidal responses with a geometric mean titer of about 2600, and approximately 130 meanfold rise in titer.

When we went offshore in developing countries, in both adult and pediatric populations, we found that the vaccine behaved very differently. This is a summary of dose response studies in Indonesian 5- to 9-year-olds. One sees that these children have serologic evidence of having had contact -- considerable contact with cholera. These are quite elevated, vibriocidal baseline titers.

An 8-log dose in this population caused almost no seroconversion and barely elevated the geometric mean titer. By administering a log higher dose of organisms, we were able to reach credible seroconversion rates of 75 percent with a mean 9-fold or 8-fold rise in titer.

So the first point to be made is that when we go offshore in developing countries, in poor populations, we find a very different immunologic response.

In Peru at a time when there was considerable transmission taking place in 1992, we had an opportunity to compare the immune response to an 8-

log versus a 9-log dose in both high socio-economic level and low socio-economic level populations. Three points to be made.

First, in the low socio-economic level population a 9-log dose was more immunogenic than an 8-log dose, in both instances though, the geometric mean titers are much lower than what we had seen in North Americans.

In the high socio-economic population the difference between 8- and 9-log seroconversion is small. There was somewhat of a difference in geometric mean titer but again, even at 9-logs the tiers are much lower than what we had seen in North Americans.

Why is this? We have known for many years from studies with live virus vaccines that they can be much less immunogenic when they're given to disadvantaged populations in developing countries compared to the response expected in industrialized countries.

This was first shown by Jacob John in India with the oral Sabin vaccine where six doses of oral vaccine are required to reach similar seroconversion rates as can occur with two or three doses in first world infant populations.

This was then strikingly seen in the 1980s with the RIT bovine rotavirus vaccine, was seen with the 10^4 pfu dose of Rhesus quadrivalent reassortant vaccine, and to these live viruses we now add live oral cholera vaccine.

These vaccines can be useful public health tools but something special has to be done. In the case of Sabin polio vaccine it's national immunization days. In the case of Rhesus it's increasing the dose by a log.

We've carried out many studies in a number of countries and this slide summarizes what we have learned of the factors that influence the vibriocidal response. We found that increasing the dose by a log makes a big difference.

We found that the baseline vibriocidal titer is important. Anybody who starts with a very high titer doesn't boost the vibriocidal further. The timing of collection of the specimen is important. It peaks at 10 to 14 days. If you collect an earlier specimen on day-7 or 8 or 9, one has a much lower titer than collecting here.

Blood group is the single most important host factor that's a risk factor for cholera. Blood group O are the individuals at risk and interestingly

enough as we'll show you in a moment, individuals who receive live cholera vaccine develop a significantly higher vibriocidal response than individuals of a non-O blood group.

This is believed to be due to attachment of the vibrio to blood group factors which are secreted onto the surface of the intestinal cells. The immune response is higher in high socio-economic populations compared to low, and one must neutralize gastric acidity to get a good vaccine take.

This is a summary of a large study carried out in Chilean 5- to 9-year-olds where we looked at the vibriocidal response in relation to blood group. Although the blood group O response seroconversion was somewhat higher than non-O, the difference was not significant.

But if one looks at the mean rise it's 23-fold in the blood group O, only 9-fold in the non-O. And this is about a 3-fold difference in geometric mean titer; highly significant. We believe that this has important implications in terms of protection in the field, as we'll see in a few moments.

I now want to switch very briefly to some safety data in Chilean pre-school children, 24- to 59-month-olds, and Chilean infants, because these are

kids living in an area where there's very little cholera.

We believe these data then have a degree of applicability to the U.S. and when one gets down to individual hosts as young as three month's of age, this is obviously a very sensitive host to look for adverse reactions.

In the pre-school child study there is no adverse reaction that occurred more commonly in vaccinees versus placebo recipients. Similarly, in infants and toddlers, looking at kids who received -- who ingested 70 percent or more of the vaccine cocktail -- that is, they truly got a full dose -- there is no difference. The vaccine was quite well-tolerated.

In this slide I want to show the immune response comparing infants and toddlers, three to 17 month's of age who got a full dose of vaccine -- that is 70 mls or more of the 100 ml cocktail -- versus children who got the cocktail or who got less than a full dose.

And the important point is, there's a 63 percent seroconversion rate in the fully-vaccinated, and in the intend-to-vaccinate there is no difference. In these much smaller children even ingesting a

fractional dose seemed to give a good seroconversion rate.

The mean-fold rise was about 8-fold, but note how much lower these are than even the adults in developing countries.

Just mention in passing that this vaccine is minimally excreted and is minimally transmitted, perhaps one percent. For reasons of time I'm just going to gloss over these data. You have the data in your handout.

We'd now like to switch to Dr. Tacket who will tell us about the efficacy data from the challenge studies.

DR. TACKET: We have heard about safety and immunogenicity and now we'll turn to the efficacy measured in volunteer challenge studies among volunteers recruited from our Baltimore community.

There are nine such studies that have been conducted, that are listed here: six in volunteers who were vaccinated with CVD 103-HgR, and three among volunteers vaccinated with the parent, CVD 103. I'll ask you just to focus on these six challenges here.

The challenge strain involved both the Classical biotype or El Tor biotypes. In this column is shown the vaccine efficacy in each of these

challenge studies. In challenges using the homologous, Classical Inaba parent the efficacy is very, very high in this model.

I'll point out another feature of the challenge studies is the interval from vaccination until challenge, which for most of the studies was about four to five weeks. In this study these 14 vaccinees received vaccine four or six months before challenge. And actually, 11 of these volunteers received vaccine six months before challenge and there was still efficacy.

In this challenge volunteers were vaccinated eight days before challenge, and again, there was a high degree of efficacy very quickly after vaccination.

Similarly here among this challenge, some volunteers were vaccinated a month before challenge; some as recently as ten days before challenge, using an El Tor Ogawa challenge strain. The efficacy was about 50 percent.

Now, if you take all of those volunteers who underwent challenge after having received CVD 103 or 103-Hgr -- and there are 88 controls and 101 vaccinees -- and resort those data, you can see that the protective efficacy against diarrhea that was severe

-- defined as five liters -- or moderate -- defined as three liters -- is very high; 100 percent in our studies. Among volunteers who had milder purges there's still a significant efficacy.

This is a similar resorting of that data looking only at volunteers who received CVD 103-HgR against any challenge, so our denominators here are lower. But again, very strong efficacy against cholera gravis or even moderate degree of cholera.

And here's the most difficult challenge in a sense, and that is CVD 103-HgR vaccine protecting against El Tor challenge. So again, our denominators continue to shrink but nevertheless, even against El Tor we have good, protective efficacy against moderate or severe cholera.

Finally, we were interested in determining whether there was a correlation -- specifically a negative correlation -- between vibriocidal antibody titer and protection from experimental cholera challenge.

So what is shown in this slide is, for each of the challenge studies which I've just shown you previously, the correlation between the peak vibriocidal titer when the target strain of the vibriocidal assay is the same as the serotype of the

cholera challenge.

Now most of these studies are too small to be able to show a statistically significant negative correlation. However, if you look for example, at peak vibriocidal titer versus the stool volume, in all six cases in which the correlation is non-zero there's a negative sign. And the combined probability by the sign test is significant.

When you look at the peak vibriocidal titer versus attack rate for diarrhea, in five of the six cases there's a negative correlation which approaches significance.

Perhaps most interesting is in this one study in which the challenge was El Tor Ogawa. There was a clear, negative correlation between attack rate for diarrhea and peak vibriocidal titer, as well as stool volume and peak vibriocidal titer.

And it's interesting to point out that these Ogawa vibriocidal titers were engendered by our Classical Inaba vaccine.

DR. SIMANJUNTAK: I'm Cyrus Simanjuntak from the National Institute of Health Research of Development, Jakarta, Indonesia.

Based from the results of immunogenicity and side effect study, we conducted (unintelligible) so we

conduct a large scale, double-blind, placebo-controlled field trial to assess the efficacy of a single dose of live, oral cholera vaccine CVD 103 mercury study in presenting cholera in North Jakarta.

The primary objective of this study is to determine the protective efficacy of a single dose of CVD 103 mercury resistant in preventing clinical cholera of a severity that caused an individual to seek medical care at a hospital or clinic irrespective of age, over the entire follow-up surveillance period as well as after each year during the surveillance period.

The second objective of this study is to determine -- one is determine the particular efficacy of a single dose of CVD 103 with mercury study in preventing clinical cholera irrespective of severity, and on young children aged two to five years of age at the time of vaccination of course, over the entire surveillance period as well as eight each year during the surveillance period.

Number two is to determine the protective efficacy of a single dose of CVD cholera 103 mercury resistant in preventing severe cholera. Cholera is characterized by marked dehydration. And on all study participants, irrespective age, over the entire

surveillance period as well as after each year during the surveillance period.

Number three is to compare the protective efficacy of a single dose of CVD 103 mercury resistant in preventing clinical cholera irrespective of severity, in study participants of O blood group versus study participant of other blood groups, over the entire surveillance period as well as after each year during the surveillance period.

Number four is to determine the protective efficacy of a single dose of CVD 103 mercury resistant in preventing typical cholera, irrespective of severity among young children aged two to five years of age at the time of vaccination who were eligible to participate in the vaccine study, over the entire surveillance period as well as after each year during the surveillance period.

This group we call it intent to vaccinate analysis. The analysis of this study will be presented by Dr. Wasserman. Thank you very much.

DR. WASSERMAN: Steven Wasserman, University of Maryland. The analysis of the primary objective was affected by incidence density comparison of cholera cases in vaccinees and placebo recipients. I'll give you the broad outlines of this.

Basically for the overall surveillance periods, you can see on the top, the point estimate of protective efficacy was 13.5 percent with a lower, single-tailed, 95 percent confidence limit of -24.4 percent.

As you can see as well, the point estimate of protective efficacy ranged from 2.3 percent to 19 percent among the various sub-periods that were analyzed. In fact, among all of the primary and secondary objectives, none of the null hypotheses reached statistical significance.

The only glimmer of hope here however, came from the analysis of blood groups where we assumed that the vaccinee population had the same ABO profile as the entire city of Jakarta from blood bank data, and then we were able to obtain for the overwhelming majority of cholera cases, the ABO blood groups.

And we used the logistic regression analysis here looking for a significant interaction turn between blood group -- this is non-O -- and vaccine versus placebo on cholera case.

This is the analysis of those people who imbibed at least 70 percent of the vaccine or placebo preparation without vomiting thereafter. And you can see that the P value for the interaction turn is .12.

However, based on the analysis from Chilean infants and toddlers where we found that the intent to vaccinate analysis, vis-a-vis vibriocidal response, was very similar to that seen in the individuals who drank at least 70 percent of the preparation, we did an intent to vaccinate analysis here as well and we find that the P value -- this included four individuals who were under age-4 who didn't drink 70 percent of the preparation -- we find that the protective efficacy hits the .06 level.

If you look at the bottom group you'll notice that there are similar numbers of cases in the vaccinees and the placebos -- that is, in the non-Os. But in one group O, blood group O, we see that there are about 55 percent as many cases among the vaccinees as among the placebo recipients.

Which suggests then, that the vaccine is protecting that group of individuals that are at higher risk for cholera; that is, blood group O.

DR. LEVINE: In this field trial this formulation of the vaccine did not work. I'd like to put those results, which were obviously very disappointing to us, in some sort of perspective.

The first point to be made is one that is quite general with respect to field trials and that

is, the same vaccine tested in field trials at different times -- in the same country for example -- may give quite different results. Many factors -- host factors, transmission factors, etc. -- impinge upon the efficacy -- the point efficacy -- estimate of a vaccine.

With respect to another oral vaccine, the quadravalent Rhesus rotavirus, at 10^4 pfu gave very different estimates of efficacy in Latin America, or somewhat different estimates than in the U.S.A. And this is true even with parenteral vaccines.

The PRPD Hib conjugate was highly protective in Finnish infants and was not protective in Alaskan infants. Thus, depending upon the particular population the same inherent vaccine can be biologically active or not.

Here we list some of the factors that impinge upon whether or not a cholera vaccine will be more or less efficacious. First is the number of doses administered. In the field trial in Indonesia we went with the minimal number of doses, which is one.

The age of subjects: cholera vaccines work better in older individuals than in very young individuals. Blood group: with some vaccines, as

we'll see in a moment, blood group O gives a less response and less protection with the live vaccine, where the vibriocidal response is greater in persons of blood group O.

You've just seen the suggestion that we actually had a degree of protection in blood group O individuals. Very important point is that with cholera vaccine the level of efficacy very much relates to when the natural challenge takes place in relation to vaccination.

If you vaccinate just before cholera season and luck is such -- epidemiologic luck is such that many cases occur shortly after vaccination, the vaccine looks particularly good in that period of time and the protective level tends to wane with increase in time.

Biotype is also very important. If there is Classic biotype, cholera vaccines seem to give better protection against Classical biotype than against El Tor biotype. And severity is important. Cholera vaccines work better against more severe disease than they do against milder disease.

In this slide I summarize the first year of surveillance for three field trials, including the Jakarta field trial, including two other field trials

carried out by very experienced field epidemiologists: this one by Dr. John Clemens, this one by Colonel David Taylor.

In this study three doses of an oral, B subunit whole cell vaccine were given. These trials were about the same size and it just shows how this collection of different factors can influence the total outcome.

Example. Here, three doses were given: 64 percent protection overall in the first year was recorded. In this population there was Classical as well as El Tor. The level of protection against El Tor was much lower than the 64 percent overall. The level of protection against Classical was higher.

In this trial they had a very high incidence over the first year, and even more importantly they had many, many cases in the first six months after vaccination, allowing a very fair estimate of the protective efficacy in the first few months after vaccination.

Two doses of the B subunit whole cell vaccine, now with a recombinant B subunit, did not protect. A year later when they gave a booster raising the total number of doses to three, they reached 60 percent protection, and they had a

moderately high incidence of cholera.

In Jakarta, we went for a home run. We went with a single dose. We did not have Classical biotype. We had a very, very low incidence; much lower than had been expected. And we had very few severe cases.

Every factor that impinges on protection of cholera was, so to speak, working against us. We swung for the bleachers and the vaccine with a single dose in that formulation didn't work in that venue.

In summary then, from this overall presentation, with respect to the three, possible, target populations to be protected by a cholera vaccine with this current formulation of CVD 103-HgR, we do not have a vaccine we can use for the protection of endemic populations, long-term in cholera endemic areas.

We do not know whether we have a vaccine that could be used in an explosive outbreak in a refugee camp situation. We have almost no cases in the first six months after vaccination. This happens with cholera epidemiology. There is a roll of the dice as to whether you have cholera, even in an area that's endemic.

We do not know how good or how poor the

vaccine would react in this situation and we have to study this further. On the other hand, we have much data that we've presented showing that we have a truly safe vaccine that in North American individuals and in Europeans, is highly immunogenic, and is highly protective.

And a single dose of the vaccine protects against either biotype and either serotype of North American, healthy adult. And this is representative, we believe, of travelers. We think we have a useful vaccine that's a step forward over the current parenteral killed cholera vaccine for protection of travelers.

Thank you.

CHAIR FERRIERI: Thank you, Dr. Levine. We're going to adhere to the scheduled break time. We'll take a break now. Committee members, please jot down your questions. When we return we will move right into questions for the sponsors before the next FDA presentation.

So if you could come back, we'll start precisely at ten-after-11.

(Whereupon, the foregoing matter went off the record at 11:00 a.m. and went back on the record at 11:14 a.m.)

CHAIR FERRIERI: As I indicated before the break, we will now take some time for questions of the sponsor's presentation. Please come to your seats now or we won't finish with the issue today. It would be too bad if we had to have an abortive presentation and no decision-making today.

So this will require great cooperation on the part of us at the table, in keeping our questions as concise as possible. We have innumerable questions for the sponsors. It will be obligatory that the sponsors present their answers in the most targeted, brief but informative way. And so they need to all be prepared to, who will answer what.

So we will take some time now before Dr. Bash's presentation, realizing that we're running behind and this is a very comprehensive issue. So I will entertain questions from the committee members, and I will start with Dr. Fleming, and the rest of you can try to pull together your ideas and questions. Write them down so you can offer them up concisely.

Tom, if you could prioritize what you feel you would like to ask now before Dr. Bash's presentation. We will have further time for committee discussion.

DR. FLEMING: Let me just begin with one

question. And this is a question where I'm trying to get a sense of the clinical goal here. And we've been given a lot of very helpful figures about what the level of risk would be. And those figures from epidemiologists have gone from .3 per 100,000 amongst travelers, to maybe on the order of 3 per 100,000 -- 10-fold higher.

When we talk about this rate, is this the rate of detected cholera? What would be the rate of severe purging amongst travelers? Do we have an estimate of that? And in particular, the sponsor has tried to give us a targeted population: high risk countries, high seasons, travel in rural areas, host problems, etc.

Do we have any way of quantitating what the risk for such a targeted cohort would be of cholera cases that would lead to severe purging or worse?

CHAIR FERRIERI: Who would like to answer that? Who feels the most qualified to answer this question?

DR. MINTZ: I'm not sure I feel the most qualified but I can comment from the CDC perspective. Again, we only hear about cases in which Vibrio cholerae has been confirmed by a laboratory or is suspected.

Clearly, asymptomatic cases are not counted and it's my supposition that the milder cases of diarrhea in travelers probably don't result in visits to physicians or clinics, and even if they did, the physician or laboratory is less likely to think of Vibrio cholerae -- even in a traveler returning from an area where cholera is present. They're more likely to consider that traveler's diarrhea, perhaps not obtain a culture, and perhaps prescribe an antibiotic.

So the cases that we report and the estimates we have of the rate in travelers, are based presumably on the moderate or severely ill cases. And again, I don't have systematic data on all of the cases but the typical case in a traveler is someone who had diarrhea of moderate or severe nature that brought them to a physician's attention.

And often the physician or on occasion, the microbiologist, made the necessary extra step to consider a cholera. And that I think, is often triggered by the severity of the illness. So that's the best information I can present.

CHAIR FERRIERI: Does that answer your question Tom? Not really.

DR. FLEMING: Only partially. What it's telling me is, as I would expect, your statistics

which give 10-fold lower rates than the Japanese figures, are explained by the fact that your statistics probably represent the more serious cases.

But in your words, those are moderate to severe or worse cases. So that would lead me to conclude that .3 per 100,000 might be a realistic figure if we focus on cases that are severe purging or worse, amongst cholera.

DR. MINTZ: Well also, the estimate of .3 per 100,000 is based on all air travelers -- to Europe, Denmark -- places where they're very unlikely to acquire cholera. Whereas, the Japanese study looked at a group of travelers returning, I believe, from Indonesia and Thailand -- two very high risk areas for cholera, particularly during the years that study was done.

Similarly, the U.S. Embassy study in Peru during the peak years of cholera in Peru found a much higher rate. And this would be expected.

DR. FLEMING: But those also included less than severe -- the Japanese figures -- because that was an active surveillance. And so even with an active surveillance including less than severe, to Indonesia and Thailand, the rates were only 3 to 13 per 100,000.

And so if I return to my, again to my question -- what is the frequency of severe purging even if you look at going to Indonesia -- I'm coming up with something that sounds to be on the order of one, to at most 10 per 100,000.

I don't know if anybody is viewing that to be inappropriate. In fact, I'm thinking that might even be high.

CHAIR FERRIERI: It may be on the high side. Dr. Levine, would you care to comment on this question?

DR. LEVINE: Yes. I think that that's a very difficult question to answer because if the denominator is air travelers, for example, you have to look at the hosts. If you look at the cruise ship outbreak in Asia, for example, which included many elderly individuals, there the cholera, the morbidity, was much greater than in some other venues. Host factors are very important.

One of the things that the prospective surveillance has shown is that if you do bacteriology -- proper bacteriology -- you come up with cholera cases. If there are cholera cases and there are enough of them, there'll be some severe dehydrations.

There are instances of travelers -- there

was one a few months ago who got off a British Airways flight at Gatwick, prostrate and with severe dehydration; Vibrio cholerae O-1, El Tor Ogawa was cultured.

Most of those individuals in other situations will not have a culture, so they may clinically seem cholera but they don't go into the statistical quantitation because they didn't have a confirmation.

DR. SNIDER: Could I ask for a clarification around this --

CHAIR FERRIERI: Dr. Snider, go ahead.

DR. SNIDER: Thank you. With regard to the Peru study, Mike, two questions. One, the study was published in 1996 but when was it actually done? Was it during a period in which there was a lot of epidemic activity in Peru?

And secondly, it says the study of the U.S. Embassy workers in Peru and as many of us who have been in embassies know, a high proportion of the people who usually work in embassies are locals, not U.S. citizens.

DR. LEVINE: That's correct. The person who did the study is sitting here, so I'll make a brief answer but he may want to correct what I say.

He divided up, for both non-U.S. citizens and U.S. citizens. The rate that I gave you was U.S. citizens who came from the U.S., were working for a year or two years in Peru.

And the years were '93, '94, '95. Is that -- no, '91, '92, '93.

CHAIR FERRIERI: Tom, did you want to pursue a couple other of your questions?

DR. FLEMING: I think I would rather prioritize while other people are speaking.

CHAIR FERRIERI: Okay; terrific. Dr. Greenberg.

DR. GREENBERG: On this issue, another way of looking at this though, for severe cholera one -- they usually do come to attention -- people who arrive on airplanes dehydrated with sunken eyeballs frequently make the news.

And if I read your statistics correctly there were eight such people in the United States if you look at simply tourists and business traveling, excluding homeland travelers, in the last three years. There were a total of eight cases.

DR. MINTZ: Yes. I think that's correct. Now, many of the cases though, we didn't know the reason for travel. And so that doesn't necessarily

represent an unbiased sample of all cases.

CHAIR FERRIERI: Other questions? Yes, Dr. Holmes.

DR. HOLMES: Yes, I had a couple of questions. The protection in the volunteer studies against heterologous challenge with El Tor strains is substantially less than it is against the challenge of Classical strain.

The latest challenge with the heterologous strain that I saw in the data was 28 days after immunization. Are there any data about the persistence of immunity against a heterologous challenge later than 28 days?

CHAIR FERRIERI: Dr. Tacket? As each of you from your team gets up if you could just announce your name for the transcriber, please.

DR. TACKET: It's Carol Tacket. No, we've not done challenges -- heterologous challenges as you've described -- beyond 28 days.

DR. HOLMES: And the second is also about data that may not be available. From the Indonesian study and a variety of others, it looks as if partial unity against cholera substantially limits both multiplication of the vaccine strain and the immune response to the vaccine strain.

The question now is, in volunteers are there any data available on re-immunization and whether the vaccine is immunogenic in a volunteer from a developed country like the United States who has previously been immunized?

DR. CRYZ: Stan Cryz. We did a study in healthy adults, Swiss, where they received a single dose of the vaccine and then were boosted between 18 and 24 months later. And although their vibriocidal antibodies for the most part reached baseline at the time of boosting, there was a minimum rise following boost.

CHAIR FERRIERI: Do you remember the GMTs, Dr. Cryz?

DR. CRYZ: I don't think there was a significant rise in the geometric mean titer after boosting. If it was it may be a two- to a three-fold rise.

CHAIR FERRIERI: Dr. Snider and then Dr. Edwards.

DR. SNIDER: My question has just been answered.

CHAIR FERRIERI: Thank you. Dr. Edwards.

DR. EDWARDS: Could you please review the dose that was used in the Indonesian trial, one, and

then two, could you also comment on the bloody diarrhea that was seen in the child -- the one-and-one-half-year-old child that got the vaccine? Obviously less than two years of age that was reported in your dossier.

DR. LEVINE: The dose of vaccine used in the Indonesian field trial was approximately 3×10^9 colony forming units.

DR. CRYZ: Stan Cryz. That adverse reaction was spontaneously reported to our medical department as passive surveillance. And we have no additional information other than the doctor, even though the child was under the recommended vaccination age in the country where the vaccine was licensed, decided to go ahead and administer the vaccine.

And you know, shortly thereafter the child presented with what was described as bloody diarrhea. We've tried to get additional information. All we know is the child recovered, and other than that we have no additional information.

DR. EDWARDS: And no additional stool cultures were taken.

DR. CRYZ: To the best of my knowledge they didn't do stool cultures to try and resolve what the cause was.

CHAIR FERRIERI: Dr. Pierce and then Dr. O'Brien.

DR. PIERCE: Mention was made of the low number of cases occurring in the first six months of the trial done, but these weren't described. I wonder if we could have those figures just so we know what they are, for the vaccine and placebo group?

CHAIR FERRIERI: If it takes you a moment or so to pull that out we could move ahead with Dr. O'Brien's question. Or are you prepared to show that now? Please. Dr. Levine.

DR. LEVINE: These are vaccinees; these are placebo recipients. Up to this point would be cases in the first six month's of age -- in the first six months after vaccination. And this is the number of -- this number is ten. So there were only a handful of cases. I believe it was six or seven, eight, as I recall. I have a handout of that slide as well.

CHAIR FERRIERI: Any other comments on the data shown? Questions? Dr. O'Brien.

DR. O'BRIEN: Regarding the O blood group issue and the small glimmer of hope that perhaps there was a reduced incidence in O blood group individuals in Jakarta, in the volunteers are there any data that says there is or is not a difference in efficacy among

the O blood group positive versus non-O blood group positive individuals, A; and B, is there any difference in colonization by vaccine strain in the O blood group positive versus non-O blood group positive, or did you look?

DR. LEVINE: There is no difference in the level of protection in the North American volunteers in relation to blood group. There is no difference in excretion of vaccine in relation to blood group. And the immunological differences are seen in offshore studies.

DR. DAUM: Dr. Kohl and then Dr. Hall, and then Kim.

DR. KOHL: Dr. Kohl. In some of the early challenge studies, particularly the ones reported in Lancet in '88, not only were lyophilized vaccine used but I believe fresh, arterial vaccines were used. In the El Tor strain studies -- 903, 2, and 7 -- I'd like to know if all of the vaccine used would be equivalent to the commercial preparation of lyophilized vaccine?

DR. TACKET: Yes. All the challenges in which the vaccine was CVD 103-HgR were the lyophilized formulation.

CHAIR FERRIERI: Thank you, Dr. Tacket. Dr. Hall.

DR. HALL: Dr. Hall. I'm curious more about the vibriocidal, the antibodies since this seems to be the best marker that we have. And I wondered if you could tell us a little more about the one thing, the kinetics? It seems that it -- how long it takes to rise, it doesn't seem that it lasts very long.

And secondly, the effect of prior antibodies on that response and that duration. I noticed that you had in your children's study that there were -- with three to 17 months that the GMTs were in the 80s. But was what the pre-level of that?

And in contrast, you mentioned in the -- that was being mentioned in the adults, that the vaccine was more immunogenic than in children. And I would suspect that they would have had higher pre-antibody levels.

And I guess the other question I just wondered is, how long is the vaccine shed? You said in 19 percent, one or more days. Is that in general one day, or how long afterward?

CHAIR FERRIERI: And as part of that answer, Dr. Levine, could you address and affirm that the pre- and post-samples were run simultaneously as pairs? And the assay itself -- I'm trying to recollect -- this is a complement-dependent lysis, Classical assay?

DR. LEVINE: Correct, with guinea pig complement. I think there were seven questions. You'll need to help me as we work backwards.

CHAIR FERRIERI: Right.

DR. HALL: Sorry.

DR. LEVINE: It indeed -- the testing is done blind; that is, with coded specimens and always with pre- and post-vaccination specimens run at the same time. The geometric mean titer before vaccination and the Chilean three to 17-month-olds was 10 or 11, and it went up to approximately 85 post-vaccination.

Now, the good news about that is, that's an 8-fold rise with a single, oral cholera vaccine which, in the history of cholera vaccines, is quite -- is very good. The bad news, if you will, is that a geometric mean titer of 85 is a fraction of what one sees in North Americans.

With adults and in every venue that we've looked at, adult or child, if an individual has a baseline titer above 640 reciprocal titer -- 640 or above -- there's very small chance of a vibriocidal seroconversion.

To best look at the comparison or the geometric mean titer response by age, I think we need

to look at the Chilean data because Chile is a site that's had a few, small outbreaks of cholera but really there's very little -- there's very, very little Vibrio cholerae in the population, very few localized outbreaks.

In that population there was an 85 percent seroconversion rate when low socio-economic level adults were vaccinated and the geometric mean titer as I recall, was somewhere around 300. It's in your packet. It's from a study by Lagos, et al.

In 5- to 9-year-olds geometric mean titer, depending upon blood group -- the overall geometric mean titer was in the 200 range. It was 400 in blood group O and 180 in non-O. You must compare that then, with the geometric mean titer of 80 which was seen in the preschool children and in the infants and toddlers.

That is a low level compared to what one would see in Indonesian toddlers which had about 3-fold higher baseline geometric mean titer than the Chilean infants.

DR. HALL: Can you tell me a little about the kinetics of the antibody, too?

DR. LEVINE: Yes, I'm sorry. Vibriocidal antibody response in North Americans or in the Chilean

population -- that is, a non-endemic population -- there is a very rapid rise of vibriocidal antibody. It's IgM class. It peaks between day-10 and 14.

The person who has studied the kinetics in relation to live vaccine is Steve Wasserman who made the important observation that in fact, the antibody level at day-10 to 14 is higher than at day-7.

Since it's an IgM antibody we assume that day-7 was as good as day-10. Post facto that turned out not to be true. So in some of the studies the geometric mean titer is a bit lower than we would have seen if we'd collected specimens at day-10 or 12 or 14.

DR. HALL: So that you're really relying on an IgM response here?

DR. LEVINE: Yes, but it's just a proxy. I don't think -- we don't believe that the vibriocidal antibody is the mediator of protection. What this is viewed at is, evidence of the vaccine take. We have looked exhaustively, painstakingly for years, as have other groups working in cholera, looking for mucosal, immune response correlates.

The fact of the matter is we truly don't know what the relevant antigens are that everyone would agree are the protective antigens, and we

certainly don't have local mucosal immune response measurements that correlate as well with protection, as does vibriocidal antibody.

But it's almost certainly not the vibriocidal antibody itself in North Americans -- immunological naives. That just is a marker of a vaccine take. That comes fairly quickly back to baseline -- within a couple of months -- but the protection can be long-lived.

And that's best seen in re-challenge studies in volunteers where the re-challenge was carried out three years later, and their vibriocidals were down to baseline but they were solidly protective against re-challenge three years later. These were, you know, Marylanders.

DR. HALL: The other -- shedding of the virus?

DR. LEVINE: Shedding of the vaccine strain -- if you collect every stool from North American recipients -- every stool -- about 25 percent will excrete. And typically it's for one to two days. It's a max of seven days.

Offshore and offshore studies, the max as I recall, is about 16 percent. It related to age, how many stools are collected, etc.

DR. HALL: But no longer than seven days would be your --

DR. LEVINE: That's right.

DR. HALL: Thank you.

CHAIR FERRIERI: Dr. Kim, you're next.

DR. KIM: I have several questions I'd like to address one by one. Related to the bacteriocidal antibodies, are these antibodies cross-strained or biotype, or is it specific to a strain or a biotype or serotype?

DR. LEVINE: They are in relation to serotype, but there's considerable cross-reactivity. The antigens, the O antigens of Vibrio cholerae O-1 share common antigens as well as specific antigens that are specific for the Inaba and the Ogawa.

So an Inaba live vaccine or an Inaba challenge will stimulate vibriocidal antibodies that will give a higher Inaba vibriocidal response but a moderately high -- in general about two-thirds the height Ogawa response.

And the same is true vice versa. An Ogawa vaccine strain, live vaccine, or an Ogawa challenge, will stimulate higher Ogawa titers than Inaba titers, but the Inaba titers are up to about half to two-thirds the level of the -- the heterologous is about

half to two-thirds the magnitude of the homologous titer.

Cross biotype -- we don't recognize a biotype but we're sure there are antigens -- the biotype-specific antigens. The epidemiology tells us that.

DR. KIM: Thank you. The second question is that -- regarding safety data presented. Was the study presented -- the data presented on the safety in children from Chile, I understand it was in placebo control, but was data collected in a blinded fashion for the safety?

DR. LEVINE: Yes, they were. This is an NIH-funded, a CDER study. The study protocol was carried out under IND. It was a randomized, double-blind, placebo-controlled study of the following design.

It was a 2-dose regimen in which, at the time of the first dose half of the children were randomly allocated to receive vaccine, and the other half were randomly allocated to receive placebo. They were maintained under double-blind surveillance for 14 days.

At 14 days a blood specimen was collected for vibriocidal antibodies and a stool specimen to

look for copra-antibodies. And then all participants, all subjects received a dose of vaccine. This was carried out for reasons of bioethics to provide some possible benefit to the participating children.

The safety data that I showed you were from the 14 days of surveillance of the vaccine versus placebo where there was double-blindness.

DR. KIM: Thank you. One more question is that -- I know H. pylori was listed in the handout for possible effect of vaccine efficacy and immunogenicity but was deleted in your presentations. Was there any reason for that?

DR. LEVINE: There was a very good reason. We had an hour-and-thirty-minute presentation that we were told not too long ago, had to be cut down to 50 minutes. And so a number of our slides were simplified and we plucked out as many slides as we could. And we apologize; we still ran over by about seven minutes.

CHAIR FERRIERI: We'll move on to Dr. Mintz.

DR. MINTZ: The anti-cholera toxin antibody certainly does not correlate well with protection, but it's a useful serologic marker for infection. Can you tell me how the anti-CT antibody response compares in vaccine recipients to those with natural infection?

DR. LEVINE: In the volunteer model the serum anti-CT response which is -- the easiest marker, the easiest measurement -- is with CVD 103-HgR, is approximately two-thirds to three-quarters the level that's seen with wild type challenge.

CHAIR FERRIERI: Anything else, Dr. Mintz?

DR. MINTZ: No.

DR. DAUM: Dr. Greenberg.

DR. GREENBERG: I just want to -- the numbers for El Tor challenge, did you exclude the ten patients -- I guess it was ten patients who were challenged at ten days -- the data for efficacy against El Tor is based as I see it, on 15 challenged patients. Is that correct? There's a total of 15 volunteers vaccinated?

Maybe I counted wrong. No, I counted wrong; excuse me. Excuse me. So we have 17 plus nine, right? If you exclude them. So it's 26 -- that were vaccinated with the actual, commercial vaccine? Yes or -- I guess -- I'm just trying to get in my own mind how much data -- maybe I'm not adding right.

DR. CRYZ: No. All of the 103-HgR challenges were with the commercial formulation.

DR. GREENBERG: Okay.

CHAIR FERRIERI: Anything else then, Dr.

Greenberg?

DR. GREENBERG: No, that's it.

CHAIR FERRIERI: Dr. Kohl is next.

DR. KOHL: In all the -- Kohl -- in all the placebo-controlled trials as far as I can tell, the placebo was an E. coli -- a large dose of killed E. coli. Are there any studies where you used other kinds of more inert controls, and/or are there studies where you've used this placebo compared to another inert control?

Because it's easy to say that the difference between the placebo and the vaccine is low, yet the placebo itself I think, may be causing considerable abdominal -- or some abdominal complaints and diarrhea, etc.

DR. LEVINE: That's a very fair point. There are almost no data other than the use of the E. Coli K12 control, and the reason the E. coli K12 control is used is that's kind of forced as an issue since that was the control, the placebo control that was selected for evaluations of other, non-living, oral vaccines. And therefore, in order to have applicability of safety patterns or profiles, the same placebo was used.

CHAIR FERRIERI: Dr. Karzon. I'm sorry,

Steve, that didn't -- did you wish to pursue another angle there --

DR. KARZON: Well, I guess what I'd like to know is, how much symptomatology occurs from the placebo? Do we have that on the --

DR. LEVINE: I'm not -- we have some minimal data, but not too much data. What we have though, Steve, are -- the E. coli K12 at that dose was actually used in volunteer studies. In the early, early days, circa 1980, the early days of recombinant DNA technology when there was worry about the biosafety of certain cloning vector plasmids.

That E. coli K12 was used as the organism into which these various plasmids were put and were then fed to volunteers, along with just a control group getting that E. coli K12 on the same research isolation ward under intensive surveillance. And there were no adverse reactions observed even with the live strain.

That led to that being selected as the placebo for comparing the reactogenicity of the oral, killed vaccine. In other words, it was based on the observed safety of that strain being fed at 50 billion organisms. Those data are published. They go way back so I don't have those off the top of my head.

But we have those data.

CHAIR FERRIERI: And the vehicle in which the E. coli K12 was suspended, was it a complex sugar, or what --

DR. LEVINE: Buffer.

CHAIR FERRIERI: Just buffer?

DR. LEVINE: Yes. It was just bicarbonate as opposed to this slightly different buffer.

CHAIR FERRIERI: Dr. Karzon.

DR. KARZON: I'd like to review the status of vibriocidal antibody. First, its own natural history after immunization or natural disease, and then how it may play a role in indicating infection.

It's always -- it appears how rapidly; what is the curve of appearance and disappearance? And is it always an IGM? Does it ever revert to G? Do you find IGA component in there? That's the first set of questions.

DR. LEVINE: In a non-immune it appears as an IGM antibody that rapidly falls with the kinetics being clearly measurable -- clearly elevated at seven days from the time of ingestion of organisms, peaking at 10 to 14 days, typically back to baseline at about four months -- perhaps six months. So close to baseline you can hardly tell the difference.

In endemic areas like the Maclabazar field area of Bangladesh where there's repeated ingestion year after year -- perhaps multiple times within a year -- repeated ingestion of Vibrio cholerae O-1, what one sees is if you do a seroprevalent survey in the population, the vibriocidal antibody increases with age.

For every 2-fold rise in that population, that has been under surveillance for a couple of decades, with every 2-fold rise in geometric mean titer of vibriocidal antibody, there's a halving of the cholera incidence. In that population --

DR. KARZON: Is it always M?

DR. LEVINE: No. In that population consequent to the repeated -- presumably -- consequent to the repeated stimulation, the antibody reverts -- a proportion of the antibody becomes IgG.

Virtually nothing -- very little is known about IgA, but in that endemic population a long-lived antibody is IgG and in several -- in three different studies where the design was an index case of cholera, then go into the household and bleed the household contacts who are at higher risk of developing cholera than households that don't have cholera, and you look then, for the attack rate of cholera in contacts in

the household, there's a clear, inverse correlation between the level -- the baseline level of vibriocidal antibody versus whether or not one gets cholera.

DR. KARZON: Have you measured the amount of the vibriocidal antibody during an attack of watery stool cholera? Does it get into the gut and is it acting in this gross way as a neutralizing antibody?

CHAIR FERRIERI: A brief answer will suffice.

DR. LEVINE: We don't know that for sure. There's an assumption that perhaps the way the parenteral killed cholera vaccines worked -- and they showed a moderate degree of short-term protection -- was by leakage of antibody onto the mucosal surface.

CHAIR FERRIERI: Just a couple of more questions and then we'll have Dr. Bash's presentation. First, Dr. Clements-Mann and then Dr. Snider, and then Dr. Bash, The other questions will have to hold.

DR. CLEMENTS-MANN : Just two questions, related to -- since the children in the Indonesian trial were ages two to five -- which is also a time of high rates of other diarrheal disease -- is there any indication or any record of whether the children had diarrhea post-immunization?

And then secondly, whether the diarrheal

illnesses that were identified and associated with cholera, might have also included a co-infection or other pathogens?

DR. LEVINE: There was a nested, reactogenicity which showed no incrimination of the vaccine for any of the adverse reactions that might be expected --

DR. CLEMENTS-MANN: I meant just, you know, any other types of diarrhea that might have occurred that might have interfered with the immunizations -- during the post immunization period?

DR. LEVINE: Yes. I don't think we looked at vibriocidal response in relation to whether there was diarrhea in that nested study.

To answer your second question, we do not have extensive bacteriology and did not build that in for reasons of economy, into the field trial. But your question is very well taken. One of the factors that determines the level of efficacy is the specificity of diagnosis.

That includes, if you look for multiple pathogens and you find another recognized pathogen, do you include or not include that case? In some other studies where they had the ability to do more complete screens for pathogens, up to 20 percent of the cases

had co-pathogens. And that's where the severity of diarrhea actually adds a fair amount of specificity.

CHAIR FERRIERI: Dr. Snider.

DR. SNIDER: Is there any information on either natural disease or this vaccine with immunocompromised individuals -. particularly I'm thinking about HIV-infected individuals -- with regard to severity of disease or shedding of organisms?

DR. LEVINE: Yes. This is a very important question. With sponsorship of the World Health Organization, a randomized, double-blind, placebo-controlled trial, crossover trial, was carried out in HIV-positive and HIV-negative subjects in Mali, which is an area that has considerable cholera.

To make a long story short, there was no increased reactogenicity of the live strain. There was no increased excretion of vaccine strain in the HIV-positive subjects. The seroconversion rate was comparable.

The geometric mean titer in the HIV-positives was lower, and the lower geometric mean titer was due to those individuals who had CD4 counts below 500. They were flat, as with many other vaccines used in that population.

The publication of that is in the January

issue of Bulletin of WHO.

CHAIR FERRIERI: If there's any comment on this precise issue we can hear it now, otherwise we'll go to Dr. Bash.

Dr. Bash, you are here? Many of you will wonder why Nancy left abruptly. Her mother has been in the hospital for surgery and took a turn for the worse today. So she has left for the hospital. Many of you will want to stay in touch with her on that, I'm sure.

DR. BASH: I will be discussing in summary, some of the clinical studies regarding the use of Mutacol Berna, with particular emphasis on studies that relate to the questions that we have posed to the Advisory Committee.

As you've heard, Mutacol Berna is a live, oral, attenuated vaccine consisting of 2 to 10 X 10^8 dose of strain CVD 103-HgR. Indication requested in this product license application is as a single, oral dose in adults and children greater than the age of two, for the prevention of cholera in U.S. travelers at risk of exposure to Vibrio cholerae.

As an overview -- and I will try to shorten this in aspects that have been well discussed already -- I will summarize some of the safety data which

pertains particularly to use of this vaccine in U.S. adults .

I will focus most of my discussion on the efficacy data on studies designed to evaluate efficacy, particularly in the U.S. population. I will briefly mention only in summary, the Indonesian efficacy trial.

Immunogenicity will be discussed from two aspects: one in terms of the potential for needing to bridge from U.S. efficacy data to the pediatric population; and also from the perspective that immunogenicity supports the view that data obtained supporting efficacy in U.S. volunteers may be a more applicable source of that data than efficacy data obtained in endemic regions.

And lastly I will discuss the pediatric safety and immunogenicity data because our questions regarding this data I think, are better understood after reviewing the adult data.

This chart you have already seen and I will discuss it only briefly. This is the pivotal safety study that was performed in Baltimore, Maryland, as a randomized, blinded, controlled study. We've already discussed that the controls included 5 X 10^8 heat killed E. coli in the same buffer as that used in the

administration of the vaccine.

These do show relatively high rates of headache and gastrointestinal symptoms. Volunteers rated the severity of their adverse events as mild, moderate, and severe, and the rate of severe complaints was less than two to five percent in all cases.

As you can see, the majority of complaints are gastrointestinal in nature. And there were no statistically significant differences except that seen with nausea.

Diarrhea was defined as greater than four loose stools in a 24-hour period. And as you can see the rates meeting this definition were quite low. In addition, milder forms of diarrhea were evaluated to include the complaint of one or more loose stools in which case 19 percent of those receiving the 5 X 10^8 dose and 17 percent of those receiving 5 X 10^7 dose had a complaint of a single or more loose stools.

These were statistically significantly different from the control arm but it emphasizes the mild nature of the symptoms experienced.

There are additional, blinded, controlled studies conducted in the U.S. and in Europe. There's an error here -- this is not 188; as you heard this

morning this is 94. A Swiss study involved 25 patients who received vaccine and an equivalent number with control.

In an Austrian study one arm included 65 patients who received CVD 103-HgR in combination with Ty21a. In comparison, there were other arms to this study so the placebo arm here is significantly larger.

Essentially, there were no statistically significant differences in gastrointestinal or systemic adverse events. Overall, the rate of diarrhea ranged across these studies between eight and 30 percent.

A number of open, Us. immunogenicity studies have been performed and adverse events data was collected in all of these. The initial studies were performed as inpatients using the definition of diarrhea of a single loose stool greater than 300 mls, or two loose stools greater than 200 mls in 24 hours.

Using this definition, 3 of 47 individuals, or 6.4 percent, experienced diarrhea. The subsequent immunogenicity studies were performed as outpatients using a definition of four or more loose stools. And using this definition, one percent or 2 out of 205 individuals experienced diarrhea.

In a subset of these outpatient studies the

complaint of any diarrhea of one or more loose stools was obtained. And meeting that criteria were 34 percent, or 22 out of 65 individuals.

Across all U.S. and European open studies including a large European, open safety study, diarrhea was recorded in 15 percent of 2,254 individuals .

The safety data from studies conducted in endemic regions I will not discuss other than to mention that there have been no serious, adverse events reported in any of that data.

In addition, this vaccine is licensed in several European countries and in Canada, and from 1994 through 1996, 40,000 doses have been distributed. We do not have a denominator specifically for this as it is unknown how many of these doses have actually been administered, but these constitute the only two reports to the company during this period of time.

This was already discussed and unfortunately, as was mentioned, there was no etiology reported for the young child with bloody diarrhea.

The second report is of a 50-year-old woman who , on her second dose of vaccine, developed s systemic hypersensitivity reaction. She also was treated and recovered fully.

So in summary, the use of Mutacol Berna in U.S. adult volunteers appears to be safe, resulting primarily in gastrointestinal symptoms which are mild and self-resolving.

The clinical data supporting efficacy, you have heard about the Indonesian efficacy trial which was designed to evaluate efficacy in individuals in the endemic region. It utilized 5 X 10^9 cfu dose of CVD 103-HgR, enrolled 67,508 participants ages 2 to 41 years of age.

This has only recently become available to us and has been provided to us as summary data, so I will not discuss it further unless there are specific questions. I would like to focus my discussion on human volunteer challenge studies, and specifically 75 vaccine recipients, and I have limited my comments to only those studies utilizing the CVD 103-HgR strain, and not the earlier CVD 103 strain challenge studies.

Seventy-five vaccine recipients and 63 unvaccinated controls have been challenged between the years of 1987 and 1993 in six open, non-randomized, non-blinded studies.

These studies were conducted as inpatient, quarantined studies. Diarrhea was the primary outcome of interest and was defined as a single, loose stool

greater than 300 mls, or two loose stools 200 mls in 24 hours. All stools were graded by study nurses and recorded, and those of grade 3 being thick liquid, 4 opaque watery, or 5 rice water, contributed to the definition of diarrhea.

Tetracycline -- a course of tetracycline was administered to all the participants including those who were asymptomatic, beginning on day-4 after challenge, or 24 hours after meeting the definition of diarrhea, or earlier as clinically indicated, based on the severity of diarrhea.

I have separated the challenge studies by challenge strain. In this table the three studies in which a Classical Inaba strain were used are shown. All three of these studies used the strain 569B which is the parent strain for the CVD 103 vaccine.

In this first study conducted in March of 1990, vaccine recipients who had been given a single dose of 5×10^8 were challenged 28 days after vaccination. The vaccine dose was 1.5×10^6 cfu and the diarrheal attack rate in the control arm was 38 percent.

The mean number of loose stools indicated here in the mean stool volume indicated here shows that this was a fairly mild development of diarrhea in

comparison to studies that you'll see in a minute.

The second challenge was conducted in October of 1991 and included individuals who had received a single dose of 5 X 10^8 six months prior to challenge, and a small number, three individuals, who had received a 5 X 10^9 dose four months prior to challenge.

In this study a challenge dose of 4.1 X 10^6 was used, and consequently a higher attack rate in the control arm was seen at 67 percent. Again, based on mean number of loose stools and means to volume, this was a fairly mild challenge.

Additionally, for the most part these control recipients were not treated with tetracycline protocol at 24 hours after meeting the criteria but were observed for the four days of observation, further indicating the mild degree of diarrhea developed in these challenge studies.

In the final study individuals were challenged after receiving a single dose of 5 X 10^8 of vaccine eight days prior to challenge. The challenge dose was higher at 2.6 X 10^7 cfu. The development of diarrhea in the control arm was 73 percent. A slightly higher degree of diarrhea was experienced in these control volunteers.

Across all of these studies the vaccine participants -- the vaccinated participants were protected from the development of diarrhea. However, it should be noted that there was a dose escalation across these studies, and in the study that examined challenge farthest away from vaccination there was a small number of individuals included who had received a higher dose of vaccine, a slightly shorter period of time prior to challenge.

This chart summarizes the three challenge studies undertaken with El Tor challenge strains. Each of these challenge studies used a different El Tor strain and the challenge dose was fairly consistent between one and 1.7 X 10^6 for each of these studies.

In the first study individuals were challenged. One was after receiving a single dose of 5 X 10^8. Diarrhea developed in seven out of eight, or 88 percent of the control arm and 33 percent of the vaccine recipients.

In looking at the mean number of loose stools, including the range, and the mean stool volume near three liters, ranging from .9 to over six liters, you can see that this was a more aggressive challenge and that there's evidence for amelioration of disease

in the vaccine recipients, even in those who did meet the criteria for diarrhea.

The second study conducted in September of 1989 challenged with an El Tor Ogawa strain one month following two doses of 5 X 10^8 vaccine. In this challenge, 100 percent of controls developed diarrhea, 36 percent of vaccine recipients developed diarrhea, and once again there was a substantial degree of purging seen in the control volunteers, with a fairly high number of loose stools and a fairly high mean stool volume in comparison with the vaccine recipients.

In the final study in December of 1993, individuals were challenged to either ten days or one month following a single 5 X 10^8 dose of vaccine. This strain, El Tor Ogawa, is the clinical isolate strain and diarrhea resulted in 88 percent of the control participants and 40 and 44 percent of the vaccine recipients.

Again, a fairly significant stool volume and mean number of stools is seen in the control arm, with evidence of amelioration of disease in the vaccine recipients who met the criteria for diarrhea.

In all, four patients in these studies required IV fluids and early antibiotic treatment for

heavy purging. And all four of these patients were in the control arms of these studies.

However, it should be noted that one of these studies challenged individuals who received two doses of the intended vaccine and that the longest duration between vaccination and challenge for the El Tor studies is one month.

I should point out, we included the P values in those charts as reported by the sponsors. However, there are trial design issues which raise questions regarding the validity of that statistical analysis.

In these studies there was no randomization and there was no blinding of patients, study personnel, or laboratory personnel providing the immunogens to these studies.

Specifically, vaccinated subjects were recruited from seven of 15 open, immunogenicity studies, with recruitment rates from the individual immunogenicity studies ranging between 33 and 76 percent. Overall, 150 patients were immunized in these seven studies that led to challenge studies, and 50 percent, or 75 of those individuals, went on to challenge.

Reasons for not being included in the challenge studies are varied and unfortunately in a

number of them these reasons were unknown or not recorded.

The inclusion criteria for the challenge portion of the studies were different from that for the immunogenicity portion of the study, so a number of individuals either developed or had medical reasons which prevented them from participating in challenge.

A psychological evaluation was required because of the inpatient and quarantined nature of these studies, and a number of individuals failed on this account. Some individuals received poor rating during the first study and were not included in the inpatient challenge study.

One individual was recorded as being violent; one had been incarcerated; four withdrew; and a number were not interested in participating in a challenge study or didn't show up for other reasons.

The control arms were recruited separately from those participants who were in immunogenicity in the challenge studies.

The other difficulty in combining this data to get a sense for the overall efficacy of this vaccine I've already mentioned, including the fact that the immunization dose, although in most instances was a single dose of 5×10^8, in one instance included

5 X 10^9 and in another study included two doses of 5 X 10^8.

To whatever degree that we could, in looking at the vibriocidal titers of the subpopulation from the immunogenicity studies that went on to be challenged, there was no difference in their immunologic parameters in terms of peak vibriocidal, post-immunization titers between those who were challenged and the entire group that was immunized.

And it should be noted that the primary outcome in these challenge studies being volume of liquid stool was a fairly objective criteria.

However, these two issues cannot address the potential for having significant differences between individuals willing to participate in a challenge study knowing that they are unprotected, and individuals willing to participate in a challenge study who have been vaccinated and who consider themselves likely to be protected.

Immunogenicity study data I mentioned I would discuss both in terms of the potential necessity for bridging from the U.S. efficacy data to the pediatric populations.

And also as it's the immunogenicity data that provides a rationale for why efficacy data

obtained in the U.S. volunteers may be more applicable to protection in U.S. travelers than that obtained through efficacy trials in endemic regions.

As has already been discussed, the actual immunologic mechanism of protection is not known. These vibriocidal assays are really considered only potential markers of protection. And the sponsors have presented data regarding the inverse relationship of peak serovar. It's not specific, actually.

It's either specific or across serotype, vibriocidal titers, being inversely related to stool volume and diarrhea in the challenge models. And they have presented data regarding baseline titers related to protection in endemic regions.

This is the Spearman's correlation analysis of the six challenge studies. And in fact, these correlation coefficients are negative in all instances, although only a few of these earlier studies reached statistical significance.

Interestingly, it does look in these first two studies that it is across serotype which shows a greater inverse correlation here with an El Tor Inaba challenge, the Ogawa vibriocidal titer. And here with an El Tor Ogawa challenge the Inaba vibriocidal titer, which was more statistically significantly inversely

correlated. But clearly there's not a well-defined correlate of protection for this disease.

In this chart which I apologize -- it may be very difficult for people to see -- I tried to summarize the studies for which pre- and post-vibriocidal geometric mean titer data is available and grouped this according to where the studies where performed.

The yellow bars indicate post-immunization vibriocidal titers. What is virtually invisible are the pre-titers which are in front here. And I won't discuss those; you really can't see them. There are some differences in some instances in the pre-immunization titers, but this is not consistent across the board and in Peru and Chile -- specifically in Chile where there is little, or has been little cholera, the pre-vibriocidal titers were not significantly elevated in comparison with the non-endemic data.

As you can see, the majority of these immunogenicity studies resulted in very high, post-immunization, vibriocidal, geometric mean titers. In the European studies the same was seen that this in fact -- this value here is the study that was referred to in the question discussion prior to my talk in

individuals who were boosted 15 to 24 months after having received an initial dose.

And as you can see, they really had a very low post-immunization, vibriocidal titer even though their pre-boost tiers had returned to baseline.

In Thailand, several studies -- two studies were conducted comparing high socio-economic status and low socio-economic status individuals, and as was indicated earlier, there's a dramatic difference in the response to vaccine in these two populations.

The remaining studies with orange bars, indicate studies conducted using the 5 X 10^9 dose -- the one log higher dose of vaccine. And whether in Indonesia or Peru, where ongoing cholera was occurring at the time of these studies, or in Chile where there was very little cholera ongoing, the post-immunization, vibriocidal titers even at the higher dose, are significantly or substantially less than that seen.

Now, several of these, I'm sorry, this may be hard to understand, but C refers to children five to nine years of age, and P refers to pre-schoolers, two to four years of age. It is unclear to what degree the age difference between responses in adults versus responses in children contribute to this, but

even in the adult populations the post-immunization titers in these populations are significantly lower.

This data on the end that's a little bit cut off there is the nested immunogenicity study from the Indonesian efficacy trial. The first bar being for all participants and the second bar being for those who were aged two to five years of age.

Here is the next immunogenicity study from the Indonesian efficacy trial. And as you can see the pre-immunization, vibriocidal titers were fairly low in the youngest age group and were as expected, higher in the older age groups and in all participants combined.

The seroconversion rate was really not lower than expected, however the post-immunization, vibriocidal peak titer is really quite low compared to those seen in non-endemic, or developed countries.

CHAIR FERRIERI: Could you leave this on for one more second, Margaret? Thank you.

DR. BASH: The issues regarding the pediatric data that we would like to focus on and to point out, is that there has been no administration of this vaccine to U.S. children. The Chilean population has been proposed as representative, or somewhat representative of the U.S. population for the

indication in U.S. travelers two years of age or older.

However, all studies conducted in Chile have utilized 5 X 10^9 dose and as was seen in the chart earlier, the immune responses appear to be similar to those attained in endemic regions. I think this raises issues regarding the applicability of both estimates of protection as well as safety data in going from a Chilean population to a U.S. pediatric population.

Safety data in children have been obtained in blinded, controlled studies conducted in Chile, Peru, and Indonesia. Overall, 279 2- to 4-year-olds and 466 5- to 9-year-olds have received a 5 X 10^8 or greater dose, and the majority of these children did receive the higher, 5 X 10^9 dose.

In summary, diarrhea occurred in one to 13 percent across these studies; vomiting in one to 14 percent; and abdominal pain in 11 to 50 percent.

Fever was generally very low except in the single, subgroup of an Indonesian study, and other than in this outlying value there were no statistically significant differences between the placebo arms or the control arms and the vaccine arms.

The only pediatric data available in

developed countries comes from an Austrian open safety study in which a very small number of children, 14 patients aged six months to seven years of age, and 15 patients aged seven to 12 years of age, were enrolled.

In this limited number of patients abdominal pain, diarrhea, and rash occurred each at seven percent of the younger group, and diarrhea at 20 percent, and nausea and rash at seven percent of the older group.

The analysis of this data by the sponsors indicated there was no difference in either the type or severity of adverse events experienced by children versus the large number of adults enrolled in the study.

In terms of the pediatric immunogenicity data, I'll focus here on the Chilean data. This is at 5 X 10^9 dose of vaccine divided in ages five to nine years of age and ages two to four years of age. The pre-immunization, vibriocidal titers are fairly low, and lower than that seen in Peru and Indonesia.

The peak post-immunization, GMT titers remain, as was mentioned earlier, fairly low: the seroconversion rates of 74 percent in the 5- to 9-year-olds, and 51 percent in the 2- to 4-year-olds.

Interestingly, I would like to point out

that the anti-cholera toxin titers are fairly high as baseline in this population, indicating that cross reactive -- as was mentioned, there's not cholera endemic in this region but cross-reacting E. coli toxins may result in this.

And what effect this has is unclear; however seroconversion rates across all the endemic and the Chilean populations are fairly low compared with seroconversion rates to anti-cholera toxin in the U.S. adults in the immunogenicity studies.

So in summary, I have been I hope, fairly brief. Safety data would indicate that in U.S. adults administration of Mutacol Berna is safe and results in the development of gastrointestinal systems which are generally mild and self-resolving.

I think the issue of the control arm does complicate deciding what proportion of those adverse events can be attributed to the vaccine and the fact that the control arm includes the buffer that is also a part of the vaccine adds into that difficulty.

Our primary focus has been on the efficacy data as it refers to U.S. travelers. I hope I've provided some data that would support the rationale for examining efficacy in U.S. volunteers. However, I have also pointed out some issues with regard to the

efficacy data that has been presented in these challenge studies with regards to study design.

The pediatric data concerns may make selection of the population and effect of the dose as compared to that which would be indicated in the U.S. license. I'll try and answer questions.

CHAIR FERRIERI: Thank you very much, Margaret. That was very helpful in pulling together a lot of detail that we needed to see presented like that.

We'll take about 15 minutes for questions from the panel and then we will adjourn for lunch. And so there are a few people who have been waiting patiently and top of that list is Bob Daum and then Greg Poland.

DR. DAUM: Thank you, Pat. It's not bad to be at the top of any list, I guess. My questions are more directed toward the sponsors than the agreeably, informative presentation we just heard. And although anybody could comment.

I'm struggling with the fact that the baseline titers were increased in the Suharyono paper in the Lancet, and I thought Dr. Levine, you said that frequently in developing countries you see this higher baseline titers.

So I guess my question is, is to comment on that with regard to several things. Is that because of ongoing exposure, and if it is, why aren't we getting any kind of booster phenomenon? It also seems like it's a dampening phenomenon when these kids are vaccinated.

And I guess in a bigger framework, I don't understand the overall biologic plausibility question with respect to why these vaccines would appear to work in certain totally naive populations but not work apparently at all, at least sometimes, in endemic populations.

So some comment on the fact that the elevated baselines are there -- baseline titers -- the fact that there's no boosting, and the biologic plausibility question of the different populations.

DR. LEVINE: I'm going to have trouble again, with the six questions.

DR. DAUM: I'm sorry, I --

DR. LEVINE: Well, run them by me again, one at a time and let me answer.

DR. DAUM: Sure. Let's first comment on the fact that the titers were elevated in developing country populations -- at least in some of the data I saw flash by this morning -- compared to a naive

population. And if that's the case, how does that observation feed into the failure of the vaccine in the population with an elevated initial titer, and why don't we see any kind of boosting phenomenon? Almost appears to be a dampening --

DR. LEVINE: Ah, one question at a time. I'm sorry.

DR. DAUM: It's the same question.

DR. LEVINE: I'm sorry, ask it again then. It sounded like it was -- I'm sorry.

CHAIR FERRIERI: It's the same question.

DR. DAUM: I'll be happy to ask it again.

CHAIR FERRIERI: Go ahead, Bob.

DR. LEVINE: Please. Is that okay?

DR. DAUM: The baseline titers are elevated, are they not --

DR. LEVINE: Yes.

DR. DAUM: -- in developing country populations?

DR. LEVINE: That's correct. Where there's cholera, yes.

DR. DAUM: And my question is -- I guess I'll ask one at a time -- why is that?

DR. LEVINE: That's from contact with Vibrio cholerae in that, in the Suharyono study and the

Simanjuntak study where bacteriology was done in conjunction with the safety immunogenicity studies, wild type Vibrio cholerae were grown from approximately one percent of the placebo contracts or the household contacts.

The geometric mean titer, the baseline titer, indeed increases with age, and it was about -- it was almost 30 -- 28 or 29 in the 2- to 4-year-olds in Indonesia as you point out, elevated, compared to U.S. adults or Chilean infants, and then went up to about 50 in the 5- to 9-year-olds.

Now, that geometric mean titer of 50 includes some children who have very high titers and some children who have low titers. The children who have very high titers of say, one to 640 or above, they will not seroconvert given vaccine. That's why the seroconversion rate is not 97 percent like it is in North Americans.

That proportion of kids with really, really high titers, you can't boost them further. And we presume that they are already immune. And then there are some kids with low titers of 40 or 80 or 20, and those kids, the 10^9 dose seems to seek them out and seroconvert them.

Although it seroconverts them the geometric

mean titer, the post-vaccination titer, is only a fraction of what one sees in North Americans. And one of your questions was, why is that? This is the $64,000 question.

We believe -- we have some data to suggest that proximal, small bowel overgrowth with coliforms and anaerobic organisms interfere with the vaccine strain and interfere with vaccine take. We know that Vibrio cholerae, in particular Classical biotype strains, don't do well in the environment of the normal, large bowel because of the competitive effect of normal flora.

And when those kind of normal flora are way up in the proximal, small bowel that means that the dose of vaccine organisms that's given is interfered with.

In this poor population living in very disadvantaged conditions such as in the areas of North Jakarta and parts of South America, there exists an entity called environmental enteropathy. When those kids are biopsied -- healthy kids -- one sees a very different morphology of the small intestine than one sees in North American children or adults.

And we think that several of these together account for the diminished immune response. If we can

get a better vibriocidal response in those kinds of populations we believe that we can have more consistent protection.

The hint for that is the suggestion of protection in the blood group O individuals, which is a group that has a 3-fold higher vibriocidal response compared to non-O.

DR. DAUM: I'm going to cull from that that you did hear more than my first question. But all kidding aside, the titers are in fact, higher in this population but there's no booster phenomenon with the vaccine?

DR. LEVINE: No, there is.

DR. DAUM: In terms of the geometric mean that the kids end up with.

DR. LEVINE: Yes, there is a booster effect with 9 logs. Yes. If you look -- you've got the data. If you look at any of those studies -- for example, the 2- to 4-year-olds, the Simanjuntak study. That's a mean 8- or 10-fold -- you'll have to look it up -- I think it was a mean 8-fold rise. It may have been closer to 10-fold.

Mean fold, geometric fold rise with the 9 log dose. In the 5- to 9-year-old Indonesians it's a mean -- the baseline was 50, the filtered vaccine,

post-vaccination geometric mean was 450. So that's a mean 9-fold rise.

To have a mean 9-fold rise in the history of oral cholera vaccines with a single dose, is a clear-cut step in the direction of better immunogenicity. That's unusual compared to what was seen in the past. But it's only a fraction of the fold rise that we see in a North American or European population.

DR. DAUM: Yes, I guess it's a question of semantics in terms of what we're defining as a booster, and you're absolutely right. I was thinking of comparing it to what we would see in a developed country who were naive, and who get much higher titers.

And so I was comparing that to this and that doesn't look like a booster response there, given the fact that you're saying the higher levels meant exposure -- endemic exposure to cholera. I'd expect a bigger boost in the developing country -- people to end up higher. Do you follow me? And that didn't happen.

So I'm just asking why, and I guess the real question is the one you said is maybe a $64,000 question and it has no answer. And that is, the biologic plausibility question.

DR. LEVINE: The vaccine at 9 logs clearly leads to seroconversion in circa 75 to 85 percent of individuals in a non-endemic area, and a mean approximately 8- to 10-fold increase in geometric mean titer. But that geometric mean titer positively, absolutely is much less. It's a fraction of the post-vaccination titer seen in naives.

We think that's a function of the hosts because when you vaccinate in poor population in Chile where there's not much cholera but they're still poor and where we know from breath hydrogen surveys in kids that there's evidence of proximal, small bowel overgrowth and we have shown an inverse correlation between the presence of that proximal, small bowel overgrowth and vaccine take, we think it's a question of poverty and how the host is inherently different in responding to any oral vaccine -- including Sabin polio vaccine, rotavirus vaccine.

It's a more generic problem and an important one that we have to address if we want oral, mucosal vaccines to have a place as public health tools in the developing world.

CHAIR FERRIERI: Thank you, Mike. I don't think we can resolve this any better to your liking, Bob, so we will abandon that at the moment. Does

anyone who raised a hand have something to elucidate on this very precise point that you've heard the exchange on? Randy, was it pertinent to this, please?

DR. HOLMES: Well, possibly.

CHAIR FERRIERI: Please go ahead.

DR. HOLMES: The presentation described a difference between the CVD 103-HgR and the HgR2 variant, and I wonder if somebody could more precisely describe the data that characterized the difference in that phenotype.

CHAIR FERRIERI: Dr. Kaper.

DR. KAPER: Yes, Jim Kaper. The 103-HgR2 was constructed several years after HgR and using better techniques in terms of mutagenesis, of suicide vectors and things like that, reflecting advancements in recombinant DNA technology. So CVD 103-HgR was passed multiple times through a laboratory in order to get the recombinations and select those mutants.

HgR2 was passed far fewer times and the -- but apparently there was a spontaneous mutation that arose in CVD 103-HgR that leads to less colonization in terms of say, a mouse, suckling mouse model. It may be a log difference lower colonization of 103-HgR versus 103. Exactly what that mutation is I have no idea.

CHAIR FERRIERI: Thanks, Dr. Kaper. Dr. Poland and then we're going to break.

DR. GREENBERG: I was just going to follow up on some minor question that Dr. Snider started with, and that is in regards to immunocompromised people -- not necessarily HIV but other immunocompromised.

And the second part is, do we have any data on use of the vaccine in people where the integrity of the bowel mucosa might be altered, such as inflammatory bowel disease?

CHAIR FERRIERI: State your name.

DR. TACKET: It's Carol Tacket. No, we don't have safety data in those populations other than the HIV-infected patients that you heard about.

CHAIR FERRIERI: Anything else, Greg? Otherwise, we can have another question from Dr. Kohl. Steve, you had your hand up as well.

DR. KOHL: Yes, it's my continual quest for immunological correlates of protection. We are told that there is epidemiological data and some experimental data that vibriocidal titers correlate with protection. Is there a level of a vibriocidal titer that correlates with protection so that we can extrapolate something to pediatric studies?

DR. LEVINE: Not really, Steve. The closest that one can come are the studies of Henry Mosley and Roger Glass in Maclabazar, where they went into the households of indexed cases of cholera, bled the contacts, and then looked at the attack rate that ensued with follow-up in the contacts compared to their baseline vibriocidal level.

And there was a clear, inversed correlation. The higher the baseline level the lower attack rate. And it looked like, with the vibriocidal assay used in that laboratory, in that population, that there was a correlation as I remember, either with one to 80 or one to 160.

But this is IgG antibody in a primed population, in a very special situation. There are up to 2- or even 4-fold differences between laboratories in the vibriocidal titer that is measured on the same specimen. There have been comparative studies that show consistency, but the absolute value can vary 2- or 4-fold -- for example, between the CDC and the CVD.

So in some instances there are cutoffs that correlate, but you can't extrapolate from that one instance, to answer the broad question as far as --

DR. KOHL: That's what I was worried about. And just a follow-up on that. We were shown data from

a European study where some individuals were given the vaccine and then re-challenged. And on the re-challenge they did not appear to make vibriocidal antibodies .

Are those individuals protected? Do we think they're protected?

DR. LEVINE: The assumption is that they are protected. This is a measure of the gut immunity for which the vibriocidal antibody take at the primary immunization was the measure of take. And the vibriocidal antibody comes down and the protection in an industrialized country population is long-lived long after the vibriocidal antibody returns near baseline.

DR. KOHL : So what I'm hearing is that we can't tell by vibriocidal antibody what's going to happen regarding detection. And that I think, is going to have real implications as we get to pediatric cases -- pediatric population.

CHAIR FERRIERI: Dr. Pierce, you wanted to add to the --

DR. PIERCE : I just wanted to suggest another interpretation -- not necessarily exclusive interpretation -- another interpretation of this complex picture.

And that is that with CVD 103-HgR which is a compromised strain with regard to its ability to colonize the bowel -- its intent to compromise -- it seems entirely possible that a degree of persisting, local immunity -- not necessarily the request in vibriocidal antibody which is not (unintelligible) in the community, this is sufficient to exclude that organism at the time it passes through the gut without inducing an immune response.

And that may well be what is seen in children. In Indonesia for example, they have the highest vibriocidal titers, or even the lower ones. And it could well apply also to Austrians 24 months later.

That ability to exclude that strain may not reflect immunity to cholera because cholera -- wild type cholera -- is a much more highly adhering organism, much more capable of inducing disease. And so it's possible, maybe unfortunately it's possible, that a line can be drawn between what these strains -- the wild type strains can do and what this strain can do.

As I say, this is not necessarily an exclusive explanation, but I think it's one that needs to be considered, and it is also consistent with the

observations.

CHAIR FERRIERI: Dr. Carpenter, would you like to add to this? You look interested as if you wanted to engage on this issue.

DR. CARPENTER: Well, not this issue specifically. The only concern I have in hearing this -- these are obviously, wonderful studies that have been done over a period of years, and science has moved quite rapidly.

My concern though, is about the risk/benefit of using the vaccine for travelers. In order to prevent one case of cholera, somewhere between I guess, 50 and 100,000 doses of the vaccine will be given. Based on what was seen that's going to cause maybe 10,000/15,000 cases of what's called mild diarrhea.

Mild diarrhea, like every other thing we see in medicine, has a bell-shaped distribution. Some of those diarrheas are going to be more severe and some occur in elderly persons, and we don't know how many.

But the question is whether a benefit in preventing one case of cholera is exceeded by the risks to several -- maybe several hundred persons who will get more severe than mild diarrhea as a result of the vaccine.

That's the only concern I've had so far.

CHAIR FERRIERI: Thank you. We'll return to that issue in a serious way after lunch, and I appreciate your raising it now. A brief comment from Mary Lou Clements-Mann and then from Alison O'Brien. Then we absolutely will break for lunch.

DR. CLEMENTS-MANN: I know this is all very confusing but I just thought maybe I could give it another analogy to clear this up.

CHAIR FERRIERI: Yes.

DR. CLEMENTS-MANN: We have an infecting immunization which requires infection. We don't have a good way to measure all the immunologic parameters that would occur in the course of that infection because there's going to be replication, colonization of the strain, there's going to be secretory immunity generated, probably some cell muted immunity -- who knows -- and also there's going to be antibody production to a variety of different epitopes.

So what's being done to determine whether there was any infection whatsoever, is vibriocidal antibody measurement. Which in people that have no smidgen of background immunity -- are totally virgins like U.S. travelers happen to be in this case -- is that you can induce a good infection, reliably, and

you can detect that by this vibriocidal antibody measurement.

However, when you get out in the field this is less useful I think, in determining even seroconversion, because people already have had an immunizing infection with wild type cholera of some sort -- maybe not that particular strain. And so they have some ability to mount already interference with the immunization that you're giving them.

So that titer, again, has no meaning for protection and therefore it can only be used, yes or no, present or absent. It might help though, to stratify those kids in developing countries by whether they had any antibody or not, and then look at the height of the vibriocidal antibody.

But I think that this is where we're all getting very confused, and it just is one of the problems we face with live, attenuated vaccination. And kids who already have been -- had prior infection may be the ones that don't need the vaccine and the others do.

And it would be nice at some point to see that stratification, see how many kids you effectively did immunize even with that crude marker.

CHAIR FERRIERI: Thanks, Mary Lou. Alison

-- Dr. O'Brien.

DR. O'BRIEN: Yes. This is a question for Dr. Levine. You mentioned that there were no other really reliable markers that correlated with immunity. Did you look at antibody to TCP -- to the toxin coregulated pelis -- that's supposedly a major, if not the major adhesion for at least the Classical strains?

DR. LEVINE: Yes, that's a very good question. Shortly after the discovery of toxin coregulated pelis -- TCP -- we looked at that in the volunteer model in conjunction with the discoverers, including John Meklanos and his associates, Ron Taylor and others.

And what was found was that the TCP pelis, the major colonization factor of both Classical and El Tor Vibrio cholerae is required -- is necessary to stimulate a vibriocidal antibody response.

But curiously, the pelis itself is not immunogenic in humans. Humans don't seem to mount an immune response against this pelis. So in that sense anti-pelis immunity as we looked at it, did not appear to correlate at all with protection in the volunteer model.

CHAIR FERRIERI: Thank you. What I think we should do is, we'll break for lunch, return at

quarter-of-two, and Dr. Stibitz, the committee would like to continue for up to maximum 30 minutes of further questions prior to your presenting the questions.

And then we will discuss again and try to wrap things up. So if FDA and sponsors would please be available for us to pursue the committee questions and answers right after lunch.

So again, 1:45. Thank you.

DR. FREAS: Dr. Ferrieri, I would just like to announce that Nancy Cherry was called away from the meeting earlier this morning. I will be acting in her place this afternoon. So if anybody in the audience needs assistance getting set up for the afternoon session, please come and see me during lunch. Thank you.

CHAIR FERRIERI: Thank you. This is Bill Freas. I apologize for not introducing you, Bill.

(Whereupon, a brief luncheon recess was taken at 12:54 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:53 p.m.

CHAIR FERRIERI: Good afternoon, everyone. Could we please take our seats? Committee members. I hope everyone had a nice lunch and you feel energetic and everyone feels very smart.

My contribution to the bridging data today is as follows. This is my fortune over lunch. I thought it was very applicable to today's doings. Enjoy life. It is better to be happy than wise.

Well, we know that's not true for the VRBPAC Committee and what we have to do here. It is definitely better to be wise today. So we're still into the heart of the data and people who still have some critical issues to examine.

And I've asked Tom Fleming to start out because he's been assiduously crunching numbers a good part of the day, and we would like to hear about the issues, questions you have, Tom, as they are relevant to the questions being addressed to us.

DR. FLEMING: Thanks. Actually, what I'd like to try to do is follow up on the issue raised by Chuck Carpenter just before we broke which is, thinking through the main safety data and the main efficacy data that we have in the context of what it

is that we're trying to achieve.

And at least to the best of my ability, it's difficult to summarize the essence of the risk that we are trying to address here. And we've been given several relevant sources of information. Those sources of information from the Embassy workers in Peru and the Japanese traveling to Indonesia and to Thailand would suggest rates there.

It's not clear what severity, but rates there of maybe 15 per 100,000. And then when we look at Dr. Mintz's reviews of purported cases they are 50 times lower than that, which isn't surprising because presumably those reported cases tend to be more serious. They're in the rate of .3 per 100,000.

With that as a background, just thinking through the safety and efficacy results, what if we vaccinated 100,000 people? What would be the risk -- and we address that in the safety studies -- and what would be the intended or expected benefit as we can glean from the efficacy studies?

Well, as Chuck was pointing out, six percent rate -- by the way, the safety studies that addressed this when we're really focusing specifically on this vaccine in U.S. workers -- is the 13010 and the 4200 randomized trials, and then the open labeled

experience involving 245 workers and the specific subset of 47 inpatients.

I put all of those data together and there seems to be a pretty consistent picture of about a six-and-a-half percent rate of diarrhea. A six-and-a-half percent rate of diarrhea according to the definition of one loose stool greater than 300 ml, or two loose stools of at least 200 ml.

Which is an important point because that's the same definition that's being used in the challenge study. What we see if we were to vaccinate 100,000 with this six percent rate induced by the vaccine, you're going to have 6,000 cases, vaccine-induced.

Now, the vaccine, according to the efficacy studies -- and I'll step back -- the challenge studies do have some important issues for us to address. They've already been identified in the FDA review. The controls were non-randomly selected.

The challenged individuals are approximately one-half of those that had been vaccinated and had been selected in ways that were not entirely clear, and yet partially clear. And it's concerning because people were left out for reasons of having poor nursing ratings, failed medical evaluations, failed psychiatric evaluations, etc.

So one is left with the sense that you weren't selecting randomly from the vaccinated when you were looking at the challenge, and in turn the controls were selected separately as well. In addition, the assessments were unblinded.

But putting aside those non-trivial, scientific concerns with the challenge study efficacy evaluation, the primary endpoint was assessed on what percent cases could be prevented when you were using the same definition that we had in the safety experience, which was the one loose stool, 300 ml and you had about a 60 percent efficacy.

Well, the issue is you would have had to have had at least 10,000 cases with 60 percent efficacy in order to offset the 6,000 cases that would be induced according to the safety experience. And yet by the calculations that we're getting it would appear that we wouldn't have remotely close to 10,000 cases of cholera inducing this level of diarrhea in 100,000 workers that are traveling.

So if you're looking simply in the challenge studies at the way the primary endpoint was defined, you're not getting benefit that is more than offsetting what the risk is associated with vaccinating that number of individuals.

So we have to turn to more serious challenge, or specifically, what is the frequency of severe diarrhea that would be seen in the challenge studies? And there were in fact five -- there were in fact four individuals who had serious purging at the level of five liters -- specifically 6, 6.6, 7.1 and 11.9.

So there is some clue there, although it's based only on four cases that were seen in the controls. One has to though, also view that if you're going to vaccinate 100,000 individuals, what is the level of risk that is serious risk for rare events -- which is difficult to glean.

We do have the 39,000 doses that were delivered and we did have two serious, adverse experiences reported, which would translate to a rate of five per 100,000 -- which appears to well exceed the rate of most serious events that are associated with cholera infections, at least as reported by Dr. Mintz.

So in summary, as we look at safety and efficacy data , if we're putting into context the apparent, extremely low rate of serious consequences associated with cholera infection in U.S. travelers, the first point is as Dr. Carpenter had pointed out,

safety concerns at the level of loose stools, 300 ml, can't be completely ignored.

And certainly, efficacy from challenge studies have to be assessed at levels beyond that because we're inducing such a high risk at that level.

One would -- I would argue that these challenge studies should be done in ways that not only are randomized in a blinded fashion but would have to give us a way to be confident that you're preventing much more serious infections and much more serious clinical consequences than the way the primary endpoint had been defined in those studies.

CHAIR FERRIERI: Response from the sponsors on that?

DR. TACKET: Carol Tacket. I need to clarify, if I might, the definition of diarrhea in the outpatient vaccination studies. The 13,000, the 42,000 is not 300 mls or two stools totaling 200. The definition is four loose stools in 24 hours is the prospective definition in the protocol, although as we've seen we've analyzed fewer numbers of stools.

So in fact, we don't know the volume of stool in the outpatient, so your analysis is not exactly correct in that the definition was the four loose stools in 24 hours and not 300 mls or 200 mls in

two loose stools.

DR. FLEMING: To be precise I agree with you, although the U.S. inpatients was exactly that definition and all of these results were quite consistent at about six percent access.

DR. TACKET: The other point that I think might be made is that we certainly agree that ideally the challenge studies should have been or could have been, randomized, double-blind studies in which a cohort was initially recruited. Half of them received vaccine and half received placebo and then everybody was challenged.

The reality of doing such studies is far from that idea, and the way that the studies were done was sequential recruiting and as a result, a non-blinded study is really the most practical way -- almost the only practical way that those studies could be done.

So we certainly agree with your point that ideally they should have been double-blind and unfortunately they couldn't be for practical reasons.

And also, the exclusion criteria that are defined prospectively include the eligibility criteria for which we ended up excluding people for challenge studies. For example, failure to pass the

psychological exam, inability to show up and show some consistency in follow-up visits.

So that really, the protocol -- a lot of those exclusions were protocol-driven as well.

CHAIR FERRIERI: Dr. Kohl.

DR. KOHL: Clarify for me. Are just telling us that's it's impossible to do a double-blind, placebo-controlled study in this situation?

DR. TACKET: No, I don't think it's impossible, and I think ideally that would be the way one would do that. That would mean recruiting volunteers, say three months or so before challenge because of the time it takes to recruit, the vaccination, another month for the vaccine to perform its immunologic events, and then the challenge, yet another month.

So it's not impossible, but the practicality of conducting these studies makes it much more logistically feasible to do them sequentially.

The point that we have focused on and I hope is not missed, is that the endpoint that we use, the readout of a challenge study, is a very objective one. It's not cramps, it's not nausea, it's not anorexia. It's diarrheal stool volume.

And I think you could argue that there might

be some psychological effect of knowing that you're a vaccinee that would affect your stool volume. On the other hand, cholera as you see and have seen, results in stool volumes of three liters, four liters, five liters. And I think that's outside the range of psychological effect of being protected from that level of diarrhea.

So we think that the fact that we use an objective endpoint -- this is stool volume -- somewhat balances; doesn't completely balance that flaw in study design, but somewhat balances the fact that we're not double-blind study.

And every single stool that a volunteer passes on our ward is collected, is examined, is graded, and if it's loose it's weighed. So there's not a lot of possibility for there being bias introduced at that point.

CHAIR FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes, I'd just like to point out that while it would be ideal to do these kinds of studies you have to keep in mind that this is a disease for which American college students would see very little benefit to be involved in such a study.

And it does require a long-term commitment

on their part, and the ability of them to come in to a unit, a quarantine, isolation unit, for a period of at least seven days. And that they would undergo in that period repeated need to submit their stools and so forth.

So these are extraordinarily difficult studies to do and require a tremendous amount of cooperation. I think that's one reason the screening is so intense -- to eliminate people who could not comply with that degree of adherence once they're on the unit and being challenged with a life-threatening organism.

DR. FLEMING: Just to follow-up on both points. Mary Lou I would strongly support/understand the difficulty. In fact, I have real concerns about the appropriateness or ethics of doing a challenge study that I would have thought would have provided more meaningful interpretation.

Specifically, to my way of understanding here, the real goal isn't to prevent diarrhea at the level of one loose stool of 300 ml since we will induce a very high level of that side effect, but rather to reduce the risk of very serious diarrhea at the level of 15 to 20 liter purging that would carry serious morbidity and mortality risks, or at least --

at least, well above five ml -- five liter purging.

And I concur with the concerns about exposing volunteers to a challenge that could induce that level of risk. But to the sponsor, what is the goal here of this challenge study? Is it adequate to simply show that a vaccine is capable of reducing the risk of one loose stool at 300 ml? Is that really the goal?

Or rather would you agree that the goal is to be able to reduce the risk of much more serious purging? And if so, should the challenge study be designed in a way to show that, and is it ethical to design it in a way to show that? Thoughts about that?

CHAIR FERRIERI: Dr. Levine, would you respond to that, please?

DR. LEVINE: I'm sorry?

CHAIR FERRIERI: I said, would you please respond to that? It's one question.

DR. LEVINE: Thank you. I think there's some confusion about total purge. One wouldn't speak of a 15 liter purge as being clinically significant in an abstract sense, in that you can't get to a 15 liter purge without being repeatedly treated.

Three liter purge is more than the entire plasma volume of a human being -- an adult. Five

liter purge is equal to a total stool volume. Three liter purge, what we call moderate cholera, is a clinically, very relevant purge, even for a healthy adult. Five liter purge is very significant.

Amongst the volunteer studies there have been larger total diarrheal stool volumes, but that's only of course, with continual replacement. I think that three liters as a cutoff of moderate cholera is very reasonable. And five liters, that's a lot of diarrhea.

CHAIR FERRIERI: Other questions from the panel? Dr. Greenberg.

DR. GREENBERG: I'm still concerned about cholera as a cause of diarrhea in the traveler. And there's been lots of studies of traveler's diarrhea going the other way and looking for diarrhea in travelers.

I haven't reviewed that literature in a long time but it's my impression that cholera is virtually never found when you look at it that way. And that goes along with this eight cases.

Could you just again, describe -- you gave us some data, but the workers in Peru weren't really travelers. They were people who were going to Peru to work for, I assume, several years -- the target

population for this vaccine I assume.

How many cases do you really think there will be, that are preventable, of this type of illness?

DR. LEVINE: Good question, Terry. First of all, in terms of the old literature of traveler's diarrhea which was in its heyday if you will, in the '70s and early '80s, very few of those studies -- which were largely focused towards detecting enterotoxigenic E. coli and shigella -- very, very few of those studies incorporated bacteriologic media to look for cases of cholera that would be just severe traveler's diarrhea. That's the first point.

One of the breakthrough aspects of Dave Taylor's study is, I think, is elegance and simplicity of simply setting up a proper bacteriology to grow Vibrio cholerae O-1 in a setting where people are treating different gradations of traveler's diarrhea.

I think that a population of U.S. Embassy workers, citizens assigned to go to work in the U.S. Embassy in Lima or to work in a Consulate, that is a population that I think should have the opportunity if they like, to receive a cholera vaccine. That is a population at risk.

We need more studies. But I think the point

we made is, there have only been a few studies that have prospective surveillance with good bacteriology. And if you do that in populations going to known, cholera areas, then you find cholera in association with traveler's diarrhea and it tends to be the severe end of the spectrum of traveler's diarrhea.

DR. FLEMING: Just to follow, isn't your answer then to Harry's question on the order of 15 per 100,000? Because as you had pointed out as well, when you translate Taylor's results into 10-day exposures, those results come out very consistently with the Japanese studies, etc., and they're all in the neighborhood of 15 per 100,000.

DR. LEVINE: I think that's correct, and I think that the risk of cholera very much relates as much to the host and how the host behaves as just a quantitative number. If you develop -- cholera has a spectrum of illness. There are many cases of milder, non-dehydrating diarrhea for each case of dehydrating diarrhea and then there's the end of the spectrum which is truly dehydrating, life-endangering diarrhea.

If there are enough cholera infections there will be tip of an iceberg. The consequence of that tip of an iceberg depends on who you are and where you are.

If you're in a rural area and there's no access to bacteriology, and you may or may not have access to appropriate health care, the consequences can be disastrous. And even if you have severe dehydration, you're not a case of cholera unless you have bacteriology confirming you as a case of cholera.

DR. FLEMING: But those cases then, are much less than 15 per 100,000? Maybe closer to Dr. Mintz's level?

CHAIR FERRIERI: Dr. Mintz, do you have any disagreement with that?

DR. MINTZ: No. I'd just like to comment that I think, if I understood the sponsors correctly, this vaccine is not intended for routine use in all travelers. Rather, it's meant as a targeted measure for groups at particularly high risk; either because of the place they're traveling to and the prevalence of cholera in that area, or because of underlying host factors which would make them particularly susceptible to a cholera illness, or because of the nature of the exposures they're likely to have during their travel -- distance or time from medical care and the possibility of eating safe food and drinking safe water.

So I think that really lies at the heart of

the discussion and the utility of this vaccine.

CHAIR FERRIERI: But in their last slide which they showed, there was -- a target to travelers was the only one where they indicated they viewed it as useful.

DR. MINTZ: I think that would be -- a subset of travelers would be more correct, perhaps.

CHAIR FERRIERI: Well, perhaps the sponsors would like to clarify this.

DR. MINTZ: Okay.

DR. CRYZ: We're in absolute agreement. To suggest broad usage of a cholera vaccine in American travelers even to areas where cholera is endemic doesn't make sense, viewed on a cost benefit basis or otherwise -- just on simple cost.

However, there is one other thing that, you know, we have to consider. If you look -- you know, Dr. Levine has said, if you travel to a developing country, you get cholera, you're going to have trouble getting good medical care. If you develop cholera, you come back to the United States, you're also going to have trouble getting good medical care.

And the reason I say that is if you look at the follow-up of the 50 or so patients who landed on this airplane in Los Angeles and the treatment they

received, it's a telling story.

Before the epidemic was identified, 17 or 18 of these patients presented at a variety of hospitals. In four instances -- well, let's put it this way. All 18 did not receive proper rehydration therapy. In four cases they were sent home. One was told to drink Gatorade; I can't remember what the other ones were given.

Within two days three of those patients were back with renal failure. That's a serious consequence. And I think we have to view that -- if somebody comes back from traveling -- now most of these 18 patients told their attending physicians, I had traveled out of the United States. I was in Peru, Argentina, wherever. And that still wasn't enough of a trigger to really go and look for cholera. And I think that's another consideration for this vaccine.

CHAIR FERRIERI: Thank you, Dr. Cryz. Dr. Hall and then Dr. Karzon.

DR. HALL: I just wondered, if you are thinking of this as a target population for those who say, work in Peru or somewhere else, how often would you expect they would have to have the vaccine since we have a correlate of perhaps infection but nothing of the duration of protection?

And I guess the second part of that is, what other means of protection are there for people who are going to be there for longer than a short period? In particular -- I probably should know this -- but in terms of prophylaxis or use with antibiotics.

DR. LEVINE: Let me answer several of the questions in one set of staccato answers. First of all, we tried to present what we view as the type of traveler who would be receptive, amenable to receiving this vaccine. It's not all travelers.

It would be travelers going to areas of known cholera endemicity or recent epidemic report. It would be travelers who, because of host factors, may not even be able to sustain moderate or even mild diarrhea without increased morbidity because they have cardiac problems, because they have gastrointestinal problems, because they have chronic renal disease.

It's travelers who may be so many hours away from health care that can allow them to receive appropriate, aggressive, rehydration so that they could potentially be in real danger if they developed the severe end of the clinical spectrum.

In terms of travelers going for long-term, the data that we have to this point is protection up to six months. Now, for most travelers with the

reports of the information that we get from most sources, the overwhelming majority of travelers who go to cholera endemic or epidemic areas, go for short periods of time.

There's a subset that go for longer periods. They would have to receive -- based on a current knowledge of the upper limit of duration of protection -- they would have to receive a booster. But for most travelers that would go to such areas for work or for business -- whatever the reasons -- for shorter periods, the vaccine suffice for them.

CHAIR FERRIERI: Thank you. Dr. Karzon.

DR. KARZON: Tom has done a service to bring to the fore what the risk is. The calculation of the risk, though, is based upon cases as if all travelers had equal opportunity to be infected, and that would be the basis for these numbers.

Now hopefully, that wouldn't be the case; that this reagent would be a very special reagent for a special circumstances where the traveler, in fact, is going to be at high risk. And then these numbers of 6.5 or 15 per 100,000 would have less cogency.

If you get in the right place and do the right things I can make it closer to, you know, to 100 percent takes, so to speak.

But if you stay away, as I understand it, biology of the transfer -- which I learned at the last break thanks to the CDC experience -- that if you don't drink contaminated water, if you don't eat sea-derived, salt-water derived fish and other creatures of any sort, that chances of getting it by fecal oral contamination are very low by other means.

That in nature this is not a normal way to traverse -- which surprises me but apparently it's so. But insofar as it may be true, then I would give it to travelers if I were in a travel center, who truly were going to be at high risk and there was no way to avoid the risk. And then I would consider it seriously.

CHAIR FERRIERI: Thank you. Dr. Kohl --

DR. KARZON: And I don't know what the risk ratio would be if you do that. That is, there has to be cholera in the area and has to be rampant enough so that you have to conduct your life absolutely meticulously to avoid it.

DR. KOHL: Well, I'd like us to back up a little bit. It seems like we're talking about this vaccine being effective and who should we use it on.

As far as I can gather looking at the table that's been provided for us by the FDA, using patients who got an El Tor challenge -- which is apparently the

major critter floating around these days -- and looking at patients who got the one dose of organisms, which is what is suggested, and looking at the patients who had one month time of immunization to challenge, we're talking about a grand total of 15 patients.

CHAIR FERRIERI: Thank you for bringing this to a point that I wanted to come to, Steve. We're going to have to examine the questions now, but officially what we've just completed is the extension of the discussion before lunch. And we have another official obligation before Dr. Stibitz presents the questions, and I'll turn the meeting over to Dr. Freas.

DR. FREAS: In response to the *Federal Register* Notice published for this meeting there were no volunteers for participation in the open public session for this afternoon's discussion of cholera.

Is there anyone in the audience here now, that would like to make a presentation regarding this topic? If not, I turn the microphone back over to you.

CHAIR FERRIERI: Thank you, Bill. And we'll move to Dr. Stibitz now and we will still have a chance to do a little more committee discussion then,

before we vote on the issues. I'm grateful, Steve, for your bringing us back onto target.

DR. STIBITZ: The first question before the VRBPAC today is: In light of the recent results from the Indonesian field trial, does the panel consider that volunteer challenge studies with Vibrio cholerae can suffice to demonstrate the efficacy of CVD 103-HgR in the prevention of cholera in U.S. travelers to cholera-affected areas?

So the purpose of this question is to reassess the support or the feelings of the panel regarding this question which was asked five years ago. And specifically in light of the new developments relating to the field trial in Indonesia.

The second question, also relating to efficacy: If the panel considers that challenge studies can be adequate for demonstration of efficacy in travelers, are the data from the challenge studies presented for CVD 103-HgR adequate in this regard?

The first subpart: Were the challenge studies designed and executed adequately; are the data regarding heterologous biotype challenge -- in other words, with El Tor strains -- adequate in light of the prevalence of El Tor strains in endemic areas; c) are the data sufficient to demonstrate protection from

challenge for a period of time following vaccination that is sufficient for travelers; and d) if the panel feels that the data regarding efficacy are not sufficient to support licensure, what additional studies would be needed to address these issues?

The third question: Can immunogenicity studies be used to provide bridging data to the adult volunteer population in order to support administration of this vaccine to children?

And four: please comment on the adequacy of the data supporting safety in the target population, both in adults and in children.

And in children I think as Dr. Bash pointed out, one of our real big concerns is the fact that this is not a test of U.S. children. And then we have questions regarding the applicability of the Chilean data to address children.

So I guess I will leave this up for your discussion.

CHAIR FERRIERI: Thank you very much, Scott. It is my understanding then, that you would like us to have a formal vote on question one and all the components of question two?

DR. STIBITZ: Yes.

CHAIR FERRIERI: Okay. So our discussion

now has to be very targeted and we'll start with discussion of question one which is on the screen. Dr. Clements-Mann, I'm sorry, I had to bypass you at the end of our discussion session. Would you like to lead off?

DR. CLEMENTS-MANN: I'd just like to say one thing. Is that right now, if -- as a physician advising a traveler that one would consider at high risk for going to an endemic area, we could definitely recommend a vaccine that is licensed, which is the inactivated vaccine.

So if one looks at that safety profile -- efficacy profile -- you know, most of us I think, would be reluctant to advise people to actually get it because of the very high reactogenicity of the vaccine, the need for two doses, and the extremely short duration of minimal protection.

So that's what we're stuck with right now and these people could go to Europe or whatever, and get the vaccine that they might need. But if we look at that safety profile and this one, you know, I think that the efficacy is another question, but this is our alternative right now.

CHAIR FERRIERI: Thanks for pointing out the background. Dr. Huang.

DR. HUANG: Well, we only have -- we don't only have these studies to make our decision on since it is licensed in Europe. What is the experience with it, even though it's not a careful study?

CHAIR FERRIERI: Dr. Cryz.

DR. CRYZ: The vaccine is licensed in Canada, several European countries, several South American countries, and several Southeast Asian countries. Unfortunately we've gone around the circle trying to glean efficacy data from vaccinated and non-vaccinated travelers -- for typhoid vaccine, and we've tried to do it for cholera.

And I can't give you any indication that the vaccine is efficacious in travelers based upon data we've seen. What I can tell you is that in the countries where it's licensed we haven't seen any travelers coming back with cholera. If that means anything given the numbers I can't say for sure.

The safety profile I think, is very good. I mean, there were two serious, adverse reactions as was pointed out. One was in an infant death -- according to the packet circular shouldn't have been immunized and there was no follow-up to show that the bloody diarrhea was actually associated with the vaccine strain.

I think that the adverse reaction report profile for this product, in light of other products that we have, is very commendable. That's our experience in Europe and in Canada.

CHAIR FERRIERI: Is it licensed in England?

DR. CRYZ: No.

CHAIR FERRIERI: Because England continues to see cholera cases every week. They have reports in their equivalent of the CDC.

DR. CRYZ: Yes. Being an American living in Switzerland, the Swiss are probably the most adventurous travelers I've ever come across. It would be nothing -- a 50- or 60-year-old Swiss would think nothing of going backpacking in the Himalayas for three weeks.

CHAIR FERRIERI: Dr. Hall.

DR. HALL: May I just ask -- in the other countries I assume then it's licensed for children two and above. And do you have any idea of the number of doses that go to young children versus older people --

DR. CRYZ: The best -- I would estimate that based on the usage in Switzerland, Austria, and some data from Canada, it's probably no more than two percent of the overall.

Now, there is a subgroup, especially

missionaries, that are going into an area where they're going to bring their whole family; relief workers. But for the general travel population, no more than two percent.

CHAIR FERRIERI: Thank you. We have with us today some special consultants, and I guess I'd be very pleased if one of you might lead off the discussion -- either Dr. O'Brien, Holmes, Pierce, or Carpenter -- on question one. Do I have a volunteer?

I see Dr. Carpenter pushing Dr. Pierce forward. Dr. Pierce, would you mind?

DR. PIERCE: I of course, was not here in 1993 when discussion was considered before, so I don't know what points were raised in support or otherwise, of this.

But I think the answer to that -- I mean, I would support the answer to that question being yes; that the volunteers in principle are sufficient insomuch as they are the only model we have and which -- insomuch that there's now added evidence to support what may have been evident before and that is that there are differences in susceptibility between people who are naive and people who live in endemic areas.

And the volunteers are the only individuals who resemble naive Americans traveling abroad. And I

think it's disconcerting that the trial in Indonesia was ineffective and that we have lost perhaps the reassurance of seeing the vaccine be effective under a variety of circumstances.

But that is a narrowness that does not affect this question, I think, and I think --

CHAIR FERRIERI: So you are saying that the volunteer, challenge studies suffice to demonstrate the efficacy of this vaccine?

DR. PIERCE: For travelers -- for U.S. travelers. Yes.

DR. GREENBERG: May I --

CHAIR FERRIERI: Yes, you bet. Dr. Greenberg.

DR. GREENBERG: Does that question mean that theoretically a volunteer study will suffice, or the volunteer studies done to-date -- no, it's a theoretical answer?

DR. STIBITZ: Correct.

DR. PIERCE: Yes, theoretical.

CHAIR FERRIERI: Yes, Dr. Holmes.

DR. HOLMES: I agree with the conclusion that theoretically a volunteer study can provide evidence or protection. I think the caveats are fairly clear and one of them is that a challenge study

has usually a single, defined dose of challenge organisms of one level of virulence.

And in the natural setting there may be variations in virulence among strains and there are clearly a range of doses that you would be exposed to, so that there may not be an absolute level of protection defined. But I don't have any problem with the concept.

CHAIR FERRIERI: We will be able to address those concerns in question two then, and so I would like to further the discussion on this question. Dixie.

DR. SNIDER: Well, with regard to question one, based on the data that Eric showed us, I would have some concern in saying yes because I think that most people are interpreting the U.S. travelers as lifelong residents of the United States, but as the data show, I think all of us who keep our eyes open know, that a large proportion of U.S. citizens who travel overseas are people whose home country is overseas.

And I'm not willing to extrapolate to that particular population because they may have had earlier exposure in earlier years. And so the question is a lot more complex than it appears on the

surface, to me.

CHAIR FERRIERI: I agree. These are not necessarily cholera-naive individuals. Further discussion of these concerns? Dr. Fleming.

DR. FLEMING: In general terms I'm led to endorse the concept that challenge studies may be the only practical approach to getting a controlled assessment.

Having said that I have two serious reservations. One of them is, in a challenge study can you get adequately a duration of protection? One of the statistics that Dr. Mintz showed us was that 75 percent of these cases that showed up as U.S. reported cases were homeland visits.

And I'm led to wonder whether or not protection for a shorter time would be adequate. So one serious concern with the challenge studies is duration of protection.

The other serious concern is, I continue to think one has to put this in the context of the level of risk. And even following David's comments about maybe we can be selective, we have to be at least 100- to 1000-fold selective really, to be getting this level of risk up to the level of one percent.

And as a result, it seems to me that the

essence of what we need to learn here is not whether we can protect against a level of diarrhea that would be at least one stool, 300 ml -- i.e., it seems to me that a challenge study would have to give us evidence that we are reducing serious risk, at least at the level of five liters.

And it's conceivable you could do such a study but it's also conceivable that there would be ethical reservations or concerns about challenging at that level. So it's -- we would have to, from a challenge study, be able to have evidence that would make us confident that we were preventing serious purging.

CHAIR FERRIERI: Further comments? Yes, Dr. O'Brien.

DR. O'BRIEN: I'd just like to say, I think I would answer this question yes because we don't have many choices. You put together, in terms of how to evaluate an effective vaccine in -- let's start with U.S. travelers are not homeland visitors. We don't have many alternatives and this seems a reasonable way to evaluate, given the problems with duration of immunity and all.

I think it's a model that has been effective at least in telling us a considerable amount about

immunity perhaps, among people like us in this room.

As to the homeland visitor question I think it's even more complicated than you stated because those people are not being boosted while they're in the U.S. So they're not quite like they're just at homeland. In fact, maybe that's why they're getting infected, because they're not receiving boosters while they're here.

So they be more akin to the U.S. college student than they are to the folks that are back home. So it's not quite -- it's muddied even in that sense.

CHAIR FERRIERI: Dr. Carpenter, would you care to jump in on this issue?

DR. CARPENTER: I don't think I'd have anything to add. I'd agree with what Dr. Pierce and Dr. O'Brien said, and Dr. Holmes. I don't think I have any additional to add. In principle I approve of the volunteer studies as providing a basis for the vaccine .

CHAIR FERRIERI: When we eventually vote, which is very soon, I would rather have had discussion from those who may violently dissent what has been said now. And so are there any of you at the table who would like to voice opposite opinions? And again, I would encourage you to do that now. Yes, Dr.

Finkelstein.

DR. FINKELSTEIN: One concern I have is, it's hard for me to separate question one from two because the way the volunteer studies were carried out in this case had a lot of potential biases in terms of the selection and also the non-randomization. And it's not clear that one could get away from this.

And I think that you have to take that into account in your answer to whether these are feasible for the decision.

CHAIR FERRIERI: Anyone else? Dr. Kim.

DR. KIM: I would say yes for question one, but for question two with some limitations. Certainly I think, at least in my reading, data does not support yes for question number two.

CHAIR FERRIERI: What I've always found confusing since I received the packet though is, this question may be theoretical but it's phrased, "In light of the recent results from the Indonesian field trial".

And in view of the negative efficacy trial I still have difficulty in addressing this question. Dr. Daum.

DR. DAUM: I think one of the problems of the question is that it's so generic that we're

sitting here struggling with the things that we're worried about from the data that are presented. And imagining the trial that we would design were we presented with an answer of yes.

Who would be the subjects, for instance. How would duration of immunity be assessed? What would be the challenge dose? What would be the relevant endpoint? And so I think -- I mean, I find myself doing it also -- is struggling with designing the optimal challenge study -- for someone else, I hope, to do -- and also hearing Dr. Clements-Mann's comments about how not simple these trials are to do and so you don't want to make it too complicated.

But in terms of the generic answer to the question, I think yes, we probably could design a trial that would be relevant and have good endpoints in volunteers.

The first part of the question troubled me also and I don't think that there's any -- I've been persuaded by the discussion this morning that the Indonesian field trial results don't necessarily impinge on this question at all.

And so I think that there can be a study in volunteers to demonstrate the efficacy of this vaccine.

CHAIR FERRIERI: Dr. Karzon and then we're going to vote on this question.

DR. KARZON: I had trouble with the design of the question. If it said "could" then I would buy it, because it's a theoretical question. In other words, it's asking in so many words, could one design a trial with challenge in the United States which would answer the question? And by definition, I would say yes, that is possible.

CHAIR FERRIERI: Would you accept Dr. Stibitz then, that we have a slight rephrasing of that?

DR. STIBITZ: Yes. Well, perhaps I could clarify the reasons for the --

DR. KARZON: What you mean as author of it.

DR. STIBITZ: Yes. From five years ago the purely theoretical question in the absence of a field trial was discussed. At that time, from my reading of the transcript, it's apparent that a number of people voted -- or felt that -- challenge studies should be sufficient because it would be -- the field trials were just getting underway.

So it would be four or five years until those data were available. So there was certainly the sentiment that we did not want to wait for the field

trial.

There was also the feeling that the challenge studies were a more stringent test of the vaccine; that if the challenge studies worked, certainly the field trial would work.

And so the purpose of including that first phrase is to perhaps try and revisit the question five years later now that we have that data. And I agree that it's somewhat problematic and theoretical, and perhaps we should -- I think I hear that we're saying yes, and we should perhaps move on to the second question.

CHAIR FERRIERI: We'll vote on this question then, starting with Dr. Poland. A slight rewording: could it suffice -- could these challenge studies suffice to demonstrate efficacy in the population indicated there?

DR. POLAND: Yes.

CHAIR FERRIERI: Dr. Edwards.

DR. EDWARDS: Yes.

CHAIR FERRIERI: Dr. Huang.

DR. HUANG: Yes.

CHAIR FERRIERI: Dr. Snider.

DR. SNIDER: Yes, with serious reservations.

CHAIR FERRIERI: Yes. I would like anyone

who has any waivers, reservations, to indicate as such. This will be very helpful perhaps, for FDA. Dr. Hall.

DR. HALL: Yes.

CHAIR FERRIERI: Dr. Greenberg.

DR. GREENBERG: Yes, but I am more concerned that for reasons that I cannot understand, a volunteer study does not accurately measure what happens in real life, and that maybe the message from the field was the right message. And that there's something I'm not understanding and so it's a very -- theoretically yes, but I'm even more anxious than Dr. Snider.

CHAIR FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Because I've had that other vaccine, I would say yes.

CHAIR FERRIERI: Dr. Finkelstein.

DR. FINKELSTEIN: It's going to depend on how you're defining volunteer challenge study. If you encompass randomized and blinded and so forth, I could say yes to just the challenge aspect of it.

CHAIR FERRIERI: We will deal with that, then. Dr. Daum.

DR. DAUM: I'm going to say yes, with the caveat that it be very carefully designed with many of the thoughts and comments that we've heard, and

concerns about who the volunteers should be and how the challenge should be done and what the endpoints should be.

And also with the caveat that it not be extrapolated at all with the present knowledge base, to performance in the field. This be a very limited kind of -- that the results be interpreted in a very limited kind of way.

CHAIR FERRIERI: Thank you. Mrs. Cole.

MS. COLE: My answer is yes.

CHAIR FERRIERI: Dr. Kim.

DR. KIM: Yes.

CHAIR FERRIERI: Dr. Karzon.

DR. KARZON: Yes.

CHAIR FERRIERI: Dr. Kohl.

DR. KOHL: I'm going to answer yes but with the caveat that the studies obviously will reflect only upon those who are immunized. And since that's often a very highly selective group, that it can in no way be generalized to older individuals, to sicker individuals, to younger individuals, etc.

CHAIR FERRIERI: Dr. Fleming.

DR. FLEMING: I would say only if such studies were conducted according to proper scientific principles of high quality, randomization, etc. And

only if they would provide information that would allow us to determine whether we could prevent serious purging.

And finally, to be consistent with what we said five years ago on this committee, because such studies would not easily allow us to assess duration of immunity only if there would be additional information sought from studies such as field studies providing data from endemic regions.

CHAIR FERRIERI: Fine. Dr. Eickhoff.

DR. EICKHOFF: Yes.

CHAIR FERRIERI: Dr. Breiman.

DR. BREIMAN: Yes, realizing that this may end up being a true, orphan vaccine. And I think that the -- it's very limited use would indicate that this is probably the only way you could actually evaluate it with the -- under the conditions I think that Tom just described.

CHAIR FERRIERI: Thank you. Dr. O'Brien.

DR. O'BRIEN: Yes.

CHAIR FERRIERI: Dr. Holmes.

DR. HOLMES: Yes.

CHAIR FERRIERI: Dr. Pierce.

DR. PIERCE: Yes. I do have one reservation, though. I think the one thing that these

studies have shown is that it may not be possible to sustain protection in American -- naive Americans by boosting. So that this might turn out to be a one-time -- whatever you achieve will be achieved with the one dose.

CHAIR FERRIERI: Dr. Carpenter.

DR. CARPENTER: Yes.

CHAIR FERRIERI: This is the way we do it here at the committee. It may seem bizarre, but this gets the job done. Thank you all. We now can design the perfect study perhaps.

Question two that Dr. Stibitz has on the screen, if we consider the challenge studies can be adequate for demonstration of efficacy in travelers, are the data from the challenge studies presented for CVD 103-HgR adequate in this regard?

And each of these we will deal with separately: Were the design studies designed and executed adequately? And there was a sentiment around the table as we voted on question one that they were not. And so do you want a formal vote on that, Scott? And would you like us to say now what we would like to do in designing it?

DR. STIBITZ: You mean, just skip to part B?

CHAIR FERRIERI: I think we might have to.

DR. STIBITZ: We can certainly combine a) and d) for purposes of discussion.

CHAIR FERRIERI: I think we could do that. Although question B is very relevant as well. Did you say a) and b)?

DR. STIBITZ: I said a) and d).

CHAIR FERRIERI: So a) and d).

DR. STIBITZ: Meaning, if they are not adequate how would you design studies which would be?

CHAIR FERRIERI: Question b) is, are the data regarding the heterologous biotype challenge adequate? Dr. Huang and then Dr. Snider.

DR. HUANG: I would suggest that we do each of them separately.

CHAIR FERRIERI: Fine.

DR. HUANG: For clarification I would ask whether we're voting on the word "adequately" or "perfectly".

CHAIR FERRIERI: Please, Dr. Bash.

DR. BASH: I think these studies were designed and conducted in a fashion given the status of challenge studies at the time, that they were very well done studies. There was tremendous -- in going back to the original IND there was a tremendous emphasis placed on the safety of the participants.

I was not involved and the sponsors certainly were so they may have something to add, but my perspective is that these studies were very well designed from a safety standpoint and for looking at trying to understand the immunogenicity and protection.

What we find ourselves in now is having to use these as the sole basis for efficacy, and I think that's really what the question -- a refinement of this question is. Are they adequate as a sole source of efficacy data and do we need to do better as efficacy data than what was done.

CHAIR FERRIERI: That helps us, Margaret. Dr. Huang, I was being slightly facetious in saying perfectly. I think we can interpret adequately to any degree of scientific adequacy we wish. And so we should deal with this and vote on a), then. We'll start again, with Dr. Poland.

DR. POLAND: No.

CHAIR FERRIERI: Two a). Dr. Edwards.

DR. EDWARDS: I think some additional ramification should be added to address questions that are not addressed currently. So I think I would have to vote no as well.

CHAIR FERRIERI: As you go along you can

make your suggestions as well.

DR. EDWARDS: Well, I think issues regarding duration of protection would be helpful. I think issues regarding booster doses -- do two doses induce greater immunity than one -- would be two of the primaries that I think should be addressed.

CHAIR FERRIERI: Dr. Huang, yes or no? Or --

DR. HUANG: Yes.

CHAIR FERRIERI: There's a third choice and that's to abstain.

DR. HUANG: Yes, with the caveat about wanting to know more about the duration.

CHAIR FERRIERI: Okay, that's a persistent theme. Dr. Snider.

DR. SNIDER: I think as was mentioned, at the time that they were done they were designed and executed according to the standards. So I have trouble with the question. And the adequacy part really goes back to the issue of number one, whether this is adequate to lead to a decision to license the vaccine. And there's where I have a hangup.

So depending upon how it's being asked I'd vote yes or no, I think. Based on what I'd like to see I'd have to answer no and get some of the

additional data that has either been explicitly stated by some of the panel members or -- well, I think it's been -- they've brought up some of the concerns about the design.

One additional thing I obviously would add based on an earlier comment would be if we are including people that are going back to home country, to include some of those people in the study. But that's just one element in a number of elements that one would add if one were designing and carrying out these studies today as opposed to the time when they were originally designed and carried out.

CHAIR FERRIERI: Dr. Hall.

DR. HALL: I think that in general I'll vote yes, and particularly in light of what Margaret has just said -- that they were -- and what Dixie just also said -- that challenge studies at that time for what they were designed, were probably adequate.

Whether or not we have all the information or will ever have all the information from a challenge study that we feel is necessary or ideal for licensure, I think is questionable. At this point I will say yes.

CHAIR FERRIERI: Dr. Greenberg.

DR. HALL: With the caveat I made that we'd

like more information on age, including younger children.

DR. GREENBERG: I am assuming -- these studies were absolutely done with great care when they were done. I am assuming that the question adequacy implies to adequacy for license and not adequacy at the time they were done.

DR. STIBITZ: That's correct.

DR. BASH: Yes.

DR. GREENBERG: And so my answer is no to that question and I would say the one thing I would add is that I guess, had trouble saying something should be licensed based on 15 people. And so numbers of people studied as well as the diversity of people studied would be another thing that I would add to the challenge study.

CHAIR FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Well, I think that I would vote yes. I realize that ideally -- and we would like to have randomized, double-blind studies -- but these are free living volunteers, they are closed studies. And so we don't really have -- if I were to design it, it would be very difficult to get all the people in the study that would then reflect the general viability of the results, or the

representation of, so you might want to generalize these results, too.

And I guess the question about children, I can't see how in the world we would ever do challenge studies in children. So I think that other than just having larger numbers to provide reassurance, I think we're going to have to strike a balance between what's feasible in a volunteer model in a real world situation, and keep the data as objective as possible for the readout.

CHAIR FERRIERI: Dr. Finkelstein.

DR. FINKELSTEIN: I have to answer no, because there's a couple of aspects. One is just the scientific method itself; that really one has to be cautious about potential biases of this study. And I realize it's difficult to do the appropriate study but we're being asked to conclude as to whether this is evidence enough of the efficacy of the vaccine.

The second aspect of it is the population; whether it could really be generalized to the target population for the vaccine is really in question to me.

And then the last aspect is the endpoint that was used for the study. And this really sort of is a bridge between two and I think four. I never

really, from the discussion today, got a handle on the real case rates that they would expect in the target population for this vaccine -- not in just all travelers or some of the other things we have.

And you have to know the attack rate to know whether the safety versus efficacy profile is good, especially with an endpoint like the less severe diarrhea.

So again, I realize these are all difficult aspects of it but those are the aspects that made it less than convincing to me. So the answer is no.

CHAIR FERRIERI: Dr. Daum.

DR. DAUM: I think, no.

CHAIR FERRIERI: Dr. Kim -- Mrs. Cole, sorry.

MS. COLE: My vote is also no. I don't think there were enough people involved in the study.

CHAIR FERRIERI: Dr. Kim.

DR. KIM: No. I think I have again, stated earlier that particularly challenge studies appear to have some limited data regarding that a study was conducted in a fashion that will be blinded and also provide a scientifically useful information as indicated by others.

CHAIR FERRIERI: Dr. Karzon.

DR. KARZON: I vote no. What I would do is to increase the numbers in the study -- that's need in any case -- and take this opportunity to have tighter control, blinded in the usual fashion. And certainly I would like to see the placebo control looked at very hard.

I'm suspicious that that placebo control has its own inherent toxicity in it -- E. coli. But if you look at the numbers I feel very sorry for a group of people who had these volumes at 30 days. It's not a normal panoply for (inaudible) dose.

And I'm not sure I understand the need for E. coli there. Or if you want to have two controls, have a two-blinded -- you need a blinded control and my suggestion would be to use a packet which resembles the design of the packet to choose for the study, whatever.

The handling should be blinded and have a blind control or something, which is absolutely benign and should not cause headache in 40 percent of the people, etc, and some nausea. Diarrhea, four booster in 24 hours should not appear in any one person. In other studies I just wouldn't suspect it.

So I'm suspicious of this group and I think it gives a false sense of safety in terms of the fact

that your P value is equivalent to the others when I don't think -- it's possible it may not be the true value.

CHAIR FERRIERI: Dr. Kohl.

DR. KOHL: No, for all the reasons enumerated.

CHAIR FERRIERI: Dr. Fleming.

DR. FLEMING: No. No for a number of reasons. The integrity of the inference here is certainty at some risk with the selectivity that was used in those that were challenged with the selectivity, or the non-randomized selection of the controls with the lack of blinding.

But my concerns are more serious than that; the concerns about the small numbers that we have for this inference, with these numbers. Even if we're using all 36 here we're estimating 60 percent protection against levels that are at least one stool, 300 mls.

It's difficult for me to know how we go from that to confidence that we're preventing serious purging. So the answer for all of those reasons, is no.

CHAIR FERRIERI: Thank you. Tom. Dr. Eickhoff.

DR. EICKHOFF: Well, I vote yes, based in very large part upon consideration of the practical realities of doing challenge studies. It's a provisional yes, however. I would certainly like to see somewhat more diversity in patients studied, more attention paid to the direct duration of protection and to the protection, if any, afforded by booster doses and whatever interval seems appropriate.

I agree with, I think, Dr. Clements-Mann. It's going to be very, very difficult, if not impossible, ever to do challenge -- direct challenge studies in children. So we will have to come up with some other mechanism to derive that.

CHAIR FERRIERI: Right. We can get to that point soon enough. Dr. Breiman.

DR. BREIMAN: Recognizing those practical issues that Dr. Eickhoff just mentioned, given the question though, I would have to vote no.

CHAIR FERRIERI: Dr. O'Brien.

DR. O'BRIEN: Well, I think the bottom line for me is yes, and it's yes because of practical issues of trying to ask this question, it's yes because of what we have right now as a vaccine.

I would, like everybody else, like to see more information on duration of immunity and the

necessity or the consequences of a booster challenge.

CHAIR FERRIERI: Dr. Holmes.

DR. HOLMES: I think the experiments were very carefully performed and have yielded a lot of very useful data. I think there are serious, practical problems with making this into a perfect study. Nonetheless, I would have to vote no in terms of the adequacy of the database for supporting licensure at this time.

I see the critical issues as being the duration of immunity against the El Tor challenge, and defining the nature of the response to a booster, not only in the people who are immunized initially with the current vaccine strain, but also in volunteers who have recovered from wild type cholera among naive -- immunologically naive Americans (inaudible).

We have to know whether a booster will ever have an effect and under what conditions it can be useful.

CHAIR FERRIERI: Dr. Pierce.

DR. PIERCE: As I listen it seems to me that to a considerable extent, we're saying yes and no to two different questions, in that a lot of the no's are really responding to b) and c) which are not subquestions of a).

If a) is a distinct question from b) and c) I would say yes. But I recognize that the issues in b) and c) have different comments as they come along.

DR. CARPENTER: My comments are very much the same as Dr. Pierce. I think that the challenge studies were designed and executed adequately within the framework of what they were designed to do, and my comments are exactly the same as those of Dr. Clements-Mann on that regard.

I think b) is a separate question. I don't think we've had adequate demonstration of protection against El Tor challenge but that will come up subsequently.

CHAIR FERRIERI: Your vote then, Dr. Pierce, is yes as well?

DR. CARPENTER: Yes.

CHAIR FERRIERI: And for the record, my vote is no for all of the reasons stated by those who voted no. And it's with some regret the vast majority of panel voted no, however.

We'll move on to question b) then. Are the data regarding heterologous biotype challenge (with El tor strains) adequate in light of the prevalence of El Tor strains in endemic areas?

Any clarification needed by anyone on the

question? Otherwise, we'll move into discussion of it. Would anyone like to volunteer to lead off any discussion before we would vote on this issue? Yes, Dr. Pierce.

DR. PIERCE: Just a question. I mean, maybe just so we know, we can agree what we're talking about as to how many individuals are in fact -- we are considering to qualify as the El Tor challenge? Because different numbers have been used -- anywhere from 15 vaccinees, I believe, to 36 -- which seems to depend -- oh no, sorry, 15 to 25.

Maybe there's not a big difference between those numbers but the 25 includes individuals who were challenged either at ten days or one month, whereas the 15 individuals were challenged at only one month.

Going up to 36 would require a different immunization regimen -- that is, two doses -- and I presume we would not include that in the comparison.

So my question is, are we talking about 15 or are we talking about 25?

CHAIR FERRIERI: CBER, would you like to respond? Dr. Bash.

DR. BASH: I feel comfortable for the discussion of this question including all of the individuals challenged with an El Tor strain, which

would be the 25. I would not include those who had been vaccinated with CVD 103, and so I wouldn't go to that extent.

DR. PIERCE: And not the 2-dose regimen?

DR. BASH: Well, the 2-dose regimen was a part of the -- this includes that.

DR. PIERCE: I thought the 25 would be studies 9003 and 19002.

DR. BASH: Correct.

DR. PIERCE: Okay.

DR. EDWARDS: What about 9007? That's also on the chart.

DR. PIERCE: That's a 2-dose regimen.

DR. BASH: I think it would be interesting to receive people's comments regarding that. Sorry.

CHAIR FERRIERI: Any comments on this? Are the data adequate on the heterologous biotype challenge?

DR. GREENBERG: I have one comment.

CHAIR FERRIERI: Great.

DR. GREENBERG: Coming from a virologist, challenge within shortly after an initial, live infection is really not a good experimental approach because there are all sort of acute phase reactants that are stimulated by the initial infection that

could in a non-immunologic way, alter your challenge.

And so I personally, I assume that could also happen with cholera; that this could be -- the effect could be non-immune mediated rather than immune mediated. So just personally, I don't like the idea of a challenge ten days after the immunization of an experimental approach, and I sort of discounted that.

Now, people can pay their money and take their choice, but I don't think -- when I do a mass experiment that I really want it to work, that's how I do the experiment.

CHAIR FERRIERI: Those of us who are rat and mouse doctors, we completely agree. Yes, Dr. Pierce.

DR. PIERCE: My comment about what is needed is, I believe we need in a general way -- perhaps the details to be worked out -- more information on what I would call the time course of protection.

And I think there's been -- you know, the 10-day challenge was probably an attempt to begin to get an early point in that time course; the one month data obviously, are another point. And we've had a lot of discussion about duration of protection.

And I would add to that the need to be able to show that you can not only boost -- that you can boost protection, if you show that protection

disappears in an unfortunately early time, like three or four months when you'd really like to have it last a year -- then I think you have to be able to show whether you can boost it.

DR. GREENBERG: I agree.

DR. PIERCE: And so it's those that -- now, exactly how one works out a schedule on how many different points you have on that I think requires a lot of thought. But it's basically a time course of protection that's not defined here in sufficient -- especially because protection is partial. If protection was higher level that might be a little less important, but it's because it's partial you don't know what it's doing at different point than what you have here.

CHAIR FERRIERI: Again, question 2b), Dr. Hall.

DR. HALL: I just have one. The ten days that was not at the time that the IgM antibody was peaking at that particular point. So there is some real rationale for using that in terms of at least infection.

CHAIR FERRIERI: I thought that was interesting also, Caroline. There was 40 percent -- well, 40 percent attack rate out of the ten. Someone

else have a hand up here?

DR. SNIDER: I had a question about the challenge and how -- is that just -- how does that determine -- how does the challenge dose determine what relationship does that have to natural infection, if known?

CHAIR FERRIERI: Dr. Levine, do you want to comment, or anyone on the agency side want to? Why don't you start?

DR. LEVINE: The dose of 10^6 with buffer is undoubtedly much, much higher, perhaps three logs higher than would be a natural challenge dose, and of course a natural infection. We have carried out dose response curves or dose response studies with several of the challenge organisms, with an El Tor Inaba strain N16961.

We went all the way down to four and three logs. And what's interesting is that the attack rate remained high at four logs and at three logs given with buffer, but what went progressively down was the total diarrheal stool volume.

We also have administered the 10^6 dose of organisms with a quasi Bangladesh meal rather than with buffer, and the attack rate and the severity of illness was identical, as was seen giving the dose

with buffer.

We also administered 10^6 in 300 ml of water to fasting volunteers without any buffer, and there was no infection and there was no diarrhea.

CHAIR FERRIERI: Thank you.

DR. SNIDER: Maybe I would like to clarify something anyway. I guess one of the things that I'm having trouble with is that -- I mean, I would really like to have this vaccine available compared to the alternative, but I know that I have to tell people something when I propose to administer a vaccine to them.

And the thing that's bothering me is the database leave a lot of questions that are unknown and it makes me really uncomfortable in thinking how in a clinical setting, or in developing a public health recommendation, I could make any sort of definitive statements, either to individuals or to populations about what they could expect.

CHAIR FERRIERI: Well, I think you've summed it up. That's exactly what we've been talking about all day and what has taken us all day and why we are so behind is the inadequacy of the data.

And so for those of you who have just joined us for the next session, slight apologies. We might

catch up. We're a little behind. We will get to the last issue of the day.

Does CBER have a response to what Dr. Snider just said?

DR. BASH: In terms of the challenge studies? It's my understanding that the goal was to design the challenge in such a way that between 70 and 80 or 90 percent of your control arm developed diarrhea as defined by the study outcome definition.

And that I think in a challenge study you need to have an adequate challenge that would result in a range of disease in that level, but not such a heavy challenge that you overwhelm whatever degree of protection might be seen.

The El Tor challenge studies for the most part fit that criteria. The Classical studies for the most part, did not.

CHAIR FERRIERI: Do you think we're ready to vote on part b) then? Fine. We'll start on this side of the room, then. Dr. Carpenter. This is part b). Yes or no.

DR. CARPENTER: No.

CHAIR FERRIERI: No, okay. Dr. Pierce.

DR. PIERCE: No.

CHAIR FERRIERI: Dr. -- I'm sorry, I have to

start at the bottom here. Dr. Holmes.

DR. HOLMES: No.

CHAIR FERRIERI: Dr. O'Brien.

DR. O'BRIEN: No.

CHAIR FERRIERI: Dr. Breiman had the lead. Dr. Eickhoff.

DR. EICKHOFF: No.

CHAIR FERRIERI: Dr. Fleming.

DR. FLEMING: No, for reasons indicated in the answer to a), and to also add that none of these studies except the 2-dose even hit a traditional level of statistical significance.

CHAIR FERRIERI: Thank you, Tom. Dr. Kohl.

DR. KOHL: No.

CHAIR FERRIERI: Dr. Karzon.

DR. KARZON: No.

CHAIR FERRIERI: Dr. Kim.

DR. KIM: No.

CHAIR FERRIERI: Mrs. Cole.

MS. COLE: No.

CHAIR FERRIERI: Dr. Daum.

DR. DAUM: No.

CHAIR FERRIERI: Dr. Finkelstein.

DR. FINKELSTEIN: No.

CHAIR FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: No.

CHAIR FERRIERI: Dr. Greenberg.

DR. GREENBERG: No.

CHAIR FERRIERI: Dr. Hall.

DR. HALL: No.

CHAIR FERRIERI: Dr. Snider.

DR. SNIDER: No.

CHAIR FERRIERI: Dr. Huang.

DR. HUANG: No.

CHAIR FERRIERI: Dr. Edwards.

DR. EDWARDS: No.

CHAIR FERRIERI: Dr. Poland.

DR. POLAND: The sample size is inadequate so I vote no.

CHAIR FERRIERI: And for the record, my vote is no for some of the reasons cited.

We'll move to part 2c) then. The question -- thank you, Scott -- Are the data sufficient to demonstrate protection from challenge for a period of time following vaccination that is sufficient for travelers?

Again, the wording is a little bit puzzling, perhaps. Scott, do you have any further clarification of this?

DR. STIBITZ: Unfortunately I'm not able to

add a lot. I think this is a question which is difficult for us to define as well, and I think some of the problems in addressing this question have become apparent today in terms of perhaps the lack of data about travelers and their habits.

What is a typical stay? So I'm afraid I'm not able to shed a great deal of light, but we'd be interested in the input of the panel.

CHAIR FERRIERI: Any comments here?

DR. STIBITZ: I believe Dr. Hardegree was --

CHAIR FERRIERI: Dr. Hardegree, did you want to say something?

DR. HARDEGREE: Well, the only thing is whether or not the discussion that you had about duration at this time and saying the additional data on duration is something you would want to see. Whether it makes this question moot.

CHAIR FERRIERI: It does make the question moot and I was hoping that someone on the panel would say that. So I think that our previous discussion covers it and that all the nods at the table are affirmative. And so we can move on.

If the panel feels -- and we have covered this to some extent but I think we should firm it up. If the panel feels that data regarding efficacy are

not sufficient to support licensure, what additional studies would be needed to address these issues?

What is the desire of the panel? Dr. Edwards.

DR. EDWARDS: Well, I know that number 3 is going to address pediatric issues, but I don't think we're going to vote on 3. So I do want to make it clear that that -- although I think the studies done in Chile are excellent and certainly bridging data, looking at reactogenicity of pertussis vaccines that have been done by this superb investigator in Chile, are very similar to those that we obtained in the United States.

I think that the antibody levels in children in Chile are higher than what I would expect in children in the United States, and also that the situation where we have one child who had a very severe, bloody diarrhea that was clearly not adequately worked up but do make me have concern about the pediatric population.

So I want to make sure that we're not -- without further data we're not going to give this to young children.

CHAIR FERRIERI: Again, I don't know what we can vote on this cluster. We could suggest additional

studies if that's all right with you, Margaret and Scott.

Yes, Dr. Clements-Mann.

DR. CLEMENTS-MANN: I just wondered if we could take advantage of the natural opportunity in other countries where this vaccine is being administered to children, if that data could be obtained. I think it may be very difficult to do these Phase I studies here in children where there's absolutely no risk of cholera to the U.S. population.

But if travelers are receiving this vaccine and at the indicated ages allowed by other regulatory agencies, if maybe there could be some study of safety -- at least in that vaccine.

I'd just like to point out that cholera -- I'm not aware of any cholera that causes bloody diarrhea. And this is not an invasive organism. So I'm -- just knowing the pathogenesis of cholera a little bit, I suspect that that was some other occurrent problem.

CHAIR FERRIERI: Other points from the panel? Other suggestions? We've talked about the diversity, we've talked about numbers, we've talked about the challenge dose, the strains, duration of protection being critical, endpoints, the issue of

booster doses, and so on. Dr. Pierce.

DR. PIERCE: From some of the comments made in the previous round it seems that there may be concerns about combining data from cohorts studied at different times. In other times, comments were made that only one study reached statistical significance but there was another identical study done.

I think it should be clear whether or not studies of identical design can be combined in order to empower them appropriately. Because again, the practical matter is that you cannot, in the volunteer situation as far as I know, study 60 volunteers at one time or whatever the number might be.

So if we are requiring more numbers at one point in time or several points in time, it just would be helpful to clarify that point, I think.

CHAIR FERRIERI: Who would like to clarify that? The agency, do you have any response to that?

DR. BASH: I think if the studies are designed in such a way that would allow comparison similar to studies where you have several multi-center studies.

There isn't a problem combining the data; there's a problem with combining data with vaccination schedules and immunization time between challenge that

really limited our ability to be able to put this data together.

I think that undoubtedly, given the inpatient status of these studies they would have to be done, but I think as long as that was planned ahead of time there wouldn't be a problem with combining data.

CHAIR FERRIERI: Any other -- Dr. Eickhoff.

DR. EICKHOFF: I would like to sound just a note of caution of this issue of challenge dose. I recognize Dr. Fleming's desire to really push the envelope and be able to show that we're preventing -- or the vaccine preventing severe purging in the placebo recipients in the control arm.

But this is severe disease and I think we're beginning to push the envelope of what a human research committee is likely to approve.

CHAIR FERRIERI: Absolutely. Dr. Poland.

DR. POLAND: The only other thing, Pat, that I might add to the list that you wrote is to be sure that we do include the elderly since they are a major fraction of travelers.

And the second is, it's apparent that blood group may play an important role here and I think -- I would want to know something -- or just at least for

different -- for group O versus non-group O blood when I saw results.

CHAIR FERRIERI: Very good. Well, the numbers convinced me. I think that was an excellent suggestion. Shall we move on to question 3? Dr. Hall.

DR. HALL: Can I just ask -- my comment earlier had been actually, made similar to what Mary Lou had made, in the use of data from other countries. But I wondered if, particularly in Canada, have there been any post-licensure studies or other data that someone knows about that could somehow -- at least the demographics of those who received the vaccine. Is that available? And I think those studies would be available -- or the information available in Canada.

CHAIR FERRIERI: Thank you, Caroline. The agency can pursue this perhaps. Dr. Karzon, you had your hand up, and Dr. Fleming.

DR. KARZON: There is one thing that we really ought to know and that is, the duration of protection. And secondary to that I suppose, is to extend the need for a repeat dose and the consequences of that.

I find that a very difficult experiment to design in inpatient service. But somehow we need a

line on that item. I'd like the suggestion of following up work that's been done in other countries as one lead, at least to get some serum possibility as a guideline to that. We do need to know that.

CHAIR FERRIERI: I think everyone agrees on that. Dr. Holmes.

DR. HOLMES: Yes, at the time these studies were begun the relative colonization defect in CVD 103-HgR was not known. And now that that data has emerged I think it would be appropriate reasonably early in the continuing studies, to look at the protective efficacy of the HgR to variant, if it's not too reactogenic, to see whether it will induce immunity more comparable to recovery from wild type El Tor infection. If so, I think it would change the direction of ongoing studies.

CHAIR FERRIERI: Tom, did you have another point?

DR. FLEMING: I think it's important from my perspective, to clarify that I endorse Ted's concerns in pushing the envelope. I would be very concerned about designing a trial if in fact, we were exposing volunteers to a level of risk that would be unacceptable.

In some discussions that I've had I've had

it articulated that it could well be, in the views of a number of people acceptable to provide a challenge that would yield risks at the level of five liter purging. If in fact though, that's not acceptable ethically, I understand.

But if in fact, it is not acceptable it doesn't alleviate my concerns about whether low challenge studies are really going to be meaningfully reliable.

And real quickly on the issue of meta-analysis, meta-analysis certainly is an informative tool; it's a descriptive tool. One has to be very cautious for reasons as pointed out; that you're not pooling apples and oranges, and also for -- your interpretation of strength of evidence has to be on a different scale because you're doing something somewhat retrospectively and you generally look for much more striking level of significance if you're going to base your inference on a meta-analysis.

CHAIR FERRIERI: The last two questions will have to be dealt with very briefly. Number 3 is very important: Can the immunogenicity studies be used to provide bridging data to the adult volunteer population to support administration to children?

Dr. Daum.

DR. DAUM: Pat, could I make one last comment about the previous question?

CHAIR FERRIERI: All right.

DR. DAUM: I think the multiple dose regimen was also intriguing and I don't think we sort of said that that might be something really worth exploring if additional studies were going to be designed as well.

And to echo Dr. Hall's comment, I think the idea of pursuing people to whom it's been administered in other countries, and maybe even surveying them for diarrheal illness or trying to gather information about what happened to them after they received it, might be really valuable information.

CHAIR FERRIERI: We'll continue. There are some people who plan to leave early which will certainly be a detriment to our whole discussion here. We will miss you. If you have to leave you can leave any time you wish. Dr. Pierce.

DR. PIERCE: Well, on question 3, I mean, I would just comment that I don't see right now unless I'm missing the boat entirely, how we have any handle on the efficacy of this vaccine for children since they do not seem to respond immunologically in the same way that adults do, since we do not know precisely what an immuno-response in an adult means,

and since we cannot challenge them.

I don't see a way into an answer. The only way I can see of eventually getting information on how cholera vaccine would be efficacious in children would be to have a vaccine that's efficacious in the field. And then under a variety of field study conditions perhaps back into information where immunization of children is possible and where gathering the perfect data is possible.

But I don't see how we can get a handle on this unless somebody else has a clearer idea than I do.

CHAIR FERRIERI: Thank you. Dr. Kohl.

DR. KOHL: I strongly concur with that as a pediatrician.

CHAIR FERRIERI: Yes. I agree. Dr. Daum.

DR. DAUM: Just yes.

CHAIR FERRIERI: You agree completely. Dr. Edwards. All of those of us who have a foot in pediatrics. Similarly, question 4: Comment on adequacy of data supporting safety in the target population in adults age 18 and higher.

I think we've certainly discussed this sufficiently. And then we've also indicated what the gaps are in our knowledge for children.

Are there any concluding comments that anyone would like to make? Thank you all who have contributed so greatly but have to leave before the last session. Dr. Greenberg, thank you. Did you wish to say something?

DR. GREENBERG: Actually, in a parting comment, vis-a-vis safety. Can the sponsors say anything about the genetic stability of the unknown mutation? I would assume that if that mutation was not genetically stable the parent cholera is somewhat more reactogenic. Is that correct? And how do you assess that stability?

DR. KAPER: Jim Kaper responding. The genetic characterization of colonization is, we don't know how stable it is. We couldn't determine that except for in large scale trials, perhaps. But certainly I would emphasize the mutation -- the attenuating mutation and deletion of cholera toxin is absolutely stable as 500 base pair deletion.

CHAIR FERRIERI: We can take a 5-minute break. There may be other members of the panel who haven't yet made an appearance who can sit at the table. Dr. Evans and Ms. Rovner, we'll make room for you at the table. This is an open session that we're moving to, dedicated to the box warning or packet

insert for oral polio vaccine. I want to thank those of you who have so patiently waited for us to start.

(Whereupon, the meeting of the Advisory Committee was concluded at 3:31 p.m.)

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