

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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NATIONAL INSTITUTES OF HEALTH

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NATIONAL INSTITUTE OF ALLERGY AND
INFECTIOUS DISEASES

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WORKSHOP ON ADJUVANTS AND ADJUVANTED PREVENTIVE
AND THERAPEUTIC VACCINES FOR INFECTIOUS

DISEASE INDICATIONS

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WEDNESDAY
DECEMBER 3, 2008

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The workshop convened at 8:00 a.m. at the
Bethesda North Marriott Hotel & Conference Center,
5701 Marinelli Road, Rockville, Maryland, Jay
Slater, M.D., Deputy Director, Center for Biologics
Evaluation and Research, Moderator, presiding.

Roundtable Discussion:

CARL ALVING, M.D., Walter Reed Army Institute of
Research

BRUCE BEUTLER, M.D., Scripps Research Institute

MARTIN FRIEDE, PhD, World Health Organization (WHO)

NATHALIE GARCON, Pharm.D., Ph.D., GlaxoSmithKline
Biologics

HANA GOLDING, Ph.D., Division of Viral Products,
CBER, FDA

SARAH GOULD, Ph.D., Sanofi Pasteur

MARION F. GRUBER, Ph.D., OVRP/CBER/FDA

EMMANUEL HANON, GSK Biologicals

EUGENE MARASKOVSKY, Ph.D., CSL Limited

DEBORAH NOVICKI, Ph.D., Novartis

DEREK O'HAGAN, Ph.D., Novartis Vaccines and
Diagnostics, Inc.

FABIO RE, Ph.D., University of Tennessee Health
Science Center

ROBERT SEDER, M.D., Vaccine Research Center, NIAID

ELIZABETH SUTKOWSKI, Ph.D., Co-Chair, CBER/FDA

GEERT VAN den BOSSCHE, DVM, Ph.D., Bill and Melinda
Gates Foundation

JAN WILLEM VAN der LAAN, Ph.D., National Institute
for Public Health and the Environment, The
Netherlands

WILLIAM WARREN, Ph.D., VaxDesign Corporation

Session 4: Clinical

JAY E. SLATER, M.D., Co-Chair, CBER/FDA

W. RIPLEY BALLOU, M.D., Bill and Melinda Gates
Foundation

GIOVANNI della CIOPPA, M.D., Novartis

CHARMAINE GITTLESON, M.D., CSL Limited

STEVEN REED, Ph.D., Infectious Disease Research
Institute

HEATHER DAVIS, Ph.D., Pfizer

GARY DUBIN M.D., GSK

GREG GLENN, M.D., Intercell, USA

MARTINE DENIS, Ph.D., Sanofi Pasteur

OFER LEVY, M.D., Ph.D., Children's Hospital Boston
and Harvard Medical School

RINO RAPPUOLI, Ph.D., Novartis

Session 5: Roundtable

W. RIPLEY BALLOU, M.D.
HEATHER DAVIS, Ph.D.
GIOVANNI della CIOPPA, M.D.

MARTINE DENIS
GARY DUBIN, M.D.
MARTIN FRIEDE, Ph.D.

CHARMAINE GITTLESON, M.D.

GREG GLENN, M.D.

THOMAS HOLDICH, MBBS, ATL

OFER LEVY, M.D., Ph.D.

RINO RAPPUOLI, Ph.D.

STEVEN REED, Ph.D.

DAN ROTROSEN, M.D., NIAID/NIH

FLORIAN SCHODEL, M.D., Merck

JAY E. SLATER, M.D.

THOMAS VERSTRAETEN, M.D., M.Sc., GSK

Session 6: Wrap-Up

HANA GOLDING, Ph.D.

CHUCK HACKETT, Ph.D., NIAID/NIH

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P R O C E E D I N G S

(8:01 a.m.)

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2
3 MODERATOR SLATER: Good morning,
4 everybody. As you work your way to your
5 seats, I will ask the participants in the
6 roundtable to please work your way up to the
7 front to our not-quite-round table.

8 Just again a couple of brief
9 comments. You all notice that we are in the
10 bigger space. That is not a mistake. The
11 group that was supposed to take one of the
12 rooms canceled at the last minute, and so we
13 benefit from that.

14 Those of you who parked in the
15 parking lot, please make sure to get a parking
16 voucher today again.

17 I have had several questions about
18 the slides and whether they would be available
19 for distribution. I will give the answer that
20 I have given to everybody, and the answer is
21 maybe. I have not secured permission from any
22 of the speakers to make their slides public

1 and disseminate their slides, which I will
2 attempt to do in the day or two following the
3 conference.

4 Once we have received an answer
5 from each of our speakers, then those
6 presentations for which we have received
7 permission will be posted. What I would
8 suggest is that you go back to the website on
9 which you registered for this meeting and
10 check, and there will be a link there, my
11 guess is, in about a week for those
12 presentations for which we have secured
13 permission.

14 At that, I will turn this over to
15 Dr. Gruber, and have a good roundtable.

16 DR. GRUBER: Well, good morning,
17 and welcome to the second day of this
18 workshop. We will begin the discussions with
19 the nonclinical issues.

20 As I was saying yesterday when I
21 presented the current approach to nonclinical
22 testing requirements for adjuvants and

1 adjuvanted vaccines, some of the approaches
2 were really devised from recommendations that
3 stand for testing of vaccine antigens, and we
4 didn't really focus on adjuvant-specific
5 issues.

6 Thus, I had mentioned yesterday
7 that some of the approaches and parameters may
8 need to be revisited to really make the
9 nonclinical testing approach fit the adjuvant-
10 specific issues.

11 That is actually the purpose of
12 the roundtable discussion this morning. What
13 I would like to do is to start with a series
14 of questions. Now I think some of these may
15 be a little bit ambitious, and we are probably
16 not going to get to discussing them all in
17 detail. I think, therefore, it may make sense
18 to just prioritize, and starting perhaps with
19 the most practical concerns and
20 considerations.

21 Let me just go through the
22 questions. Then I am going to be circling

1 back to what I thought are the issues that we
2 need to be focusing on this morning.

3 So question number 1 was: If the
4 current approach to adjuvant toxicology
5 testing is sufficient or should it be revised?
6 Is it sufficient to test only the highest 1x
7 human dose of the vaccine-adjuvant
8 combination, as we do currently, as well as
9 the adjuvant alone, or should dose ranging
10 studies be conducted on the adjuvant alone?

11 Should additional parameters such
12 as cytokine levels or other biomarkers, C-
13 reactive protein or fibrinogen levels be also
14 assessed? And what about other aspects of the
15 current study design?

16 I mentioned yesterday that the
17 route of administration should mimic the
18 clinical dose, and what about the dosing
19 regiment? To remind you, we are using
20 episodic dosing in toxicology studies to mimic
21 the proposed clinical dosing regiment. Is it
22 adequate for adjuvant testing as well? Should

1 there be more frequent dosing?

2 I think one of the issues that I
3 personally would like to really touch on a
4 little bit this morning is really the animal
5 species and the animal models. Well, that is
6 challenging because, I guess, even now we
7 already tried to get at this issue a little
8 bit in 2002 in the workshop we had then on
9 nonclinical testing of vaccines.

10 At that point, it was thought that
11 there were perhaps some animal models that
12 would allow testing in special subpopulations,
13 but that the series really hasn't moved, and
14 I guess we may want to revisit this a little
15 bit this morning.

16 The first question is whether it
17 is sufficient to test in only one animal
18 species, as the current recommendation is; and
19 then again, what really constitutes a relevant
20 animal model?

21 To remind you again, we consider a
22 relevant animal model as a model that is able

1 to mount an immune response to the vaccine
2 antigen and whereby the adjuvant would enhance
3 the immune response to the vaccine antigen.
4 But how do we get our arms around the specie
5 specificity of the innate immune response, and
6 also the mechanism of action of the antigen
7 and adjuvants in that context.

8 Then again, should toxicology
9 studies be conducted in specific animal models
10 to support the safety of adjuvant in special
11 subpopulations? So if you develop a vaccine
12 specifically indicated for the pediatric
13 population, should toxicology assessment be
14 conducted in a juvenile animal model, for
15 example?

16 Additional questions get at the
17 issue about the immunologic parameters that
18 should be evaluated. Again, should it be the
19 vaccine antigen-specific response only or
20 should we now also consider the adjuvant-
21 specific responses?

22 How can we, and how do we, best

1 incorporate in vitro assays into nonclinical
2 safety assessments to supplement safety
3 assessments in animal models?

4 Then here are a couple of
5 additional questions. I am not optimistic
6 that we maybe even get to this this morning,
7 but at least I wanted to put them up, because
8 of these issues that the regulatory agencies
9 are grappling with.

10 That gets at the issue of what to
11 do with combination adjuvants. So as we have
12 heard yesterday, some of these adjuvant
13 systems include a variety of adjuvants, such
14 as QS21 MPL, for instance.

15 So the question is: If it is
16 adequate to assess only the combination when
17 assessing a combination adjuvant, so the
18 adjuvant system in its totality, or should
19 toxicity studies -- and I said here dose
20 ranging studies -- be conducted on each
21 separate component?

22 Then what additional tox studies

1 should be conducted? There may be some
2 concerns about an adjuvant system to either
3 cause or exacerbate preexisting conditions
4 such as autoimmunity or inflammatory disease.
5 Should this be evaluated a priori?

6 Of course, there is the issue
7 about do we have adequate animal models to
8 assess that. Then what about additional
9 studies such as genotox or chronic toxicity
10 studies that are currently not required in
11 vaccine toxicology assessments?

12 The reason about chronic toxicity
13 studies or long term evaluation is coming from
14 the fact that some of the vaccines that are
15 currently in clinical development are those
16 that may be given as repeated doses over a
17 long period, such as the adjuvanted influenza
18 vaccines that are currently in development.

19 So an individual would get every
20 year seasonal influenza vaccine, and that
21 would result in exposure to perhaps even
22 multiple types of adjuvants that are either

1 concurrently administered over multiple years.
2 How can this be studied? Should it be
3 studied?

4 That is the overview of the
5 questions, and I think that is quite loaded,
6 that program. So let's go back to the first
7 issue, because I think that may be the one
8 that we can tackle this morning, and that is:
9 Looking at the current approach and the
10 testing paradigm, should it be revised or
11 should we keep it, as we have done it for the
12 last couple of years?

13 So the first sub-bullet that I
14 have put up here is: Is it sufficient to test
15 only the highest 1x human dose, if that is
16 feasible in the animal model, of the
17 vaccine/adjuvant combination or should we
18 include dose ranging studies here or should
19 dose ranging studies only be conducted on the
20 adjuvant alone?

21 So whoever wants to take that
22 first question -- Dr. Van der Laan? Thank

1 you.

2 DR. VAN DER LAAN: Thanks, Marion,
3 for this question, for this opportunity to
4 discuss.

5 When we first were thinking about
6 the guideline for vaccines, it was just in the
7 period that vaccines became under a normal
8 regimen in Europe, and there was a normal
9 toxicity to be done on the final product, and
10 should we replace the normal toxicity testing,
11 at least a test of the final product, in an
12 animal species.

13 That is why we have thought about
14 just the human dose, the human formulation,
15 and a vaccine is not a simple formulation. It
16 is not a drug product. It is just a complex
17 formulation. It is not easy to halve -- It
18 might be easy to halve the dose as a type of -
19 - just half the volume. But it is not easy to
20 increase the dose because of the volume, and
21 that is why, just for my first practical
22 reason, the human dose is the highest dose.

1 Of course, we can think about
2 other approaches, although just for the last
3 few years also, starting with revising
4 toxicity approaches for biologicals, we are
5 more focusing on the pharmacological effect
6 than on the toxicological effect, far away
7 from the human dose.

8 So in my view, the approach should
9 be handled with some flexibility, but is in
10 general okay. For an adjuvant, of course,
11 you should have your developmental studies:
12 What is the optimum in the dose of an
13 adjuvant? But that is more proof of concept
14 than toxicity.

15 DR. GRUBER: Thank you very much
16 for this comment. Are there any other
17 comments from the roundtable on this issue?

18 MR. ACKLAND: Jim Ackland,
19 independent consultant. I guess my question
20 that I have been grappling with is why do we
21 need to change? What is it that the
22 regulators are seeing that means that we

1 should change our existing toxicology
2 assessment of new vaccines with new adjuvants?

3 So is there something that needs
4 to be changed, needs to be fixed, and that
5 might help us say how we should change it. So
6 what is being seen in the clinic that is not
7 being seen in the preclinical studies that we
8 need to be looking for?

9 DR. ALVING: I could make a
10 comment on that. I am not a regulator,
11 obviously, but there are some instances when
12 in human trials there have been clear toxic
13 effects that have occurred, systemic effects,
14 not life threatening, but --

15 So the question is whether we want
16 to be able to pick up those potential toxic
17 effects at an earlier stage in an animal
18 model. I would really wonder about that
19 myself, actually -- I think this is an
20 excellent question -- because in all of the
21 studies which I have seen in which there have
22 been comparisons of different adjuvants, the

1 conclusion, I believe -- maybe I'm wrong; if
2 somebody would correct me, I would appreciate
3 it -- that all of the adjuvants that were
4 tested were considered safe, even if there was
5 some degree of reactogenicity.

6 So I would say, actually, the
7 whole vaccine per se, including the adjuvant,
8 is a more appropriate thing to look at rather
9 than focusing only on the adjuvant, just based
10 on the historical apparent lack of clinical
11 problems that have been observed.

12 DR. NOVICKI: So I guess some of
13 these questions are so broad, it's a little
14 bit hard to get my head around it. But one
15 comment I would like to make is that
16 toxicology studies are not the only
17 opportunity to gain safety information.

18 When one is conducting studies
19 where you are dose ranging in pharmacological
20 studies looking at the immune response, to
21 build in some parameters there is an
22 opportunity to capture some information.

1 So I think, in a way, we have to
2 think more creatively around the nonclinical
3 package perhaps than just zeroing in on the
4 GLP toxicology studies.

5 I think that some of the questions
6 that we are asking are somewhat limited by the
7 type of material that we are dealing with. So
8 if you've got a liquid emulsion, in order to
9 do -- and it is set at a certain concentration
10 and physical characteristics, etcetera -- you
11 are not going to be able to keep the dose
12 constant and increase the concentration of
13 components. So you are changing it already.

14 So your dose is going to be
15 limited by how many times you want to poke an
16 animal, and that might be a completely
17 different situation than if you are trying to
18 incorporate an immunologically stimulatory
19 biologic into a PLG microsphere.

20 So I think that there is no way to
21 make the guidelines or guidance cover all of
22 the different situations that the people in

1 this room are working on. I think that it has
2 to be broad enough to give people general
3 guidance on what to do, but then an individual
4 developer of the product has got to think
5 rationally about what they really need to know
6 about the molecule in order to safely test it.

7 So it's just some thoughts.

8 DR. SCHODEL: Hi. This is Florian
9 Schodel from Merck. I've had a question that
10 sort of I have been thinking about since
11 yesterday.

12 We are mostly concentrating on the
13 acute responses, and the tests are mostly
14 concentrating on what happens in the acute
15 phrase reactions, and they are really not an
16 issue; because that is what you see quickly in
17 your Phase I studies. That is where you have
18 very good instruments. They are also
19 frequent. I can very easily figure out
20 whether they do that and, as the colleague
21 before me said, the toxicology armamentarium
22 that we currently have, I think, answers these

1 questions quite adequately, LPS responses,
2 fever, pyrexia, those kinds of things.

3 Now what I was hoping for a little
4 bit yesterday -- maybe that is a question I
5 would like to ask the panel: Are there any
6 tests that could be used in preclinical work
7 that would actually help us grapple with the
8 much more difficult to answer questions in the
9 clinic, such as, for example, this suspicion
10 that there might be autoimmune responses
11 generated. That could have negative
12 consequences, which you can't test in the
13 clinic, because they are too infrequent.

14 So you see one case, and then you
15 would have to test millions, as somebody -- I
16 think it was you -- laid out yesterday, in
17 order to get a clear clinical answer.

18 So are there mechanistically based
19 animal tests that we could use to exclude a
20 mechanism -- basically say, if we put the
21 adjuvants in a preclinical test and it doesn't
22 show that mechanism, then we don't have to

1 suspect that we will really need to test for
2 it in the clinic; because those acute things,
3 as I said, are frequent, and they are easy to
4 deal with.

5 I don't know whether there is an
6 answer to that, but that is the question I
7 would like to get an answer to.

8 DR. FRIEDE: Okay. So let me try
9 and just give some thoughts which covers that
10 and a lot of what we heard yesterday.

11 So I would like to begin with the
12 observation that we have actually been giving
13 adjuvants to people for the last 100 years.
14 We have been giving wholesale pertussis
15 vaccines to most of the people in this room,
16 and that contains a lot of Toll4 agonists.

17 We have been giving IPV to most of
18 the people in this room. That contains a
19 Toll3 agonist. We have been giving meningitis
20 vaccine, which is a Toll2, a bit of Toll5 in
21 there.

22 So we actually have a tremendous

1 clinical background of administration of
2 adjuvants to people, and we haven't picked up
3 in any post-market surveillance any evidence
4 of these vaccines which contain very potent
5 immunostimulatory molecules having any
6 correlation with autoimmunity. And certainly,
7 there has been a significant study looking at
8 this with the Hepatitis B vaccine, multiple
9 sclerosis and a number of other things.

10 So I think, just to get the
11 pendulum swinging back in the right direction,
12 we need to set up an environment where we
13 actually facilitate adjuvant development, not
14 impede it. So we must remember that we have
15 this background of having administered
16 adjuvants, many of them in large quantities
17 and relatively impure, for the last 90 years
18 or so.

19 So then to move forward from this,
20 I think looking for autoimmunity in animal
21 models is going to be extremely complex,
22 because if you look for something, you will

1 find it. If you inject into an animal model
2 that is susceptible to autoimmunity, be it
3 lupus, be it the studies we saw yesterday,
4 immunostimulants, I am sure that you will be
5 able to trigger something. But the test would
6 be that we actually administer all of the
7 vaccines we already have used, which we know
8 that there is no correlation of autoimmunity,
9 and I'm sure that in this animal models these
10 vaccines would induce such responses.

11 So I think those animal models are
12 actually inappropriate.

13 PARTICIPANT: I would like to
14 amplify on the comment just made about how
15 there are vaccines out there that have a lot
16 of TLR adjuvants. Another, of course, is
17 Bacille Calmette-Guerin or BCG that is given
18 around the globe at birth and has Toll2, Toll4
19 and other innate immune adjuvants as well. So
20 you might add that to the list.

21 DR. GOULD: I think those are good
22 points. I just want to take us back maybe to

1 the question that we are trying to deal with
2 first, because, obviously, that is a question
3 that, I think, is important to come back to in
4 the autoimmunity. But here we are trying to
5 look at whether one human dose is sufficient
6 with vaccine and adjuvant alone or whether we
7 should be looking more at dose ranging.

8 I guess it depends what we are
9 trying to achieve. I come from a background
10 from the pharmaceutical industry where I've
11 spent 10 years dealing with small molecules,
12 and there you push the dose. You want to
13 check toxicity. There you are looking at
14 chronic dose often, and you are trying to find
15 a signal, and we know for sure that there is
16 a lot of time that drugs get into the clinic
17 and then eventually fail because of some
18 toxicity or other, which actually hasn't been
19 picked up in the preclinical.

20 The vaccines, yes, they have a
21 very safe record, and we have been testing
22 adjuvants and vaccine adjuvants, and on the

1 whole we are not seeing any major issues, and
2 we have been pushing adjuvants up because of
3 the safety concerns.

4 I gave the case history yesterday
5 of why don't we push the dose up, just to see,
6 well, what could we really induce if you
7 really pushed the dose up; and we didn't see
8 anything.

9 Now you can talk about endpoints
10 and autoimmunity. Okay, we weren't looking
11 for that. So that would only be detected by
12 normal parameters we were picking up. But we
13 pushed the dose, and we didn't see anything.

14 So I'm not sure that there is much
15 value in pushing the dose, because it depends
16 on what your adjuvant is, because there's new
17 adjuvants coming onto the field. So is there
18 going to be something coming onto the field
19 that we don't understand?

20 DR. GRUBER: Yes, and I think that
21 is a good point, and I think that is why, at
22 least from the FDA perspective, we wanted to

1 bring up this issue about should dose ranging
2 studies on the adjuvant alone really be
3 incorporated into toxicology assessment?

4 You can look at history and say so
5 far we haven't seen any red flags. I also
6 want to make the point that, by no way, do we
7 want to link all of these questions that we
8 have put up here to the concern for
9 autoimmunity.

10 I think we all realize that may be
11 one potential concern, but I don't want to be
12 misunderstood to mean that the overriding
13 concern here was adjuvants as an autoimmune
14 induction. That really is not where we are
15 coming from.

16 When we were saying to look at the
17 possibility to include dose ranging, it is
18 because sometimes if you are stuck with one
19 dose -- and I have seen final study reports;
20 my colleagues have seen it, that you have a
21 signal, and you don't know what to do with
22 that. If you would have dose ranging studies

1 in different study arms, you are able to
2 explain it, and you can say, okay, I see it
3 perhaps at higher dose but not at lower doses,
4 not at a lower dose, and it doesn't compare
5 well with the clinical dose; so let's not be
6 too concerned about it.

7 If you just have this one dose,
8 you don't really have anything to compare it
9 to, and then it makes data evaluation somewhat
10 complicated. So, therefore, we brought up the
11 point, where feasible -- and we realize that
12 some adjuvant systems do not allow dose
13 ranging because of concentration issues and
14 things like that, but where feasible, should
15 the recommendation be made, because it does
16 help and facilitate data evaluation and
17 interpretation at points.

18 DR. VAN DEN BOSSCHE: So I would
19 like maybe to add a little bit of complexity
20 to the discussion.

21 First of all, I think, when we are
22 talking about adjuvants, we should really be

1 specifying what type of molecules we are
2 talking about. Personally, I think adjuvants
3 is not the right definition even, because I
4 would prefer to talk about adjuvanticity. Why
5 is this? Because we know that, for example,
6 antigens could have adjuvant effect as well.

7 On the other hand, we know that
8 adjuvants are going also to impact
9 presentation and one of antigens. So I think
10 basically the discussion here is the
11 difference between small molecule adjuvants
12 where we are afraid of systemic distribution,
13 where we know that this is happening. That is
14 the reason why we try to change these
15 molecules in order for them to be more
16 targeted.

17 The other type of molecules or the
18 other type of compounds that have
19 adjuvanticity effect are -- this could be
20 fibrous particles, inactivated, attenuated,
21 whatever. These are the more complex super-
22 molecular, macro-molecular surrecia, which we

1 know that they are less likely to distribute
2 systemically.

3 These are the type of compounds
4 where we have definitely less problems. These
5 are the compounds that are going to be very
6 targeted, have a local effect.

7 I think the discussion should
8 really be more focused on how do we make sure
9 -- unless we think, we do think that we should
10 be using adjuvants as drugs. I don't think
11 so. I think it is fundamentally different.

12 If we agree upon this, that not
13 only adjuvants but vaccines in general should
14 have a local and targeted effect, then we
15 should, first of all, stay away of these drug-
16 like molecules and use them as such, which I
17 think is one of the major problems and the
18 major issues of discussion.

19 I also don't understand why we
20 need to test adjuvants alone. It is very
21 clear that the antigen will impact or may
22 impact on the effective of the adjuvants, if

1 you are talking, for example, tolerance or
2 breaking tolerance.

3 It is also very clear that the
4 adjuvant is going to impact on the
5 presentation of the antigen, on the processing
6 of the antigen. Both of these things go
7 together, and you may be observing completely
8 different effects if you don't use them
9 together and if you test them separately.

10 So I am really sorry, but I think
11 these are the type of things we need to
12 discuss first. What do we really expect the
13 adjuvant to do? Should it be a kind of
14 systemic effect? Should it be a localized
15 effect?

16 If we think -- If we agree that
17 the vaccine should induce a generalized effect
18 through, first, local triggering of immune
19 competent cells and then by expanding through
20 the lymph nodes, T cells, B cells and so on,
21 then we may be thinking about what is the best
22 way for these molecules to be administered.

1 I don't think it is in a drug-like
2 form like small molecules, which will be
3 readily distributed and into circulation and
4 which then may elicit this type of questions,
5 autoimmunity, breaking tolerance, immune
6 pathology and so on.

7 DR. VAN DER LAAN: May I comment
8 on that also from practice. Although I agree
9 that there is something to say to support the
10 feeling that vaccines should be handled more
11 locally, the final effect of a vaccine is that
12 it is a complete systemic protection of the
13 body. So the definition of local is a bit
14 difficult.

15 With respect to adjuvants, whether
16 or not adjuvants are drugs or non-drugs or
17 should be tested alone, there are some Toll-
18 like receptor agonists such as imiquimod for
19 TLR-7 or CpG for TLR-9 that are used and
20 administered separately from the antigen in,
21 for instance, a cancer vaccine study.

22 That is why we in Europe have

1 defined that specific remark on what is an
2 adjuvant, what is an immune therapeutic. The
3 current practice is that in some clinical
4 studies CpG is given much more frequent and
5 with much more repetitively than only once
6 with the antigen.

7 So it is not a final solution to
8 have adjuvants not as handled as drugs, and I
9 am not discussing about the legal aspects.
10 then we have also to change the laws, but that
11 is not a scientific issue.

12 DR. GRUBER: I would like to make
13 one more point to ask a question to the panel
14 before we perhaps go to the next question.

15 That is: Mention was made that
16 there doesn't seem to be a clear reason why
17 adjuvants should be tested by themselves.
18 First of all, to clarify, from a regulatory
19 perspective, of course, we strongly feel that
20 the adjuvant system needs to be tested in the
21 context with the vaccine antigens.

22 So the final clinical formulation

1 that is administered to the human subject will
2 need to be studied on the toxicity study.
3 However, we have felt from a regulatory
4 perspective that there is value in terms of
5 studying a novel adjuvant at least by itself
6 to tease out potential adverse effects that
7 you may see with the adjuvant alone to sort of
8 explain what the signal or the adverse event
9 would be, realizing that certain synergistic
10 effects, of course, could take place and would
11 lead perhaps to an adverse outcome. But we
12 felt that trying to discern the, if you want,
13 reactogenicity between the vaccine adjuvant or
14 the adjuvant alone would be helpful. I would
15 like to hear some comments from the panel on
16 this.

17 DR. VAN DEN BOSSCHE: Well, sorry.
18 Again, I would like to make the same kind of
19 comment. I understand the logic behind this.
20 The only comment would really be what we are
21 testing there, according to my opinion,
22 doesn't make sense, because it is not going to

1 be relevant for the action of the adjuvant
2 once you have it in the formulation, once it
3 is in the presence of the antigen.

4 The action will be different, as
5 well, the intrinsic activity of the adjuvant
6 as its distribution, for example. We know
7 that this is the trick, is to formulate. It
8 is to put it into particles, if these are
9 small molecules, for example, in order to
10 change the distribution, in order to change
11 the uptake by the cell, in order to change the
12 processing of the antigen, and so on.

13 So testing the adjuvant alone -- I
14 understand the logic behind, but again I think
15 we need to get away of this kind of
16 perception, that adjuvants are drugs. I mean,
17 we want to use them as vaccines. What are we
18 going to do with all this complex formulations
19 like VLPs, virosomes, where everything is
20 integrated? Do we consider them being
21 adjuvants?

22 As Martin just pointed out, they

1 do contain adjuvants. Are we testing them
2 separately? What are we going to do about
3 these guys? So I really don't know. I mean,
4 if we want to follow this drug-like approach,
5 there is no way we can test them.

6 DR. O'HAGAN: I think we end up
7 with that problem if we talk about adjuvants,
8 and there are so many different kind of
9 formulations, of materials, of components.
10 Fundamentally, I think the argument, to me, is
11 if it is something that is really novel that
12 we have not seen before, that we have not
13 utilized as an adjuvant at all, then it seems
14 appropriate to investigate the inherent
15 potential for toxicity of that compound.

16 So if there are issues that are
17 going to arise, you would like to know early.
18 Ultimately, it is really about the safety of
19 the vaccine product you would make with the
20 adjuvant formulated into, which is the GLP
21 standard toxicology, etcetera. But for the
22 new compound and new agents and new approach

1 where there isn't a solid background, I would
2 say it is wholly appropriate to investigate
3 the inherent potential for toxicity of a
4 compound.

5 DR. NOVICKI: I would just add
6 that I think that to do entire, full blown
7 programs of long term studies with an adjuvant
8 alone, I don't think, is appropriate. But to
9 understand the fundamental basically hazard
10 identification in the early stages when you
11 want to understand what are the potential
12 risks, are there special studies that you
13 might see that are indicated by some early
14 signal, or do you get a very sort of flat kind
15 of signal, no concerns, and then you do -- I
16 mean, every study that we do with a vaccine
17 containing an adjuvant, we incorporate very
18 frequently adjuvant alone and then also a
19 saline control.

20 So in every study where we are
21 looking at the product, we are also
22 incorporating these other control groups. So

1 historically, if it is an adjuvant platform
2 that a company is developing, then you are
3 continually collecting data on that compound
4 over time with more and more antigens.

5 So being able to build that kind
6 of a history with it is really important. It
7 is a little bit more challenging if it is a
8 company where you've got a one-up adjuvant, it
9 is only going to be used with one indication,
10 and then doing an entire program for that one
11 shot is perhaps onerous for a smaller company.
12 But I think some fundamental information that
13 shows you what you need to be looking for in
14 subsequent studies can be very helpful.

15 MR. BALLOU: I would like to
16 comment as a clinician who has had to -- who
17 has worked with many adjuvanted vaccines over
18 the years.

19 I have found the preclinical
20 toxicology -- and I read those reports in
21 depth before we start a clinical trial -- have
22 been very helpful in helping me understand how

1 to design a clinical program. I think the
2 value of having the adjuvant control and
3 looking at that histology and understanding
4 what the adjuvant is doing in terms of local
5 or systemic reactogenicity in an animal model
6 helps you guide what you are going to do in
7 the clinic.

8 What I have been very impressed
9 with is the fact that sometimes the fixed dose
10 that one proposes from preclinical is not, in
11 fact, the dose that you end up using in the
12 clinic, and that can only be determined
13 through a proper trial design and actually
14 asking these questions.

15 So I have found the current
16 testing process to be very helpful in helping
17 us guide clinical development, but not highly
18 predictive about where we are going to end up
19 with in terms of a clinical dose.

20 Certainly, I have very clear
21 examples of where there is a difference when
22 the adjuvant is added with an antigen versus

1 the adjuvant alone, and sometimes it is very
2 unpredictable how that happens.

3 Where I do have concern, I think,
4 echoing Derek's comments, is for completely
5 novel adjuvants where we don't have a track
6 record yet, I think it is very important to do
7 pretty careful dose ranging studies on this,
8 particularly for adjuvants where it is
9 difficult to disassociate the antigen dose
10 from the adjuvant dose, and we know that there
11 are adjuvants being proposed where the two are
12 linked, for example.

13 My final comment is: I do not
14 like the idea of breaking down adjuvant
15 systems into component parts. We know they
16 behave differently, and Qd QS21 by itself is
17 a very different molecule than when it is
18 quenched in liposomes, and I think you can get
19 completely misleading results by breaking them
20 down and trying to tease out individual
21 toxicities when, in fact, what you are testing
22 is a compound designed to give you a

1 particular outcome.

2 DR. GRUBER: I think we will take
3 you first. I don't know who came up first.

4 DR. WARNER: So I want to
5 reiterate some of the things that I just
6 heard. I am glad to hear those comments.
7 This is Garvin Warner from Wyatt.

8 We got to remember what these
9 studies are really designed to do. They are
10 designed to give the clinician some guidance
11 about what target organs are. Now those are
12 traditional tox endpoints, right?

13 I am not talking about pushing
14 things to an MTD necessarily, but having the
15 appropriate safety margin for a novel, a new
16 chemical entity or a new biologic entity is
17 useful information to know that you don't have
18 a catastrophe.

19 Now I do use, and I like having in
20 terms of regulatory guidance 1x the human
21 dose, but I got to admit, I often go to 2x to
22 give me some margin, because of body weight

1 issues with infants and things like that.

2 I guess my point is here that for
3 a novel, a new biologic entity, new chemical
4 entity, there is some advantage to making sure
5 that you have pushed the dose so that you can
6 identify potential target organs.

7 Some of the things we are working
8 with are very potent biologic agents, locally
9 or systemically, indirect systemically, but I
10 think there is some advantage to early on at
11 least understanding whether you have a
12 catastrophe and you have some reasonable dose
13 multiple over a body weight basis or a
14 millimeter squared basis, just to help
15 instruct the clinic and help the clinical
16 program.

17 I don't think dose ranging in
18 animal studies is very useful for either an
19 efficacious dose, but again identifying target
20 organs and coming up with those potentials is
21 a useful thing.

22 DR. GRUBER: Thank you. I think

1 we will take one more comment, and then we
2 will move on to the next point.

3 DR. CHEN: This is Bob Chen from
4 CDC. Most of my work has been vaccine safety
5 in the post-marketing setting, and I would
6 like to, hopefully, bring some of that
7 experience to the discussion here.

8 So I would like to first address
9 Martin's comment, that while in the past
10 certain vaccines have been used a lot, and the
11 fact that we didn't see certain problems -- is
12 that adequate by itself to say that things are
13 okay?

14 I would say that perhaps not in
15 the sense, for example, the yellow fever
16 vaccine or smallpox vaccine have been used
17 forever, and it is really only in the last
18 five or six years that we know this yellow
19 fever vaccine associated with viscerotropic
20 and neurotropic disease as well as the
21 smallpox vaccine myopericarditides as problems
22 really emerged, because we now have the

1 surveillance systems that look at these things
2 carefully.

3 That being said, these true, rare,
4 serious associations are probably most likely
5 genetically mediated, and it makes sense. We
6 are introducing a relatively large exposure to
7 a distribution of kind of biological genetic
8 background, and so it is probably the tail of
9 the curve, and that is why kind of the post-
10 marketing surveillance is really when you are
11 likely to see that.

12 Therefore, the issues of
13 autoimmunity are probably akin to that. So it
14 would be very difficult in the pre-licensure,
15 in the animal model necessarily to detect that
16 unless you know of a specific way to study
17 that.

18 The concern that I would like to
19 raise to the group, however, is really the
20 thimerosal lesson, and that is the problem we
21 got into with thimerosal is that we looked at
22 each issue and each vaccine by itself, but we

1 didn't recognize that in real life what
2 happens is that the child or the adult
3 frequently gets multiple vaccines, and that
4 when you add up the thimerosal dose across
5 that schedule, that is when you run into
6 trouble.

7 So then, given the previous
8 comment that, if we are introducing kind of
9 new adjuvants that attack -- or kind of induce
10 different parts of the immune system in kind
11 fairly strong ways, is there an animal model
12 way in which we want to look at that before we
13 actually move forward with a schedule?

14 DR. GRUBER: Yes. I think that is
15 a good point, and it was a question that comes
16 later on. We will see if we can get to this,
17 to evaluate this a little bit more.

18 I just wanted to finish up on at
19 least this part, considering the time. In
20 toxicology studies for vaccine antigens, one
21 of the parameters that we are looking at is
22 the antibody response, and then in terms of

1 other parameters that we checked they are
2 looking at clinical chemistry, hematology
3 parameters.

4 Recently, because of the
5 formulation of vaccine antigens with novel
6 adjuvants, recommendation has been made to
7 also evaluate additional parameters such as
8 CRP and fibrinogen levels.

9 I would like to hear a little bit
10 thoughts from the podium from the roundtable
11 on this. And again, I wanted to stress the
12 point, just because this is in a question
13 doesn't mean that the agency is making this a
14 requirement or says this because of some
15 safety signal. These are just things that we
16 thought about to perhaps -- You know, if we
17 look at these parameters, could it lead us to
18 a more comprehensive evaluation of the safety
19 of the adjuvant component and, if not, well,
20 we are happy to hear your comments and
21 concerns on that issue.

22 So should other parameters such as

1 cytokine levels or additional biomarkers be
2 assessed? Who wants to take that question?
3 Okay, we will take Deborah first and then Jan.

4 DR. NOVICKI: I think that it is
5 fairly straightforward to look at things like
6 CRP or fibrinogen, and I mentioned yesterday,
7 if there's people in the audience who weren't
8 here yesterday, we routinely measure
9 fibrinogen along with the other coagulation
10 parameters in our tox studies.

11 So adding CRP, it may give you a
12 slightly more sensitive measurement perhaps or
13 a slightly different time course post-dose
14 than measuring fibrinogen, but they are
15 probably telling you about a similar aspect of
16 the biology.

17 As far as looking at cytokine
18 levels, my favorite species, because I can
19 give the clinical dose by the clinical route,
20 etcetera, is the rabbit whenever it is
21 appropriate and there is no reason not to use
22 it, and reagents are not readily available for

1 doing cytokines and cell sorting, etcetera, in
2 rabbits.

3 Now is it an area of interest for
4 me, for companies or something, to start to
5 work on these kinds of things? Yes. That
6 would be a really good tool. Then you could
7 actually make a better link.

8 We do a lot of our preliminary
9 work in mice. We ultimately end up in people
10 where a lot of companies now are starting to
11 take translational medicine approaches and
12 generating some similar data in humans. Then
13 you've got the tox species sitting in the
14 middle where you don't look at some of the
15 parameters that might bridge from the mouse to
16 the man.

17 So I would be very interested. It
18 is an area that I think we would have to work
19 on, though.

20 DR. VAN DER LAAN: Thanks. For
21 the biomarkers, there are numerous cytokines
22 and other endpoints possible. I think that

1 you have to make a reasonable choice for that.
2 It should have any relationship. Why are you
3 just studying a type of cytokine? Is it to
4 different shapes and type of response? I
5 think that should be clearly indicated, and
6 why is that then chosen as a type of
7 biomarker? What should it tell you?

8 Then if it is to tell you, for
9 instance, comparability between species, what
10 is the most relevant species? I think that
11 that is very important. Do mice, or can be
12 used also other species. But is there any
13 relationship between a biomarker and a final
14 effect? Is the studying of CRP or fibrinogen
15 then a response indicator for a clinical
16 effect? That is an important issue. You
17 first think for a blind.

18 Toxicology is just trying -- and
19 I'm happy with the discussion that, from the
20 clinical point of view, toxicology is indeed
21 mainly -- and you see that in WHO documents --
22 mainly to guide the study design for the

1 clinic. All other effects are later on and
2 just highlighting some aspects, but some
3 aspects in animal studies can be done at a
4 higher dose and might be more -- give more
5 feeling of what can happen in an organism;
6 whereas all that type of studies cannot always
7 be done in humans.

8 So we have to be careful in this
9 type of using of biomarkers. What is the real
10 meaning of these type of biomarkers?

11 DR. GRUBER: Thank you very much
12 for this comment. We will take one more, I
13 think, on this issue. then we will move on.

14 DR. VAN DEN BOSSCHE: Just a very
15 short comment. I think we may be discussing
16 this question not that much in terms of what
17 cytokines exactly. I think we should be
18 thinking about what are really cytokines,
19 depending on the animal species we are testing
20 that are, for example, relevant for local
21 inflammation.

22 I think the parameters that are

1 there, I guess, in most of the animals are
2 relevant, the CRP, fibrinogen, for example,
3 and also which are the parameters could be
4 markers, not necessarily biomarkers but
5 markers, for systemic distribution.

6 These are really the two types of
7 phenomena we are concerned about, local
8 inflammation, systemic distribution. So to
9 the extent that the parameters we are testing
10 are relevant for the animal species we are
11 doing the testing in, I think this would make
12 sense, yes.

13 DR. LEVY: Just a quick comment.
14 This is Ofer Levy, Harvard Medical School in
15 Boston Children's Hospital.

16 It is something we have struggled
17 with, and I think some of the members of the
18 panel touched on it, which is it is easy
19 enough to do to measure these cytokines, but
20 does it correlate in any way? Is it at all
21 predictive of toxicology or other downstream
22 problems? I think that is very important to

1 keep an eye on.

2 It would be nice if we had a body
3 of literature that indicated the level of
4 cytokines for the already approved vaccines
5 that are induced in humans, so that you have
6 a backdrop on what you are comparing to.

7 My concern is that, if you start
8 measuring for a lot of things with novel high
9 sensitivity assays and pick up trace
10 production of certain cytokines and then
11 somebody pulls out a paper from Journal of
12 Immunology and says, well, cytokine X has been
13 associated with encephalitis in a certain
14 model, the next thing you know somebody takes
15 that as proof that your vaccine is going to
16 cause autoimmunity. That is very weak kind of
17 thinking.

18 So, obviously, we need to proceed
19 in a thoughtful way and with some caution. I
20 think it is good to measure these, but in a
21 thoughtful way, and I think it is complicated.

22 PARTICIPANT: I don't know if I

1 need to say anything more than what was just
2 said, because just adding things on is
3 regulatory creep. Even CRP -- you know, we
4 have been asked -- We do fibrinogen, and then,
5 hey, why don't you do CRP? Well, that's not
6 going to help us understand anything better.
7 It is just another marker.

8 Cytokines? I can see -- you know,
9 after the TeGenero event, I can see everybody
10 freaking out about some cytokines. If I am
11 working with many of the adjuvants that I work
12 with, I expect to see a lot of cytokines. So
13 -- systemically, whether it is happening
14 locally or systemically or whatever.

15 So I don't see much value in the
16 safety. If the biology requires you to do it
17 or there is some reason -- we are making this
18 adjuvant because it doesn't produce IL-6
19 systemically -- well, there's a good reason.
20 It is not necessarily there's a "check the
21 box" safety endpoint.

22 If you had an extended acute phase

1 response, you would see that in other ways.
2 You would see that in histopath in the liver.
3 You would see it everywhere.

4 DR. NOVICKI: I don't want to be
5 misinterpreted and having anybody think that
6 I am proposing to measure all of these
7 materials in large clinical trials. That
8 wasn't the point at all.

9 Really, what I was thinking about
10 was trying to grapple with some of the
11 disconnect between what we see in animals --
12 I mean, vaccines -- The vaccines that we have
13 worked with, we almost see -- We see very few
14 signals, and actually seeing a reversible
15 elevation in fibrinogen is one of the only
16 things that we see with a lot of our products
17 that are adjuvanted with MF59.

18 So for me, in a way, it is a
19 marker that something is happening that I am
20 seeing an effect that I expect to see, and
21 seeing that its reversibility is happening in
22 the appropriate time frame that I am used to

1 seeing is helpful from the standpoint of
2 evaluating that the biology is similar to
3 things that we have seen before, and it is not
4 something that is persisting for much longer,
5 which might be an indication of a longer
6 systemic reaction.

7 So I'm not saying that we should
8 measure fibrinogen necessarily in clinical
9 trials even. I am just saying that for our
10 purposes that is a helpful marker for our
11 adjuvant.

12 I think that -- I was also
13 thinking a little bit more in an investigative
14 mode when I was thinking about trying to
15 bridge between mouse, rabbit and man. So I
16 think, when we -- A mouse can't complain about
17 malaise. A rabbit doesn't tell us that it's
18 got a headache. So some of the adverse things
19 that we capture in clinical trials, if we are
20 trying to select, say, internally amongst a
21 panel of adjuvants, some of this sort of
22 information could be helpful from a selection

1 standpoint to try to -- you know, if you can
2 find a profile that is predictive of
3 immunogenicity without as much systemic
4 inflammation, that might be a better choice to
5 investigate than another that has a slightly
6 different profile.

7 So I was not strictly thinking
8 about GLP and clinical trials as much as areas
9 where you might want to be a little bit more
10 investigative.

11 DR. GRUBER: One more comment.

12 DR. GOTTESDIENER: Yes. Keith
13 Gottesdiener, Merck. I am fairly new to the
14 vaccine area. I am a clinician who actually
15 grew up in the small molecule area.

16 To me, the issue really is how
17 predictive is -- The previous speakers had
18 said, how predictive are the things we measure
19 in the animal tox studies to help us in the
20 clinic I don't see any other purpose, really,
21 of doing these things.

22 On the other hand, I share the

1 concerns of other speakers that just measuring
2 these things without understanding their
3 meaning is really worthless and will cause a
4 lot of anxiety.

5 This reminds me, actually, a lot
6 of the discussions that happened with the
7 agency a couple of years ago about genomics
8 testing and clinical trials where the agency
9 actually took -- in the U.S. and in the EU
10 took really a leading role at forming a safe
11 harbor type of approach.

12 What they said is we would like to
13 collect that data. We are not going to make
14 interpretations upon that data today, because
15 we have no basis upon which to make those
16 interpretations, but we are going to begin
17 collecting a database so, as we take those
18 things into the clinic, we can begin slowly
19 over time -- maybe it will be a 10-year plan -
20 - to sort how valuable those things are going
21 to be.

22 At the moment, if we measure these

1 things and we don't have that safe harbor, I
2 think many companies are worried that those
3 tests will be misinterpreted.

4 On the other hand, I think
5 everybody would agree that trying to
6 understand prospectively how valuable things
7 are in tox studies to eventually predicting in
8 the clinic would be a laudable goal.

9 So I actually challenge the
10 agencies to think about ways where they could
11 actually be the mediator of our process, where
12 we could collect the information without
13 detriment to the present and yet still build
14 plans for the future.

15 DR. GRUBER: So we decided we are
16 going to advance to the next slide, because we
17 wanted to actually get a couple of discussions
18 going on the animal species on the point on
19 how in vitro assays should -- or can they be -
20 - incorporated into nonclinical safety
21 assessment, and then the issue that was
22 brought up by the CDC on how to evaluate and

1 test potential combinations of different
2 cytokines that are formulated with different
3 vaccine antigens and may be given
4 concurrently.

5 So this is basically -- For me,
6 this is maybe the most difficult issue to
7 answer, and that is the question: What
8 constitutes a relevant animal model?

9 Perhaps we can actually take these
10 first two questions. Is it sufficient to test
11 in only one animal species, and what
12 constitutes a relevant animal model, together;
13 because in my view at least, it is very
14 difficult to really get your arms around to
15 get even one animal species that you may
16 consider relevant.

17 That is the reason, I think, at
18 least why from a regulatory perspective we
19 have made the recommendation that it is
20 sufficient for vaccines to test in only one
21 animal species. However, the question was
22 raised again: Is that sufficient when you

1 look at the safety assessment of adjuvants?

2 I would like to make the point
3 that this issue was not necessarily raised by
4 the regulatory agency. So I would like to
5 receive some comments on the issue about do we
6 redefine what is a relevant animal model?
7 Hana, you wanted to make a comment? Thank
8 you.

9 DR. GOLDING: Yes. I think this
10 is -- Again, I am just expressing my sort of
11 personal thoughts, not as a representative
12 necessarily of the regulatory agency. But the
13 more I am thinking about this whole
14 development of novel adjuvants -- and I really
15 want to echo what Derek was saying --
16 especially when are starting to look at novel
17 adjuvants, the more we know about them, the
18 better.

19 I would like to really propose
20 that what we need to think as a group is what
21 I would call progressive testing, and this
22 progressive preclinical testing or animal

1 testing may start during the discovery period.
2 It clearly has to be tailored to the type of
3 adjuvant.

4 If it is a TLR agonist, clearly
5 you want to test it in the best animal model
6 that is appropriate in terms of specie
7 specificity, but sometimes that is not
8 available immediately.

9 So I don't think we should have to
10 think right now what are the tests to do in
11 the rabbit. Rather, we have to think how to
12 really match our evaluations of a novel
13 adjuvant to the product itself, and what
14 additional testing one can do.

15 Right now when we look at immune
16 response to a novel adjuvant in combination of
17 vaccine, really, we are measuring the immune
18 response, namely the antibody response, the
19 CTL responses.

20 We haven't actually started to
21 look about are we inducing any changes to the
22 Treg. Are we using any changes to the level

1 of T17. Some of those novel type of subtypes
2 of T cells that are so important to keep the
3 balance of effect versus autoimmunity.

4 Maybe this is the time during the
5 discovery period when you are using an
6 adjuvant with a known biological activity
7 that, on the one hand you introduce it to
8 increase the type of antigen specific immune
9 response. What other type of disturbance
10 overall to the immune system may be induced?

11 I think this kind of sort of
12 stepwise approach doesn't necessarily mean
13 that animal studies stop when the clinical
14 studies start. Very often, we really did not
15 learn anything or did not find any safety
16 signals in the rabbits or the preclinical
17 studies, moved into the clinic, and all of a
18 sudden we see reactions which we did not
19 expect.

20 There is nothing wrong of saying,
21 okay, now based on these signals in a small
22 number of people, can we go back and find the

1 appropriate animal model? It might be
2 nonhuman primate. It might be another model
3 that will help us to understand this
4 particular reaction.

5 So I think we shouldn't look at
6 the sort of preclinical studies or animal
7 studies as a sort of stand-alone, one-time
8 talks. You do it. You finish with it.
9 Whatever you get, you don't have to revisit.
10 I would like to see it more as a sort of
11 progressive approach that is tailored to the
12 type of the adjuvant and continue even in
13 parallel with the clinical trials.

14 DR. SEDER: So I would like to
15 follow up a little bit on that. There is
16 important species differences in the
17 expression of Toll-like receptors between mice
18 and primates and humans.

19 So most of the studies that have
20 been done with adjuvants have always looked at
21 antibody. You really can't assess T cell
22 responses in rabbits, and you will get very

1 different results in the case of, say, CPG
2 from what you would see in a mouse, from what
3 you would see in a nonhuman primate.

4 So if you are after T cell
5 responses, you are likely going to have to do
6 trials in nonhuman primates to try to predict
7 whether Toll-like receptor ligands or other
8 adjuvants would be effective.

9 You have reagents that exist in
10 primates similar to human to measure such
11 responses that don't exist in rabbits. So at
12 least in terms of understanding immunogenicity
13 for cellular immunity, it is likely you are
14 going to have to use primates. They also
15 represent an outbred species. So you can get
16 some idea of the type of repertoire you get
17 that wouldn't sometimes be predictive in the
18 mouse, because they wouldn't express --
19 because they are restricted by certain HLA
20 haplotypes.

21 So I think it is a problem,
22 because primates are expensive, and they are

1 limiting. But in terms of going forward with
2 more novel types of Toll-like receptor
3 adjuvants for T cells, you are likely going to
4 have to enter into doing primate studies, and
5 it will give you a lot more information than
6 what currently exists.

7 The other thing that came up on
8 this slide was using in vitro predictability
9 with Toll ligands really would mislead you.
10 So Toll-7 and 8 is a small molecule that gives
11 you very robust in vitro responses, but in
12 vivo, unless it is formulated, would give you
13 very poor responses.

14 By contrast, poly IC is very
15 robust in vivo, because it acts on a lot of
16 cells that you are not testing from peripheral
17 blood. Yet in vitro, it gives you a relative
18 modest response.

19 So in using those type of
20 screening assays, you will be very misled
21 again, unless you go in vivo and do these in
22 primates.

1 DR. FRIEDE: Okay. So just to
2 maybe combine the two slides, considering in
3 vitro analysis with animals. There is the
4 risk of high degrees of polymorphism in the
5 receptors of some of these Toll-like receptor
6 agonists.

7 So the relevant animal model would
8 be an animal model that displays a receptor
9 which recognizes Toll-like receptor agonists.
10 It would be very important to use human cells
11 and verify that the animal that you are going
12 to use actually is able to recognize in a
13 similar manner to humans, and this will also
14 then enable you to design the clinical studies
15 in a maybe more relevant way, because you may
16 see not only polymorphism between the animals
17 and people but also between people and people,
18 especially between populations.

19 For many of the vaccines which you
20 are trying to make, malaria, TB, HIV, we will
21 be going across multiple populations. So
22 being aware of receptor polymorphism at an

1 early stage will be important to design these
2 clinical studies, because this could affect
3 toxicology as well.

4 DR. GRUBER: I'm sorry. We have
5 Dr. Alving, and then Dr. Van der Laan, and
6 then Dr. Warren.

7 DR. ALVING: (Off microphone
8 comment) -- The facial palsy was observed in
9 humans.

10 I have a question. Could this
11 have been picked up with another animal model?
12 Would it have been -- Clearly, when you are
13 giving intranasal administration, you might
14 get different results if you give it to a
15 mouse than if you give it to a baboon, for
16 example.

17 The question -- but you might get
18 the same receptor binding characteristics that
19 might cause toxicity that would cause
20 neurological effects that might have been
21 observed more easily in some other animal.

22 So what I would say in a

1 circumstance like that where everybody knows
2 that e. coli enterotoxin or cholera toxin bind
3 to gangliocyte GM1 like a covalent bond, and
4 that you might get retrograde travel into the
5 neurological system, causing a facial nerve
6 palsy by giving it intranasal, is there some
7 way that that could be looked at?

8 I would advocate a more
9 intelligent thing, looking at what is known
10 about the particular adjuvant, and how can you
11 perhaps address a specific circumstance.

12 DR. GRUBER: We will have Dr.
13 Garcon commenting on this very comment first,
14 and then it is your turn, Jan.

15 DR. GARCON: I just wanted to
16 point out that that was identified, actually,
17 and there was -- we saw that in mice. When
18 you do give intra-nasal in mice, you do have
19 retrograde transport in the passage in the
20 olfactory bulb. So that was defined and seen,
21 and that is the reason why we didn't move
22 forward, actually, with clinical trials with

1 intranasal vaccines.

2 DR. VAN DER LAAN: Thanks.

3 Yesterday I had also given my view on what is
4 a relevant animal model. Also for adjuvants,
5 of course, I can describe what work has been
6 done.

7 What we have done in Europe is a
8 small study on the applicability of pigs and
9 especially many pigs in this respect. That
10 might be a very good alternative to the high
11 use of nonhuman primates, which is
12 politically, at least in Europe, highly under
13 pressure. So many pigs are -- pigs are a very
14 good track device, and many pigs are
15 immunologically not different from the land
16 raised pigs, and there are a lot of reagents
17 available. That is at least one.

18 That brings me also to the point
19 of the special populations, elderly and
20 pediatric. One of the concerns that was
21 expressed last week in the Vaccine Working
22 Party when we prepared this adjuvant workshop

1 from a regulator point of view is that the
2 adjuvants -- the response to adjuvants is not
3 well known, whether it depends on the age, and
4 especially as a lot of vaccines are given very
5 early in life, we do not know what is the
6 effect in small children on long term
7 imprinting in the immune system.

8 There are effects -- There are
9 studies, for instance, on pertussis
10 vaccination in Brussels indicating that early
11 vaccination has indeed important consequences
12 in inducing changes in the immune system, the
13 very early immune system.

14 DR. WARREN: I just wanted to make
15 a few comments as well on some of the other
16 speakers. Hana Golding made a very good
17 comment in the fact that perhaps we should be
18 a little bit more progressive in terms of not
19 necessarily thinking that animal in vitro
20 studies stop when the clinic begins.

21 In fact, in many cases we have --
22 I think it is important to look at clinical

1 samples in in vitro assays to help understand
2 why things did go wrong and understand why in
3 that subset of the population things may have
4 gone wrong. I think that her idea of these
5 more progressive studies is a very good idea.

6 Then I wanted to, in the art of
7 being controversial, go back to some of the
8 things that Bob Seder had said. Sorry, Bob,
9 I figured that this is part of the fun up
10 here, is the fact that he made sort of a
11 blanket statement of, you know, in vitro
12 models have not been as predictive and go to
13 the nonhuman primate. But we have actually
14 seen examples in our lab where the nonhuman
15 primate has actually been incorrect in in
16 vitro assays, have been correct when going to
17 the clinic.

18 In fact, I could probably come up
19 with more examples where the nonhuman primate
20 model has not been predictive for human
21 responses. You could just go to every HIV and
22 cancer trial and come up with examples.

1 I think the idea there is that
2 when making comments about in vitro studies,
3 you have to sort of take into account not
4 every in vitro study is the same. Are you
5 using just PBMC cells? Are you using one cell
6 type? Are you looking at cell lines or
7 primary cells?

8 I think that not every in vitro
9 assay is alike, just like not every animal
10 model is alike as well.

11 DR. SEDER: Can you just give me
12 any examples of what you are talking about
13 where it wouldn't be predictive and what you
14 have done, and what trials you are referring
15 to?

16 DR. WARREN: I'm not at liberty to
17 say right now, but we did indicate -- I did
18 indicate it, but I'm not at liberty to say.
19 And I didn't mention T cells. It was more
20 toxicology.

21 DR. GRUBER: I was going to take
22 two comments from the floor here. Go ahead.

1 DR. GUPTA: Rajesh Gupta from
2 CBER. I think the adjuvant situation is so
3 complex that you cannot generalize that one
4 species or more than one species. I think you
5 have to leave flexibility, depending upon the
6 relevance of the model, that if you show that
7 the animal model is relevant with the
8 appropriate receptors and all that, one
9 species may be enough. But if it is not
10 appropriate or a relevant model, maybe you
11 have to go for two species.

12 They may not be even relevant, but
13 still you have more chances of picking up
14 something, if you are doing more species.
15 Similarly, with the in vitro, I think, assays
16 also.

17 I think we can keep on criticizing
18 saying that they don't matter or they matter,
19 but doing more, if you show relevance with
20 your particular adjuvant system, I think it
21 makes sense. So I would say that we should
22 have flexibility of more than one animal model

1 in addition to the in vitro assays also.

2 DR. LEVY: Ofer Levy, Boston

3 Childrens Hospital. I just wanted to amplify

4 on the importance of different species. The

5 topic today is adjuvants, and a lot of these

6 adjuvants engage the innate immune system, and

7 it is known that the innate immune system is

8 hyper-variable between mammalian species. It

9 is one of the regions of greatest variability

10 between mice and humans, for example, and

11 several of the speakers on the panel spoke to

12 that.

13 So we are going to have to all be

14 very thoughtful as to what animal models we

15 look at.

16 The other point I wanted to bring

17 up is similar to the point I made about the

18 cytokines. I think the new subclasses of T

19 cells that have been found are very important

20 biologically, and probably important

21 clinically, but I still don't think we are

22 collectively smart enough or knowledgeable

1 enough to know how an in vitro assay of those
2 cells corresponds or not to any toxicity.

3 So if we are looking at T
4 regulatory cells, we know that they can
5 suppress adaptive immune responses, and we
6 know that, likely, a transient and local
7 reversal of T reg function is probably a
8 feature of most effective vaccinations.

9 So now we have T cell phenotypes
10 that we can test for by flow that we weren't
11 even aware of 10 or 20 years ago, and probably
12 what is happening when we use the vaccines
13 that we already have approved, is that there
14 is a transient reversal of T reg suppression.

15 So once again, I am just saying it
16 is good to gather this information, but I hope
17 we don't jump from saying, well, this adjuvant
18 can cause a local transient T reg reversal,
19 therefore it is going to lead to a massive
20 autoimmune catastrophe.

21 DR. GRUBER: One more comment from
22 the floor.

1 DR. PETROVSKY: So I don't know
2 the answer to this, but I guess an interesting
3 ethical issue has been raised here, and I
4 think Nathalie sort of alluded to this.

5 What happens when companies
6 identify toxicity issues and stop development,
7 but then watch other companies developing
8 similar or the same product, perhaps because
9 they haven't done the same due diligence? Is
10 there an ethical issue there about disclosing
11 that information, either to regulators or to
12 the public or to the scientific community, to
13 alert that there is an issue that has been
14 identified? And then maybe you avoid a
15 disaster in the clinic.

16 DR. GARCON: I would like to
17 answer that. First, 1AT is not the next. So
18 I can't comment from other that has been used.
19 The data we generated were disclosed to the
20 regulatory agencies.

21 DR. PETROVSKY: Can you comment on
22 how they handled that in terms of approving

1 the other clinical studies?

2 DR. SEDER: Can I just say one --
3 This is not one size fits all. If you look at
4 adenoviral vaccines, what you get in the mouse
5 to the primate to the humans in terms of
6 different serotypes is always predictive.
7 Thirty-five is the weakest; 26 is better, and
8 ad-five is the best.

9 So right from a mouse you can kind
10 of predict what will happen in the human.
11 That is very clear. Most of us in this room
12 know that, when you do DNA vaccines in mice,
13 it works beautifully. Then you go to
14 primates, to humans, it's much less.

15 With Toll ligands I would argue
16 that it could be just misleading based on the
17 differences in biology. So if you were
18 talking about adenoviral vaccines, the mouse
19 would be a perfectly good model to predict
20 probably what you will get.

21 So it depends on what you are
22 looking at. Since this room is focused on

1 specific adjuvants, the only point was that
2 you need reagents in the species especially
3 related to T cells. These antibodies are easy
4 to measure across multiple different
5 antibodies, but that is not really the issue
6 going forward.

7 We have plenty of adjuvants for
8 antibodies. What we desperately need are much
9 better adjuvants for TH1s and CD8 cells.

10 DR. GRUBER: Yes. So, Becky, you
11 have a comment to make? Okay. Then we wrap
12 this up. Go ahead.

13 PARTICIPANT: Thank you. So the
14 question that Carl brought up that Nathalie
15 has provided us information, I think is very
16 instructive, and I wondered, Nathalie, whether
17 this problem that you discovered was actually
18 discovered in the course of doing your
19 discovery work and non-GLP studies or if it
20 was only discovered when you actually moved
21 forward into formal GLP toxicology studies, or
22 can you disclose that?

1 DR. GARCON: So we have looked at
2 intranasal vaccination and valued adjuvants to
3 be used intranasally, and that includes the
4 adjuvant system we have. During the course of
5 those evaluations, we do look preclinically at
6 the safety profile of what we are using, and
7 that can be different assays and most of them
8 being in the European guidelines.

9 Intranasal vaccination is a
10 different aspect, which is not covered today
11 by guidelines, and we did look indeed at what
12 was the effect of immunomodulator when given
13 intranasally in the mouse. That is how we saw
14 that.

15 PARTICIPANT: But was that a GLP
16 study or was that an earlier sort of pilot
17 study?

18 DR. GARCON: That was pre-GLP,
19 yes. That was before going into human.

20 PARTICIPANT: Okay. So I guess my
21 point is I want to reiterate or sort of
22 reinforce -- I think Debbie was the one that

1 said this earlier -- that perhaps a lot of
2 these safety issues -- In these animal
3 studies, we can only look for frequent or sort
4 of severe things.

5 We are not going to find the
6 things that Bob Chen is looking for in these
7 preclinical animal studies. Only when you
8 have large databases are you going to find
9 those sorts of problems.

10 So I think that a lot of the
11 animal studies that are done in discovery work
12 and in immunogenicity testing actually could
13 be very informative for finding the kinds of
14 things that the regulators are trying to find
15 with these studies.

16 I think the drug toxicology
17 studies -- often by the time you get to that
18 point, you have already identified your
19 starting dose. You have done that in your
20 immunogenicity studies, which were non-GLP
21 studies.

22 You are going forward into the

1 toxicology study with that dose you have
2 already decided you were going to start with.
3 So I think by then it is almost too late to be
4 defining, quote, "your safe starting dose."

5 Also, Debbie pointed out the
6 difficulty in bridging between -- You do these
7 studies in the animals even measuring the same
8 parameter, let alone the fact that there are
9 many parameters you can't measure in the
10 animal, that you ask the human do you have a
11 headache, do you have malaise, do you have
12 myalgia. But even when you look at the same
13 parameters, something like ALT, when you
14 measure it in the animal, you are doing -- you
15 are comparing group means between the control
16 arm and the treated arm, and you are looking
17 for a signal based on statistically
18 significant differences between group means.

19 When you do your Phase I study and
20 you look at ALT, you are looking at the
21 individual, and you are comparing that
22 individual's result to a normal range and

1 deciding whether or not that it had an adverse
2 event based on a toxicity scale that says it
3 is so many times the upper limit of normal.

4 So you can't even bridge the tox
5 GLP data to the human data, by and large. So
6 I think it is very difficult to expect these
7 toxicology studies to do what I think the
8 regulators want done for vaccines, and even
9 for adjuvanted vaccines.

10 So I think we need to be more
11 mindful about looking for things in the course
12 of even the non-GLP studies, immunogenicity
13 studies, etcetera, and looking to those
14 studies more for our safety parameters,
15 because I think it is very difficult. These
16 toxicology studies really aren't serving the
17 purpose that, I think, we need.

18 DR. GRUBER: Thank you for this
19 comment. I don't think I fully agree with
20 that, but we are going to go ahead and hear
21 Bill, and then we are going to spent the last
22 10 minutes discussing yet another question.

1 Go ahead, Bill.

2 DR. EGAN: Thank you. Looking at
3 these questions, they are very, very
4 complicated and difficult, and if we look, for
5 example, about just one versus two animal
6 species, I think it is very likely that one
7 answer does not fit all and that it depends on
8 the type of adjuvant that is being looked at
9 and the mechanism of action of that adjuvant,
10 at least to the extent that it is known.

11 I think it also depends on the
12 questions that you want answered. For
13 example, if an adjuvant is a TLR agonist, do
14 you want to animals to measure cytokine
15 responses, and then what do you do with that
16 data? Are you looking for unexpected
17 responses or interactions with other TLRs or
18 for something else or organ pathology?

19 Also, designing what to look at
20 versus the populations for which the vaccine
21 is intended or for which the adjuvant will be
22 used, elderly or pediatric or

1 immunosuppressed.

2 I think, as we answer these
3 questions, it is necessary to remember that
4 the issues with, for example, a CPG oliogo
5 versus the e. coli labeled toxin versus, say,
6 an oil and water emulsion with squalene are
7 very, very different and difficult to address
8 with one single prescription.

9 So I think we are going to have to
10 come down to something that is more tailored
11 to the particular adjuvant.

12 DR. GRUBER: Yes. I thank you for
13 these comments, and I think they are very well
14 taken.

15 I think what we have heard,
16 really, from this discussion is that we really
17 have to allow flexibility. We have to look at
18 the compound under study. We have to see what
19 is the perceived mechanism of action, if there
20 is an animal model available, if there is no
21 animal model available, and depending on that,
22 I think, we will have to allow flexibility to

1 build in other outcome measures to perhaps
2 help us to make an informed decision.

3 That can be the pre-toxicological
4 assessments that Becky referred to, what we
5 often refer to as pilot immunogenicity and
6 mechanism of action studies, together with
7 approaches to look at in vitro models, as
8 pointed out by Dr. Warren.

9 I think, for these novel
10 compounds, we really have to sort of keep
11 thinking out of the box, if you will. That,
12 of course, is complicated by the fact that, if
13 you really want to do a toxicity study, your
14 animal model has to lend itself also for this
15 type of evaluation, which is why we usually
16 use the rabbit or the rat or the mouse.

17 There is a historical control
18 database. There is a lot of experience with
19 that, and getting into issues such as the
20 nonhuman primate -- I mean, the agency or the
21 Office of Vaccines has always taken the
22 approach that we are using these models only

1 when absolutely necessary, because we also
2 have to be mindful of the refinement,
3 replacement and reduction of animal models,
4 and then coming in saying, well, we have to
5 use the nonhuman primate, because we don't
6 have any other animal model available to us.

7 I think we have to think about
8 that very carefully and maybe have this as a
9 last resort after we look at all other
10 options.

11 So I would like to actually come
12 to the perhaps last issue to be discussed, and
13 I am going to get up and flip forward here.

14 I think we have heard some
15 comments about testing or not testing the
16 individual components in an adjuvant system.
17 We are going to skip this.

18 I wanted to get back at something
19 that was brought up by Dr. Chen, I think it
20 was, about -- Is this working? It's not
21 working, right? I'll go back to my place.

22 I wanted to actually talk a little

1 bit about the -- I think it is the second
2 bullet perhaps combined with the first, and it
3 speaks to the potential exposure to multiple
4 types of adjuvants, either concurrently
5 administered or over multiple years.

6 So let's take a theoretical
7 example. You have a vaccine that is indicated
8 for adolescents, and it is a novel vaccine.
9 It is combined with an adjuvant. The
10 adolescent population also is supposed to
11 receive a second vaccine that is also combined
12 with another adjuvant.

13 So it is getting at testing of
14 concurrent vaccine combinations that are
15 combined with novel adjuvants, and it gets at
16 the fact, what if some of these vaccines have
17 to be given or administered over multiple
18 years such as adjuvanted influenza vaccines?

19 Can we even get our arms around
20 that in the preclinical setting or is that
21 something that should best be addressed in the
22 clinical arena?

1 So if I can hear some comments on
2 this issue.

3 DR. FRIEDE: Since nobody else is
4 doing it, I may get myself into trouble.

5 I think this is very difficult to
6 do at the preclinical level. My gut --
7 shooting from the hip, I would say, that
8 initially we would have to manage this at the
9 clinical level, but I would suggest that
10 research is undertaken to actually to try and
11 examine whether at the preclinical level we
12 can pick up anything which is interesting.

13 I think we are still so far away
14 from this that we just don't know. So for the
15 moment, I would say clinical, but we should be
16 doing some research to see whether there are
17 animal models that could help us identify
18 this.

19 PARTICIPANT: I had a comment on
20 this. Probably, your pharmacological data in
21 the -- both in the clinical aspect as well as
22 preclinical data in developing this can

1 facilitate that, in that you are looking at
2 clearance from the injection site and
3 activation of the immune system, and clearance
4 of the material. So that you are not going to
5 get a cumulative effect, as was brought out
6 for the thimerosal comment.

7 If things are allowed to clear out
8 in sufficient amount of time, you won't get
9 this, say, multiple effect from different
10 adjuvants and different antigens being
11 administered at the same time.

12 DR. ALVING: I just want to point
13 out one thing, and that is that, unless you
14 are talking about one of Darwin's tortoises
15 that lives more than 100 years or something,
16 when you are talking about exposure over
17 multiple years, the life span of a mouse, for
18 example, is about two years.

19 I actually have done injections of
20 Lipid A and liposomes containing Lipid A
21 sequentially over the entire lifespan of mice,
22 and I actually published that. Actually, what

1 I found was injecting normal saline had a
2 devastating effect on the mice in the sense
3 that all of the mice -- or I would say most of
4 the mice, actually, all had tumors when they
5 were at the end of their lifespan.

6 So the question is, when you are
7 talking about giving adjuvants over multiple
8 years in animals, what is the animal species
9 that we are talking about here? This is a
10 really important question.

11 DR. VAN DEN BOSSCHE: Long term
12 studies, animals or humans, I think there are
13 -- Just to pick up the last question, there
14 are for some exogens long term studies with
15 monkeys for 10 years and ducks for seven
16 years, but those are exceptional studies.

17 Later this week I will have a talk
18 on carcinogenicity, and I would like to get
19 rid of the two-year mouse and two-year rat
20 study, because of all that spontaneous tumors.
21 They do not indicate anything. So we should
22 not go into that direction.

1 On the one hand, we have
2 limitations in our animal studies, and there
3 are important aspects in human studies. So
4 what type of endpoint should be studied in
5 humans, and how should we monitor?

6 I think it is important,
7 therefore, to have advantage of the request
8 for risk management plan in the regulatory
9 field and to ask companies to have a very good
10 monitoring for the first 10 years for specific
11 aspects that cannot be reasonably studied in
12 animals.

13 So we should not -- We cannot
14 over-ask our animals, and what is the most
15 appropriate timing? I don't know. We have
16 discussed that last week with several
17 clinicians, and some people said, yes, and all
18 the immune reactions should be public within
19 10 years and, if it is not, okay. Then it
20 should be okay, but at least there should be
21 a careful follow-up.

22 I am not sure whether that will be

1 discussed in the remaining part of the day.

2 DR. SUN: Wellington Sun from
3 CBER. I am relatively new to the vaccine
4 regulatory field, but from what I have seen,
5 these questions posed, I think, maybe should
6 be posed in a different way.

7 I don't think there should be much
8 argument in terms of looking at long term
9 effects of these adjuvants and the cumulative
10 -- potential cumulative toxicities, but the
11 way the vaccines are developed in this country
12 is by companies, and companies have their own
13 adjuvants, and some of them are proprietary.

14 So the question, to me, is not
15 whether these studies should be done, but by
16 whom. I think in developing a product many
17 companies will not be looking at adjuvants of
18 other companies and looking at how that would
19 affect toxicity. Even if we had good animal
20 models to predict those kind of toxicities,
21 that won't be done by the private sector, I
22 think.

1 So I think there is some
2 responsibility by the public sector to address
3 these questions, but I am not sure how in this
4 context right now.

5 DR. GRUBER: Thank you very much
6 then. Are there any additional comments from
7 the podium here?

8 If that is not the case, I would
9 like to conclude this roundtable discussion.
10 I thank you very much. I think it was very
11 helpful, very stimulating, and I think we are
12 going into the next -- the clinical session of
13 this workshop. Thank you very much again.

14 (Applause.)

15 MODERATOR SLATER: Thank you all
16 very much. We are going to go ahead and start
17 the next session right away. So please take
18 your seats. There will be a break at 10 after
19 10. Please take your seats.

20 Everyone, take your seats. We are
21 starting Session 4. Thank you very much.
22 Take your seats, please.

1 If you will look at the schedule,
2 Session 4 is actually quite long. It goes
3 from now -- you still can't hear? No? I'm
4 hearing an echo. Okay.

5 Session 4 begins now. We are
6 continuing for about four and a half hours,
7 but that is not so bad, because we actually
8 have lunch and two coffee breaks. Thank you
9 very much.

10 I would like to introduce my co-
11 chair, Dr. W. Ripley Ballou. He is the Deputy
12 Director for Infectious Disease Development
13 and Global Health at the Bill and Melinda
14 Gates Foundation.

15 He is going to introduce this
16 session. Just a note for all of you and for
17 the speakers. The timing today is somewhat
18 tighter than it was yesterday. For one, we
19 have only scheduled a one-hour lunch. So we
20 can't shave that down too much.

21 Second of all, there is some other
22 event, maybe a wedding or something, tonight

1 in this room. So we actually have to be
2 physically out of here by 5:15. That's good
3 news in some ways, bad news in other ways, but
4 we are going to need to stay to a good
5 schedule for the rest of today.

6 I also want to in advance thank
7 Dr. Ballou. He was really involved in the
8 planning process for this whole meeting right
9 from the get-go and just about at every twist
10 and turn, and there were many twists and
11 turns. He was really very constructive, very
12 helpful, and a good force and influence in
13 putting together this session.

14 So thanks very much, Dr. Ballou,
15 and I will turn the session over to you.

16 DR. BALLOU: Thank you very much,
17 Jay, and thank you for the opportunity to co-
18 chair this session. It is great to see so
19 many friends and colleagues in the audience.

20 Just to give you a brief agenda.
21 We will have this introduction, which I will
22 keep to less than 10 minutes, then 20-minute

1 well controlled time presentations from the
2 vaccine developers focusing on their clinical
3 experience, a 90-minute roundtable with
4 audience participation, and we ask, so that we
5 can maintain the schedule, that we hold the
6 questions between speakers for the roundtable.

7 Now the clinical goals for
8 vaccines with new adjuvants are, of course, to
9 optimize vaccine efficacy, and we believe we
10 do this by increasing the optimal -- by
11 identifying the optimal formulation. That
12 will give us an increase in the magnitude and
13 breadth of the immune response, but the flip
14 side of the coin is that we are also trying to
15 maximize safety and, inherently, one
16 approaches this by trying to use the lowest
17 amount of adjuvant that you need and the
18 fewest doses that you can deliver to reduce
19 the risk that you will have an issue with
20 safety.

21 The challenge, of course, is early
22 detection of possible safety signals.

1 Clinical trials must be designed that
2 demonstrate the need for the adjuvant, that
3 determine the optimal adjuvant dose, that
4 down-select between different adjuvant
5 formulations when that is a situation, and it
6 commonly is, that characterize short-term
7 safety and reactogenicity profiles, that allow
8 you to appropriately dose range across
9 different age groups, and to assess long term
10 vaccine safety.

11 I don't think there is a lot of
12 debate about whether these are important parts
13 of the clinical development program for new
14 adjuvants. The issue is how do we do this in
15 a cost and time effective fashion.

16 When one looks at assessing local
17 and systemic adverse events, which we refer to
18 in the vaccine community as reactogenicity,
19 there are issues about methodology, and it has
20 been very difficult historically to compare
21 reactogenicity of various adjuvanted vaccines
22 across platforms and across companies.

1 I think there has been a lot of
2 constructive work done in the last several
3 years to try and standardize approaches to
4 this, and hopefully, as we move forward, there
5 will be better comparability across platforms.

6 One of the things that I have been
7 impressed with is that at least with some
8 adjuvant formulations, there really are age-
9 specific reactogenicity. For example, in some
10 of the adjuvants that I have worked with, we
11 have seen the greatest reactogenicity actually
12 in healthy young adults and with the same
13 formulations having considerably less
14 reactogenicity in the elderly and in young
15 children.

16 Is reactogenicity a predictor of
17 long term safety? I think this is a question
18 that is not answered, and in my mind, it
19 really does -- It has been a confusing issue
20 in the clinic, because frequently early on in
21 clinical development when you are still
22 looking at the proper dose, and maybe not even

1 in the target population, you do see local
2 reactogenicity with some of these adjuvants.

3 Whether these are, in fact, going
4 to be predictors or not, I think, is an issue,
5 but it slows down clinical development as you
6 debate that question.

7 How much detail is enough to
8 collect in clinical trials? Are biomarkers an
9 appropriate adjunct for reactogenicity or
10 safety measures? And as we begin to have more
11 and more access to complex immunological
12 tools, a logical and direct consequence of
13 this is it is driving up the cost of doing
14 clinical trials, which is an issue that, I
15 think, concerns everybody.

16 If you are monitoring for rare
17 events, it is obviously an issue to be able to
18 detect a doubling over background incidents,
19 and this assumes that you know or can measure
20 these background incidents, and that is
21 obviously an issue.

22 There is a little bit of an issue

1 on my slide here, but we saw these figures
2 yesterday for incidents rates of diseases like
3 intussusception with rotavirus like SLE or
4 Guillain -Barre Syndrome where the background
5 rates are very, very small. It takes very
6 large clinical trials to be able to detect a
7 doubling of these background rates.

8 How can we better design studies
9 to assess the risk of rare, serious adverse
10 events that can be real issues for vaccines as
11 classes?

12 What do we know about the clinical
13 experience with new adjuvanted vaccines?

14 There is a handful of vaccines for which there
15 is now considerable clinical experience, in
16 particular, the seasonal influenza vaccine
17 that is adjuvanted with MF59 where there is
18 certainly well more than 10 million doses.
19 Individuals have received these vaccines over
20 a number of years.

21 The HPV vaccine that is adjuvanted
22 with AS04 is probably at least 500,000

1 individuals. H5N1 with a variety of adjuvants
2 is in the order of 10,000. Malaria vaccines
3 adjuvanted with AS02 are in the multiple
4 thousands, HSV with AS04 in the multiple
5 thousands. But this represents less than a
6 third of all the vaccines that are being
7 looked at with new adjuvants, and the vast
8 majority of these are -- the human experience
9 to date can be measured only in the hundreds.

10 So there is a large amount of data
11 that will have to be collected around these
12 other vaccine candidates as we move forward in
13 order to be able to say something about the
14 safety of these adjuvanted vaccines in the
15 future, and this represents a challenge.

16 So as we go through the
17 discussions and as the presenters come through
18 today, I would like to give you a highlight of
19 what we are going to be addressing in the
20 roundtable.

21 There are three or four classes of
22 questions: How can we design studies that

1 will detect (a) specific differences in
2 adjuvant responses, that provide long term
3 safety information, that provide dose ranging
4 data on adjuvants as well as antigens.

5 How can we design studies that
6 will incorporate safety information obtained
7 from preclinical data?

8 How can we design studies that
9 will incorporate information obtained from
10 previous clinical trials using the same
11 adjuvant?

12 These are some of the questions
13 that I, hopefully, will have addressed by our
14 series of speakers over the next hour and a
15 half.

16 So I will stop there and invite
17 Giovanni della Cioppa.

18 DR. DELLA CIOPPA: Well, good
19 morning, and first of all, thank you, the
20 organizers and the chairpersons, for giving me
21 the opportunity to be here with you and
22 present our clinical data.

1 I am going to focus on MF59, as
2 mentioned a minute ago. Indeed, we have a
3 considerable body of evidence with this
4 adjuvant, especially because it has been -- it
5 is a component of the seasonal influenza
6 vaccine Fluvad which had been on the market
7 since 1997.

8 Fluvad is marketed in 26 countries,
9 the U.S. not being one of them, but it is
10 marketed in Germany and in France and Spain,
11 and in Italy and New Zealand, in Australia, in
12 many other countries. Therefore, there is a
13 substantial amount of clinical experience with
14 this adjuvant, over 40 million doses
15 distributed worldwide.

16 There is also a substantial amount
17 of clinical trial data. We tested MF49 in
18 various permutations in over 33,000 subjects.
19 This will be the object of the talk, because
20 on request of the FDA and as part of a drug
21 master file that we recently submitted, we
22 have embarked in the big effort of generating

1 the pooled analysis on all clinical trial
2 evidence we have.

3 I am going to tell you a little
4 bit about the overall objectives. Then I am
5 going to focus briefly on the way we have
6 measured and defined the outcomes, a few words
7 on the methodology, the population, and then
8 I will dive into the results.

9 Fundamentally, this large pooled
10 analysis was carried out to address the
11 following questions: Compared with non-MF59
12 containing vaccines -- so not in absolute
13 terms but in relative terms -- do MF59
14 vaccines increase the risk of nine outcomes:
15 local reactogenicity, system reactogenicity,
16 all adverse events, autoimmune diseases,
17 cardiovascular diseases, all serious adverse
18 events, new onset of chronic diseases,
19 hospitalizations, and death?

20 So the first thing you have to do
21 when you have in front of you a task like this
22 is to be quite precise on the definition of

1 these outcomes, and I apologize for this busy
2 slide, but it is important for those of you
3 who are in the course of clinical trials that
4 these definitions are rigorous, are
5 predefined, and are agreed with the regulator
6 before you do the exercise.

7 So the first two, of course, are
8 what we call reactogenicity. They are
9 solicited, which means that in the case record
10 form the investigator and the subject is asked
11 whether or not a certain thing happened.

12 There's a number of them, but with
13 regard to local reaction, the most important
14 ones are ecchymosis, erythema, induration,
15 pain, swelling and tenderness.

16 With regard to systemic ones, the
17 most important ones that we have looked into
18 are arthralgia, chills, fever, headache,
19 malaise, myalgia, and nausea.

20 Outcome number three are all
21 adverse events. These are unsolicited events,
22 though there is no specific question in the

1 CRF, which may be occurring at anytime between
2 the moment the patient, the subject, entered
3 the study, and the moment the subject exits
4 the study.

5 The all important outcome of
6 autoimmune disease is actually defined as a
7 subset of the previous one, of the adverse
8 events. So the full AE dataset was coded
9 using the MedDRA version 10-1, and autoimmune
10 diseases were identified using the 34
11 preferred terms that are listed on the right
12 side of this slide.

13 Now in order not to miss any, for
14 7 preferred term, the search went broader and
15 also related preferred terms as defined by the
16 standard MedDRA queries were also included.
17 For instance, for aplastic anemia, in order
18 not to lose anything and to be as considerate
19 as possible, we also included the related
20 terms according to the MedDRA standard queries
21 such as leukopenia, thrombocytopenia, and so
22 on. So the most -- a very conservative

1 approach.

2 The fourth outcome, cardiovascular
3 diseases, is also a subset of all adverse
4 events.

5 Then we have serious adverse
6 events, all of them, unsolicited, occurring at
7 anytime during the trial, the definition being
8 the classical one in the clinical trial.

9 Outcome number 7, new onset
10 chronic diseases, was defined as a subset of
11 serious adverse events, where new onset was
12 defined as a condition which was not recorded
13 in the medical history of the subject, and
14 chronic was defined as no complete resolution
15 within 30 days of onset.

16 Important to note is that excluded
17 from this outcome were infectious diseases,
18 diseases associated with congenital structural
19 abnormalities, malignancies with first
20 diagnosis earlier and three months after the
21 last study injection.

22 Finally, the last two were

1 hospitalization and death, and here again the
2 point to make is that these were solicited.
3 So they were a specific question in the case
4 report form. Of course, there is a big
5 difference between solicited and nonsolicited
6 events in the way they are then captured.

7 The population: The main
8 population of the meta analysis is the one you
9 see on the far left of the slide, all
10 indications, all studies. This was then
11 divided into two subpopulations, the flu
12 trials to give a more homogeneous idea of how
13 the adjuvant could behave, which included
14 seasonal and pandemic flue trials, and the
15 non-flu trials that we have -- We have
16 conducted trials in five indications,
17 cytomegalovirus, Hepatitis B, Hepatitis C, HIV
18 and Herpes simplex.

19 Each of these populations was then
20 analyzed by age with four age categories: All
21 ages, children, adolescents less than 18 years
22 of age, nonelderly adults 18 to 65, and

1 elderly 65 and over.

2 In this presentation I will focus
3 on three populations, the main one, the
4 primary one, all indications, all ages; then
5 flu, all ages; and because of the importance
6 of adjuvants for the elderly, I have decided
7 to also touch upon flu, elderly.

8 A few words on the approach, the
9 statistical approach. We have looked at the
10 comparison between the group receiving MF59
11 and the group non-receiving MF59 in terms of
12 risk ratio. Now for events that occurred in
13 fixed time windows such as reactogenicity, we
14 use a weighted risk ratio based on the pooled
15 Mantel-Haenszel type estimator weighted by
16 size of study; whereas, for events occurring
17 at anytime during the study, the majority of
18 them, such as unsolicited AEs, we used an
19 adjusted risk ratio based on Poisson
20 regression model adjusted for the number of
21 days in the study and the number of
22 vaccination.

1 Important to keep in mind is that,
2 at least for flu studies, the number of
3 vaccination is an indirect adjustment for age,
4 because the children get more vaccination get
5 the adults and the elderly.

6 Now the population: A very large
7 population, over 33,000 subjects in total, of
8 which almost 28,000 were flu studies and about
9 a bit less than 6,000 were non-flu studies.
10 Of the flu studies, the vast majority of
11 studies were conducted in elderly, with almost
12 20,000 subjects. So the database is large.

13 Let's go now to the results. This
14 slide, which is the P slide in this
15 presentation, gives you the results for the
16 primary analysis.

17 This is the so called forest plot,
18 and I'm sure many of you are familiar with
19 this kind of graphic expression of the risk
20 ratio. The bottom line is that each of the
21 nine events has kind of a branch with a dot in
22 the middle and two whiskers on the side. The

1 dot is the point estimate of the risk ratio,
2 and the two whiskers give the 95 percent
3 confidence interval.

4 If the whole branch is totally on
5 the left or on the right of the vertical line,
6 then there is a significant difference in
7 favor of one of the two groups.

8 So this slides gives a number of,
9 I think, very interesting hints on the safety
10 of MF59 and beyond. First of all, if you look
11 at the first two outcomes, there is a marginal
12 but statistically significant increase in the
13 MF59 group in local and systemic reactions.

14 So reactogenicity is increased.
15 We knew this. This is confirmed by this meta
16 analysis, by this pooled analysis. It is also
17 true that the risk ratio, the marginal
18 increase in risk in the MF59 was small.

19 Now if we now skip to the fourth
20 outcome, and this is autoimmune disease, we
21 see that the confidence intervals are very
22 broad, and they cross the vertical line, which

1 means that there was no significant difference
2 between the MF59 group and the no-MF59 group
3 in terms of autoimmune diseases.

4 The rest of the outcomes came as a
5 surprise to those of us who have done this
6 exercise. If you look at the third outcome,
7 all AEs, you see that the risk ratio is .75,
8 and the confidence intervals are all on the
9 left side of one, .71 and .80, which means
10 that the group who received MF59 was overall
11 at a lower risk of adverse events compared to
12 the group who did not receive MF59.

13 If you go down the list with the
14 other remaining five outcomes and you look at
15 cardiovascular diseases, serious adverse
16 events, hospitalizations, and death, you see
17 the same pattern. You see that for all four
18 of them and marginally also for new onset
19 chronic diseases, you have a significantly
20 lower risk in the group that received MF59.
21 So there were fewer cardiovascular events,
22 fewer SAEs, fewer hospitalizations, and fewer

1 deaths in a statistically significant fashion.

2 I think what is particularly
3 interesting is the cardiovascular disease.
4 You look at the risk ratio of .46 with 95
5 percent confidence interval of .38 to .56.

6 Now what happens if we move from
7 all comers, all indications, all ages, which
8 again was the primary outcome to flu? Here is
9 a much more homogeneous indication. This is
10 all flu, all ages, 28,000 subjects.

11 Again, the pattern is very
12 similar. You have a marginal but significant
13 increase in reactogenicity. You have no
14 significant difference in autoimmune disease.
15 The point estimate switches from the left side
16 to the right side, but that is not really
17 relevant.

18 There's very few events. There's
19 10 in total. So one more or less makes the
20 point estimate fluctuate, but the important
21 thing is that the confidence intervals are
22 very broad, and they cross the vertical line

1 of risk ratio of one.

2 You see again then for new onset
3 chronic diseases, cardiovascular diseases,
4 serious adverse events, hospitalizations and
5 death, there is a significant decrease in the
6 risk in the group receiving MF59 compared to
7 those not -- the group not receiving MF59 in
8 flu trials for all ages.

9 Again, a similar pattern is
10 repeated again when we restrict the population
11 even further to an even more homogeneous
12 population. Here we have all flu, but only
13 elder. Of course, the -- and the numbers go
14 down, but they are still significant.

15 Again, significant increase of
16 local and systemic reactogenicity, no
17 significance difference when it comes to
18 autoimmune disease, and significant decrease
19 of adverse events, serious adverse events,
20 cardiovascular -- not hospitalization.
21 Hospitalization and deaths here are marginal.

22 Because of the importance of

1 autoimmune diseases for this discussion around
2 adjuvants, we have conducted a number of
3 sensitivity analyses to see whether the
4 outcomes were affected by changing a little
5 bit the rules of the game, so to speak.

6 So what you see here is, for both
7 all indications and for flu, three additional
8 analyses we have conducted to test the
9 robustness of the primary analysis.

10 The first sensitivity analysis was
11 done by adding a very large trial. It goes
12 under the code of V7P35, which actually had
13 30,700 subjects, but was not included in the
14 original analysis in the original database,
15 because the collection of safety was
16 incomplete.

17 In this study, only AEs were
18 collected, necessitating a physician's visit
19 and occurring only during the first week, and
20 then SAEs and hospitalization and death
21 occurring throughout the study were collected.
22 When you add this study, you obviously

1 increase considerably the database.

2 The second sensitivity analysis
3 was done by removing the subjects with a
4 history of autoimmune disease, and the third
5 sensitivity analysis was done by having both
6 combined, by adding this large study, V7P35
7 and removing the subjects with a history of
8 autoimmune disease.

9 What you see is that for all
10 indications there is a very minor fluctuation
11 with these sensitivity analyses, whereas for
12 flu the risk ratio goes down from about 2 to
13 1 and then to less than one as you conduct the
14 sensitivity analyses. But overall the signal
15 -- the direction of the signal doesn't appear
16 and doesn't change.

17 As usual with these large efforts,
18 there are a number of problems. I will not
19 even try to address them, but obviously here
20 we have a heterogeneous population. There is
21 a different observation period, different
22 number of vaccinations, different study

1 designs, different health condition at
2 baseline. In flu, the subjects were healthy,
3 and in non-flu the subjects weren't.

4 A very difficult thing was to
5 merge the extension studies to the original
6 studies in order not to double count events,
7 and also we had to include, and we did
8 include, studies with a second adjuvant where,
9 of course, the safety profile of the second
10 adjuvant, which often was much worse than the
11 one of MF59, kind of contaminated, in a way,
12 the outcome.

13 Before giving you a final slide, I
14 just want to show you what we are trying to do
15 now to follow up and to confirm the
16 observations that we have done in this large
17 meta analysis.

18 We are conducting a large
19 prospective observational study, which goes
20 under the acronym of LIVE, which stands for
21 Lombardy Influenza Vaccine Effectiveness
22 study. It is a prospective observational

1 study.

2 I would like to propose maybe for
3 the discussion later that this can be a very
4 useful tool to assess long term, with the kind
5 of numbers that were mentioned before, the
6 safety of a vaccine.

7 This study is done in the
8 population of elderlies. It is done in one
9 region of Italy, Lombardy, in different local
10 health units, and again it is comparing an
11 MF59 containing trivalent influenza vaccine
12 with the equivalent without MF59.

13 It is done over three influenza
14 seasons, and again this can be an interesting
15 and useful maybe methodological suggestion for
16 when you need to do such large efforts. You
17 don't have to do it all in one season. In
18 fact, we are doing it over three seasons, last
19 year's season, this year's season, and next
20 year's season, so that we can reach a sample
21 size of at least 150,000 subjects.

22 The goal, the main goal, is to

1 compare MF59 to no-MF59 influenza vaccine for
2 the risk of hospitalization and for influenza
3 related diseases, diagnosis of influenza and
4 pneumonia. So real bottom line, real
5 effectiveness, real hard core stuff that
6 justify the use or non-use of an adjuvant.

7 This is a number of secondary
8 endpoints that go in the same direction:
9 Overall mortality, cardiovascular mortality,
10 risk of hospitalization, direct cost, cost of
11 antibiotics, and so on.

12 It is interesting how this thing
13 was set up. Of course, all subjects -- this
14 is a prospective study, observational -- had
15 to sign an informed consent. The vaccinations
16 were delivered by the district health care
17 providers. The outcomes were collected to the
18 hospital databases, and the link of the
19 outcome to the vaccination was done through
20 the Social Security number of the subjects.

21 In the first year we enrolled
22 almost 44,000 subjects. In the second year we

1 are over 50,000, and we expect to reach the
2 mark of 150,000 by 2010.

3 So to conclude, and this is my
4 last slide, going back to the meta analysis.

5 What kind of answers do we have to the
6 questions that we have started with?

7 Is there an increased
8 reactogenicity? Yes. it is marginal, but it
9 is significant.

10 Is there increase of autoimmune
11 disease? No.

12 Is there an increased risk of AEs,
13 cardiovascular disease, all SAEs, new onset of
14 chronic diseases, hospitalization and death?
15 No. In fact, there seems to be an overall
16 trend for fewer events in the MF59 group
17 which, of course, will have to be addressed
18 and studied in different contexts and
19 confirmed by different trials and, hopefully,.
20 by different manufacturers.

21 This is the end of my
22 presentation. Thank you very much.

1 (Applause.)

2 DR. BALLOU: Thank you very much.

3 Are there any questions for Dr. della Cioppa?

4 PARTICIPANT: Giovanni, just a

5 very quick one. A very interesting

6 presentation.

7 Is LIVE randomized and blinded?

8 DR. DELLA CIOPPA: There are about

9 100 trials. About 60 percent were randomized,

10 and the remaining were uncontrolled. Of the

11 randomized, most of them were observer blind.

12 PARTICIPANT: I was speaking

13 specifically of the prospective study, the

14 LIVE.

15 DR. DELLA CIOPPA: Oh, it is an

16 observational study. So it is not.

17 DR. CHEN: Two questions. First

18 is that one of the challenges in the safety

19 field is that safety cannot be measured

20 directly. It can only be inferred indirectly

21 from looking at the routes of absence of

22 multiple different adverse events.

1 One of the challenges in the
2 safety field is that, if we take ourselves
3 back in history, that in the field of physics
4 and chemistry, without the establishment of a
5 standardized periodic table of elements, that
6 field cannot move forward scientifically.

7 So with safety, until we start to
8 standardize which case definitions and how we
9 look at the adverse events across different
10 trials, it becomes very difficult for us to
11 make sense of the data in a truly meaningful
12 way.

13 There is a collaboration called
14 the Brighton Collaboration that has been
15 established to try to standardize that. For
16 those of you in the audience who are not
17 familiar with that, I would encourage you to
18 go to that website so that, as you conduct
19 your trials, your data could be collected in
20 a more standardized format.

21 I was curious. Did you guys think
22 about using the Brighton Collaboration case

1 definitions in your study?

2 DR. DELLA CIOPPA: We are very
3 familiar with the Collaboration, and we are
4 all -- we are actually collaborating, and we
5 are using it. Clearly, in this exercise we
6 used studies that went back up to 15 years.
7 So, clearly, we had to use what we got, but in
8 fact, you raise a very important point.

9 Standardizing outcomes is
10 critical, and equal critical is to predefine
11 outcomes. That is why I tried to kind of
12 define them for you. I would go beyond that.
13 Standardizing measurements is equally
14 critical, because one of the most difficult
15 things that happens when you do a meta
16 analysis, when you have different ways of
17 measuring the same thing in different studies.

18 If you have even the most innocent
19 looking thing, such as race, if you have in
20 one study three races and in another study
21 seven races, you have to create an algorithm
22 to combine them, and you can multiply this by

1 a billion. Then you are going to have the
2 level of complexity that you are facing with
3 these pooled analyses.

4 As you said, the more complicated
5 they become, the less reliable the results
6 are. So standardization is actually a key to
7 these efforts. So it is a welcome effort that
8 you are doing.

9 DR. CHEN: The second comment is:
10 Kind of one of the most provocative findings
11 was the relative difference in deaths in the
12 trials. I was wondering, is there a way to
13 kind of go back and adjust for seasonality,
14 etcetera, and look to see if there are any
15 differences in characteristics of the MF59 flu
16 vaccine versus others to see if that might be
17 a real finding?

18 DR. DELLA CIOPPA: These are very
19 new data. They are actually unpublished, and
20 we are seeking publication for them. We will
21 indeed do that. An important thing, however,
22 is to warn against over-interpretation and an

1 attempt to over-choreograph the data. But we
2 will certain look at individual cases to see
3 whether there is any lessons learned.

4 PARTICIPANT: As far as autoimmune
5 disease, could you comment on the follow-up,
6 because oftentimes flu studies only go to 28
7 days or sometimes six months, but long term
8 follow-up in your flue studies is sometimes
9 uncommon. So that would be one question, just
10 exposure time.

11 Then the other question would be:
12 In Hepatitis B, typically, there's more
13 vaccinations in a single vaccination. So did
14 you find anything in the subset of Hepatitis
15 B, and how long were they followed for safety.
16 I think I'll stop there.

17 DR. DELLA CIOPPA: Right. With
18 regard to the second question, I don't know
19 exactly. I would have to get back to you on
20 the Hepatitis B. But I do have the data on
21 the overall, the duration of follow-up, which
22 is actually quite long.

1 The mean duration of follow-up for
2 the primary population was 234 days, about
3 slightly over eight months in the MF59 group,
4 and 188 days, slightly over six months in the
5 control group.

6 So was that enough? No. I mean,
7 if you want to see long term down the road, 10
8 years down the road, you need different tools.
9 I would venture to recommend to the regulators
10 that prospective observational studies are the
11 only tool to address that kind of question,
12 because if you do this in the course of a
13 clinical trial, above and beyond the
14 incredible amount of money that this would
15 cost, you have to face the problem of
16 dropouts, and sometimes the dropouts negate
17 the value of randomizing subjects.

18 So it is a complicated matter, but
19 I would suggest that prospective observational
20 studies are the way to go.

21 PARTICIPANT: Right. I think the
22 other question would be: Flue vaccinations

1 are recommended yearly. So in your LIVE
2 studies or other studies, are you re-
3 vaccinating and following for --

4 DR. DELLA CIOPPA: We are, because
5 these are elderly subjects, and so they had to
6 be revaccinated. But for the study
7 population, the 150,000 subjects are not
8 50,000 subject revaccinated three times.
9 Every year you have a new cohort that comes
10 in.

11 DR. BALLOU: Last question?

12 DR. VERSTRAETEN: Tom Verstraeten
13 from GSK. Very nice presentation, and very
14 reassuring that your results are similar to
15 what we will be showing in a minute from a
16 similar analysis we did.

17 I had the same question as the
18 previous one on the exposure time, but linked
19 to that, since you know your exposure time,
20 did you try to assess the number of cases you
21 should have seen, some kind of observed-to-
22 expected analysis, to assess the completeness

1 of your capture?

2 DR. DELLA CIOPPA: We haven't done
3 that, and we will do that.

4 DR. VERSTRAETEN: Thanks.

5 MODERATOR SLATER: Thank you. A
6 20 minute break. Let's reconvene at a little
7 before 10:30.

8 (Whereupon, the foregoing matter
9 went off the record at 10:09 a.m. and went
10 back on the record at 10:29 a.m.)

11 MODERATOR SLATER: Welcome back.
12 I will do some more housekeeping while you are
13 going to your seats.

14 First of all, just to clarify, we
15 will -- Because of the time, we will entertain
16 questions in this session only if we can do so
17 within the time constraints for each speaker.
18 So if your speakers, as did the last two
19 speakers, not only met their time constraints
20 but stay within them, we have plenty of time
21 for questions.

22 If, as is totally reasonable,

1 people reach their time constraints, then we
2 will save the questions for that speaker until
3 the roundtable discussion, which is coming
4 very soon. So that, I don't think, should be
5 a problem, but we do want to stay on schedule
6 so everyone can get an hour's lunch.

7 Talking about lunch, because there
8 are other meetings going on on the floor, the
9 hotel has decided that, instead of having our
10 three lovely stations placed right here, we
11 are now going to have a single but larger
12 station downstairs in the White Oak Room where
13 I have not been, but I am told there is
14 seating there, and they should be able to
15 accommodate -- I don't know how many people it
16 will accommodate, but anyway, that is where
17 lunch is in terms of the concessions.

18 There are, of course, the same
19 restaurants and local concessions that you may
20 have used yesterday. They should all be there
21 today. So, hopefully, everyone will be fed
22 during lunchtime.

1 We now go on to hear from Dr.
2 Charmaine Gittleson, the head of Clinical
3 Safety at CSL Limited. Dr. Gittleson.

4 DR. GITTLESON: So, firstly, I
5 would like to thank the organizers for
6 inviting us to this meeting. We have come a
7 long way, all the way from Australia, along
8 with some others.

9 So what I am going to do today is
10 to try and give you a sense of what the
11 clinical development challenges are that we
12 have considered whilst developing various
13 programs with our adjuvant, ISCOMATRIX
14 adjuvant.

15 This is not a presentation where I
16 am going to go through a lot of data from the
17 various clinical studies, but I will use some
18 data to try and illustrate what we have tried
19 to do and what we have considered as we have
20 gone through our programs.

21 So just as a reminder, the
22 adjuvant that I am talking about is ISCOMATRIX

1 adjuvant, the small cage-like structures based
2 upon the saponin complex with cholesterol and
3 phospholipid that, when combined with an
4 antigen, forms what is known as ISCOMATRIX
5 vaccine. This is what was presented yesterday
6 as part of Dr. Maraskovsky's presentation.

7 So what I will do today is talk
8 about some of the development considerations.
9 I will give you an overview of what the
10 clinical exposure is with ISCOMATRIX adjuvant.
11 I will talk about the challenges that we have
12 addressed in looking at how we interpret the
13 immune response, and then the bulk of my
14 presentation will focus on the evaluation of
15 potential safety signals, something that
16 already has been discussed at length today.

17 So, really, all of us are very
18 aware of the need to have a look at the
19 benefit versus risk parameters when developing
20 a vaccine or any program, and where CSL has
21 really tried to concentrate is where we could
22 show additional benefit.

1 So we are very aware of the
2 sensitivity to perceived or potential risk
3 with a novel adjuvant, and so we have had a
4 look at where we could bring additional
5 benefit to patients, for example, with
6 therapeutic vaccines, and that has been a
7 large part of our focus, or where we can have
8 a look at patient populations in whom the
9 response is suboptimal perhaps already to
10 marketed vaccines.

11 So we have concentrated a lot on
12 the elderly population and in diseased
13 patients. So as examples of the experience,
14 the ISCOMATRIX adjuvant has been now
15 administered to approximately 1,300 patients.
16 Now these are in completed or ongoing studies
17 and with CSL programs or partner programs. So
18 that number of 1300 is a moving target.

19 A lot of the evidence has come
20 from healthy adult studies which really
21 represents the Phase I programs. And as I
22 have mentioned, we have done work with elderly

1 patient populations, in some cases where we
2 have compared elderly and younger adults
3 within the same program.

4 We do have some data from HCV and
5 HIV infected, and while this workshop is
6 really about vaccines for infectious disease,
7 I do mention that there are some studies done
8 in the oncology sphere. As mentioned, we have
9 worked with prophylactic and really
10 concentrated as well on therapeutic vaccines.

11 Now this is not the total sum of
12 the exposure. There was an early development
13 program with ISCOMATRIX vaccine, and this
14 brings us to one of the first challenges that
15 we had to face.

16 So the early adjuvant formulation
17 that was being used in the late 1990s, for the
18 798 subjects who were exposed in eight
19 completed studies to at least one vaccination.
20 Really,. the work we did there was really to
21 proof of concept to demonstrate that we were
22 eliciting strong hemo responses, and we did

1 some earlier exploratory T-cell work.

2 What we did find in that program
3 was that there were patients that were
4 withdrawing due to AEs, and the AEs most
5 commonly noted that were causing withdrawals
6 were local injection site pain and a flu-like
7 syndrome of fatigue and myalgia.

8 Looking at the risk profile, we
9 felt that this was unacceptable, looked back
10 at our formulation, and tried to understand
11 what we could do to improve upon this
12 tolerability profile.

13 Some of the work that was done in
14 that reformulation work was really to try and
15 improve the purity of our vaccine, to remove
16 some of the components of animal origin and to
17 remove some of the -- to further remove bark
18 impurities from the saponin, and also to have
19 a look and see whether we could remove
20 fractions of the saponin that we felt were not
21 essential for eliciting the immune response.

22 In the program that I just showed

1 you on the preceding slide where we have used
2 the optimized version of the adjuvant, we now
3 don't see these withdrawals due to adverse
4 events. Sure, we do see reactogenicity, but
5 we don't see patients withdrawing.

6 So let me move on to what we have
7 done to have a look at the immune response in
8 our programs. One of the things that has been
9 raised already this morning is what do we need
10 to do to justify the use of ISCOMATRIX
11 adjuvant.

12 Do we use the adjuvant alone? Do
13 we, obviously, use the combination vaccine?
14 Do we compare against the antigen? Do we have
15 saline controls, and what value can be seen
16 out of those? This is a topic of debate even
17 within our own company.

18 I am going to use an example of a
19 study which is not in a vaccine for infectious
20 disease but comes from the oncology program,
21 because I think it does illustrate some
22 interesting points, and this is from early on

1 within the program.

2 What we were able to do with this
3 study design was, firstly, we were able to
4 dose escalate our adjuvant, and looking at the
5 lefthand side of the graph, this is looking at
6 antibody responses, and participants with an
7 NYE subpositive minimal residual disease,
8 patients with a history of melanoma and breast
9 cancer predominantly.

10 What one sees on the lefthand side
11 of the graph is that this was during dose
12 escalation with the antigen and the adjuvant
13 and showing that at low doses of the adjuvant,
14 whilst we had some patients, small patient
15 numbers -- some patients eliciting an immune
16 response, but what was really most interesting
17 is that, when we compared using the antigen
18 alone with adding the adjuvant, we were able
19 to show and justify the value of adding an
20 adjuvant to this program.

21 It raises the question as well,
22 though, of do we need to have a look at the

1 adjuvant alone, and we have had debates this
2 morning already about the value or not of
3 looking at adjuvant alone in the preclinical
4 programs, and does that really translate into
5 the clinical program, and we would like to
6 suggest that not as a regulatory requirement
7 but more as understanding one's own novel
8 adjuvant, that one could consider in the early
9 development stages of one's program -- so in
10 Phase I -- having an adjuvant-alone arm and
11 having a look at certain parameters, that
12 would allow you to describe the effects of
13 one's adjuvant, perhaps affect some of the
14 mechanisms, and perhaps be able to use at a
15 later stage to link back to some of the
16 clinical indications, but what to measure, we
17 will discuss later on, is really a challenge
18 in how predictive that is of further signals
19 is equally challenging.

20 So looking at the immunogenicity
21 assays, we started off using -- Because
22 looking at therapeutic vaccines, really

1 looking at CD8 responses, and started very
2 nonspecific assays looking at DTH, and this
3 has evolved for us, as we have realized that
4 we really wanted to have a very much more
5 specific look at what kind of effect function
6 there was at our CD8 responses.

7 These are very complex assays to
8 do, very difficult to do with large clinical
9 programs and require a lot of work to set up
10 labs. So one of the things that we have also
11 done is had a look at developing taking a
12 validated registered assay such as QuantiFERON
13 and looking at interferon gamma ELISA
14 methodologies to have a look at CD4, CD8
15 responses.

16 There are a lot of challenges in
17 these evaluations. These are not currently
18 validated immune correlates with the clinical
19 endpoints. So if you are using them to make
20 assessments of vaccine dose and of adjuvant
21 dose, which immune correlate does one use, and
22 how might that translate to your clinical

1 outcome?

2 Standardization is not yet
3 attained. It is difficult across our own
4 programs to be able to compare from one study
5 to the other, but even when we have a look at
6 what work other people are doing and try to
7 compare adjuvant efficacy, very difficult to
8 do. What we did realize is that the more you
9 look, the more you find, and it is worthwhile
10 digging and doing the additional assays.

11 So what this shows is the ability
12 to increase efficiency of detection to
13 tweaking of one's assay method. This is using
14 a therapeutic protein and having a look at
15 interferon gamma on an ex vivo CD8 assay,
16 intracellular cytokine staining assay, where
17 we had a look at using individual peptide
18 pools on Pool A and Pool B and saw a certain
19 standard response. We used HLA-2 restricted
20 peptides and saw a certain response.

21 Then what we did was we used
22 overlapping peptides, and where we used

1 overlapping peptides we saw an increase in the
2 response. So again, where do you stop in
3 making these decisions?

4 We can move on to the meaty stuff,
5 and that is the evaluation of potential safety
6 signals. So the question, really,. that is on
7 all of our minds is will adjuvants alter
8 clinical risk? I am going to focus on this
9 aspect: Whether it be chronic inflammation,
10 whether it be acute effects in Guillain-Barre,
11 more organ-like toxicities such as multiple
12 sclerosis, more systemic events, and then
13 hypersensitivity and vasculitis toxin events.

14 Now, obviously, I am not touching
15 on it today, but obviously, we have looked at
16 reactogenicity and done a lot of work, and are
17 now starting to try and see how we could
18 predict which patients might have greater
19 local reactogenicity.

20 We are doing some work trying to
21 link back to see patients who come into
22 studies with higher antibodies labels at the

1 start of a study. Does that predict that they
2 will have more severe reactions or patients
3 who mount a more robust immune response. What
4 kind of immune local reactions do they have?

5 Just concentrating on the more
6 rare events, there are a lot of challenges.
7 How do we assess association with the adjuvant
8 per se?

9 We know that we need to take into
10 account background population prevalence. For
11 example, just the background population
12 prevalence of autoimmunity sits at five
13 percent. How does that impact on our ability
14 to interpret what we are seeing within our own
15 clinical programs?

16 Patients may develop some markers
17 of autoimmunity just as a result of having an
18 infection, and that may happen concurrently
19 with exposure to our vaccines. Within our own
20 programs, patients may receive our vaccine as
21 well as other vaccines, vaccines on the
22 markers. How does that all impact on the

1 epidemiology?

2 Are predictive markers feasible,
3 and are they even valuable? How do we
4 actually determine whether patients have had
5 a specific case of interest? Someone
6 mentioned earlier the Brighton Collaboration.
7 Can we standardize certain case definitions.
8 As yet, Brighton Collaboration doesn't have
9 standardized case definitions for autoimmune
10 conditions.

11 How do we evaluate whether this is
12 the vaccine per se, the antigen effect with
13 the adjuvant, or what is the contribution of
14 the adjuvant alone, and how does that impact
15 when you are developing one adjuvant for
16 multiple different programs?

17 So what have we done? Well, we
18 have had a look to see are we actually
19 inducing cytokines, for example, because we do
20 want to see some cytokines. This is an ex
21 vivo assay looking at T-cell responses with a
22 therapeutic vaccine where we have had a look

1 at a time point after vaccination.

2 We do see that we induce TH1
3 cytokines that we were specifically looking
4 for in association with a CD8 response. We
5 have looked more broadly than this. This is
6 the data that I am demonstrating today.

7 What we really were interested in,
8 though, is did we get sustained chronic
9 increase in cytokines? So we have taken some
10 of our programs, and just some of the data
11 that I have brought to show today is where we
12 had a look at nonspecific -- the previous
13 slide I showed is antigen-specific.

14 This is serum showing nonspecific
15 cytokine levels, and what we did was looked at
16 post the third dose of a vaccine regiment with
17 a therapeutic vaccine.

18 What we noticed was that we did
19 not see sustained levels of cytokines, and
20 when we compared the two yellow lines,
21 compared looking at some of the pro-
22 inflammatory cytokines, IL-1 beta, looking at

1 GCSF, IL-6, that these were not sustained and
2 were in the same levels as what we were seeing
3 with the placebo.

4 This raises questions. What does
5 one compare to? Is saline placebo adequate?
6 Should we be comparing to a licensed vaccine?

7 We have also had a look to see
8 whether we could see any markers of allergy,
9 chronic inflammation or autoimmunity. This is
10 a study where we have had a look at older
11 adults as well, with a licensed vaccine that
12 contains an antigen and then used an
13 ISCOMATRIX vaccine containing the same
14 antigen, and we had a look at pre-dose, post-
15 dose, post-dose, and then looked at whether
16 there were any treatment emergents on new
17 post-dose events.

18 We didn't see any new post-dose
19 markers, IgE, CRP or any of the markers of
20 autoimmunity. What is interesting to note is
21 that there is pre-dose markers within the
22 patient population.

1 Now some of these may precede
2 clinical diagnoses. The point I want to make
3 here is that it is possibly really important
4 to collect serum in your study and bank it,
5 because if later on you do have a diagnosis of
6 an autoimmune disease and there wasn't
7 anything in the history, you would probably
8 want to be able to go back and have a look and
9 see whether there are any pre-dose markers
10 present.

11 One of the other things that we
12 have tried to have a look at is intensive
13 systemic toxicity. We have had a look at
14 laboratory evaluation and, certainly, one of
15 the things we have had a look at is liver
16 function tests to see whether there is
17 anything from more systemic immune
18 stimulation.

19 This is again looking at that
20 licensed vaccine with the same antigen that
21 was then combined with ISCOMATRIX, and this is
22 showing -- it's a bit difficult to see -- ALT

1 on the lefthand side and bilirubin on the
2 right, and what we see is that patients --
3 there is very little variability between pre
4 and post-dose, and this was having a look at
5 Day 7 post-dose.

6 So what are we trying to do to see
7 whether we can tease out what the clinical
8 signals of safety are for ISCOMATRIX vaccines
9 in our programs?

10 Well, what we have done is
11 established an adjuvant based clinical data
12 repository. This is a data repository holding
13 all of the clinical data that allows us to
14 have a look at all the adverse events data and
15 all the lab data. It is not just the SAE
16 database.

17 It's a lot of work involved in
18 doing this, and it requires excellent
19 collaboration between your biostatisticians
20 and your data management vendors and your
21 clinical safety physicians.

22 What we have done is having a look

1 retrospectively at our data using MedDRA tools
2 at this stage, similar to what the previous
3 speaker spoke about. We are having a look
4 using high level group terms to try and
5 capture it more broadly and not miss various
6 potential diagnoses across those that I have
7 shown you here, autoimmune diseases
8 specifically, and we have also combined that
9 and having a look at standard MedDRA queries
10 looking again for some more interesting
11 topics.

12 What we have not demonstrated is
13 signal, looking at any of this data. There
14 are a lot of challenges in setting up and
15 maintaining such a database. One, we have
16 multiple vaccine programs within CSL.
17 Secondly, CSL works with a number of partners
18 who have their own vaccine programs, and one
19 of the biggest challenges that we face is how
20 do we standardize AE definitions across our
21 various programs in the absence of such
22 guidances from people like -- from places like

1 the Brighton Collaboration, and how long do we
2 collect the data for? What meta data do we
3 collect around it?

4 It is really important to know
5 what other vaccines patients get, what other
6 infections they may get, what their baseline
7 medical history is, and to link all of that
8 together to be able to interpret the data is
9 really quite challenging.

10 It is really important for us when
11 we do this to go back and look at individual
12 cases and to be able to challenge the sites,
13 if we are able to get back to those
14 investigators and ask more about those
15 patients.

16 How do we present and use this
17 adjuvant data? One of the approaches we've
18 taken is we have put together an adjuvant --
19 ISCOMATRIX adjuvant investigator brochure.

20 So each vaccine has its own
21 investigator brochure, but we have done this
22 as well for the adjuvant where we have

1 concentrated on the safety signals, where we
2 have looked to integrate data within various
3 programs, and it allows us to have a look at
4 whether we are seeing anything different
5 between age populations, diseased versus
6 healthy populations, and different vaccines.

7 What we would like to suggest
8 moving forward is a prospective type of
9 analysis where we set up before we start and
10 determine how we could analyze for rarer
11 events using a meta analysis, where we
12 prospectively define the events of interest
13 and set standardized case definitions for all
14 the clinical programs within our own programs
15 and possibly with partners.

16 It would require setting
17 prospective statistical analysis plans where
18 we can have a look at trials for a particular
19 product, but we can also look across a
20 particular product with an adjuvant and then
21 look across various products with the same
22 adjuvant.

1 We feel that that may facilitate
2 and encourage us to have more standardized
3 approaches to our studies, and it would allow
4 us to have a look at some subgroup
5 evaluations.

6 So in conclusion, we think that
7 the whole concept of looking at dose ranging
8 one's adjuvant, of trying to determine whether
9 we have a successful adjuvant, using the
10 immune correlates in the ways that are
11 measured really require further development.

12 We acknowledge that predictive
13 safety biomarker development is very
14 challenging, and we are just taking
15 exploratory looks at our data at this stage,
16 but really are grappling with what does it
17 mean if we do see something there.

18 We think that there is value in
19 evaluating the safety of the adjuvant
20 technology itself by having a more integrated
21 approach to looking at the adjuvant across a
22 number of different vaccine programs, but we

1 acknowledge it needs to be done alongside the
2 development of a vaccine itself, and that one
3 has to do the benefit/risk analysis for that
4 vaccine itself, but that part of one's
5 thinking may be influenced by what you are
6 seeing by looking across the adjuvant.

7 We really do believe that meetings
8 like this are of value, because the ongoing
9 engagement between the scientific community
10 and the agency and the collaboration that is
11 required for us to further the development of
12 these adjuvants is optimal.

13 Thank you.

14 (Applause.)

15 MODERATOR SLATER: Thank you very
16 much. Are there any questions? Thank you,
17 Dr. Gittleson.

18 Our next speaker is Dr. Steven
19 Reed. He is the head of research and
20 development at the Infectious Disease Research
21 Institute.

22 DR. REED: Thank you, Jay, and

1 thank you, Rip, for inviting me.

2 I want to talk about our
3 experience with MPL in a stable emulsion for
4 development of a therapeutic vaccine against
5 Leishmaniasis.

6 Leishmaniasis is a parasitic
7 disease caused by a wide number of species of
8 Leishmania. Many of you probably haven't been
9 exposed to these parasites, even in a
10 philosophical or practical sense, but they are
11 transmitted by a sandfly, and they are
12 widespread, and they have a lot of different
13 forms, cutaneous, mucosal, visceral and so on.

14 So there is quite a challenge to
15 develop a vaccine, either a therapeutic or
16 prophylactic, for these organisms.

17 These are the form that are
18 transmitted by the sandfly, and these are the
19 forms that multiply within the mammalian host.
20 So in this regard, they are very interesting,
21 because they are obligate intrasiter organisms
22 that prefer to replicate in a macrophage. So

1 in this regard, they are like toxoplasma, for
2 example.

3 The good thing about developing a
4 vaccine for Leishmaniasis is that many of the
5 species share antigens, and they have common
6 antigens. So you can actually develop a
7 vaccine that will cross-protect against many
8 species.

9 This is a clinical form of
10 Leishmaniasis caused by *L. donovani*. So it is
11 the visceral form characterized by
12 hepatosplenomegaly. This is a severe mucosal
13 Leishmaniasis. These are pictures from the
14 World Health Organization website. This is
15 caused by *L. braziliensis*, very destructive;
16 and this is the most common form, which is
17 cutaneous Leishmaniasis.

18 So all these are caused by
19 different species, but as I mentioned, many of
20 them have similar antigens.

21 The ideal vaccine that we are
22 trying to produce here is, obviously, safe but

1 also one that induces effective T-cell
2 responses and long term immunity that we can
3 use both to prevent and treat, ideally, and
4 has broad cross-reactivity between the
5 species.

6 Of course, at our Infectious
7 Disease Research Institute we are a nonprofit,
8 dedicated exclusively to diseases of
9 developing countries. We have to make
10 vaccines that are cost effective and that will
11 be actually adopted by the countries that can
12 afford them.

13 So one thing I want to point out
14 in this slide -- and this is the only animal
15 study I will show -- is that it is very
16 important when you are trying to develop a
17 vaccine that works in any of the animal models
18 to have a formulation that is effective. This
19 is basically a mouse footpad model measuring
20 the lesion size, and all you really need to
21 see is that all the black lines are not
22 protected. On the bottom, solid orange, is

1 protected.

2 Now what is the difference? That
3 is our vaccine antigen, which comprises of
4 three recombinant proteins fused together as
5 a single molecule, and this molecule, this
6 tri-fusion protein one, when formulated in
7 MPLSE is quite protective in hundreds of
8 experiments, hundreds of animals, not only in
9 mice but in nonhuman primates, and we have
10 done a lot of dog vaccine studies and so on.

11 What is interesting about this
12 slide, though: If you formulate MPL in an
13 aqueous solution, you get almost no
14 protection. So the MPL itself isn't
15 intrinsically protective. You have to
16 formulate it in this stable emulsion.

17 By the way, the stable emulsion is
18 an oil and water emulsion. So in that regard,
19 it has similarities to MF59 and to GSK's ASL3.
20 Similarly, though, the emulsion alone does not
21 protect. So if you look at the antigen plus
22 the emulsion, it will not give you the Th1

1 response that you want or protection against
2 this parasite.

3 So these are all the controls that
4 show that you really can't protect with
5 antigen. You can't protect with adjuvant
6 alone. You can't even protect with antigen
7 and the emulsion or with MPL if it is not
8 properly formulated. So that is one thing
9 that is quite important.

10 By the way, I didn't really point
11 out, but Leishmaniasis in this model is the
12 classical CD4 mediated immunity that we are
13 trying to induce. This is one of the systems
14 that Bob Coffman worked out, a seminal
15 contribution of immunology of Th1, Th2
16 responses, and so we pretty much know in this
17 model what we are trying to achieve, both
18 immunologically and, of course, in protection.

19 We have done several trials. We
20 have three open INDs from the FDA for both
21 therapeutic and prophylactic indications. Our
22 first study was done in the United States,

1 showing good safety, some injection site
2 reactions, no SAEs or chemistry problems.

3 Usually, on the third injection we
4 would see some local reportable adverse event,
5 but nothing severe.

6 Immunogenicity: We saw most
7 people given this interferon response,
8 everyone converted to immunoglobulin as
9 specific for the parasite. I think the
10 responses were a little lower than they really
11 are, just because of the assay we were using
12 at the time. So I would expect a little
13 higher percentage of interferon gamma but,
14 nonetheless, it gave us an indication of the
15 dose range of protein that we should be using.

16 In these studies, the MPL dose was
17 kept constant at 25 micrograms of MPL, which
18 is on the low side from what most formulations
19 include. Then, as I mentioned, we did 20, 20
20 and 40 micrograms of antigen, and we found
21 that more was not better in terms of
22 immunogenicity.

1 Now we went then to therapy
2 trials, and several of them were done in
3 Brazil, Peru, and several others are ongoing.
4 I'll just talk about a couple of examples.

5 What is interesting in the Brazil
6 trials again, we got no higher amount of
7 adverse events. These were individuals that
8 are infected with Leishmaniasis, and why we do
9 these trials is because the standard of care,
10 which is pentavalent antimony, is quite toxic.

11 All individuals received standard
12 of care. However, in Brazil in this
13 particular area they like to give a lower dose
14 of antimony. That gave us a little more of a
15 window to compare drug with drug plus vaccine
16 and actually get some indication of potential
17 tendency toward efficacy.

18 These are immunogenicity studies
19 in the Brazil trial. Quite a few things going
20 on here, but focus on the interferon gamma to
21 the parasite antigen that we call 111F or to
22 interferon gamma-2, what we call the soluble

1 Leishmania antigen, the crude protein.

2 What you will see is we have in a
3 dose dependent manner increased responses in
4 the interferon gamma to the parasite antigen,
5 as well as to the -- sorry, the specific
6 antigen, as well as to the whole parasite
7 itself. This is a log scale.

8 So this points out a couple of
9 very interesting things. Even though these
10 patients are infected and they have active
11 lesions, they do not recognize strongly the
12 antigens in the vaccine prior to immunization.
13 They do recognize them post-immunization in a
14 dose dependent way, and the vaccine actually
15 leads to a greater response in interferon
16 gamma to the whole parasite, but not to Th2
17 type cytokines, which is in the blue.

18 So we know that the vaccine then
19 could induce the recognition of new antigens,
20 and the recognition was characterized by a
21 Th1, not a Th2, response.

22 In terms of efficacy, remember

1 that everyone got drug, the standard of care,
2 even though in this case the standard of care
3 was a lower dose than what is typically used -
4 - this is 10 milligrams per kilogram of the
5 antimony -- but we saw a tendency again toward
6 a higher cure rate in the individuals that
7 received vaccine plus drug versus drug alone
8 or adjuvant alone, and at this particular time
9 we haven't seen relapse, at least in two of
10 the dose groups, 10 and 20 micrograms.

11 Just parenthetically, from all the
12 trials we are doing, we think that 10
13 micrograms is probably within the optimal
14 range. We don't think we need 20, and five
15 may be a little bit too low.

16 The other interesting thing about
17 this Brazil trial is, as the investigators
18 saw, a tendency toward more rapid cure. Here
19 we see individuals receiving vaccine. This is
20 percentage cure on this axis. You'll see a
21 little higher, statistically significant
22 higher individuals that were cured at the AD-

1 4, our first observation point, in the
2 individuals receiving the combination as
3 opposed to drug alone.

4 So again, a very small trial, nine
5 patients per group, per arm, and not
6 statistically significant in all parameters,
7 but at least a good tendency toward increased
8 cure. And the investigators noted that the
9 individuals not only tended to cure more
10 rapidly, but leave no scarring. That is
11 probably not too unusual, because the more
12 rapidly you cure, probably the less amount of
13 time the lesion persists, and so the less scar
14 that you have.

15 I will point out that the other
16 reason to do these kinds of studies is because
17 this cutaneous form that we see in Brazil has
18 a tendency to progress to mucosal
19 Leishmaniasis, very destructive, very
20 difficult to treat. So it is another reason
21 you want a very complete and comprehensive
22 therapeutic approach in these patients, and we

1 think that drug plus vaccine is probably the
2 best option.

3 In Peru, we treated mucosal
4 Leishmaniasis, that destructive form that does
5 progress in some of the patients I just
6 described, and again a dose escalation study,
7 5, 10 and 20 micrograms, keeping the MPL
8 standard.

9 Again, you see a good response to
10 the antigen after vaccination and not prior to
11 vaccination -- we will point some of that out
12 in a minute -- and again a good cure rate.
13 Nothing really dramatic here, because in this
14 case we used high dose of antimony. So most
15 of the patients with antimony alone and
16 receiving placebo cured quite well, as well.
17 But we are quite happy, because as you can
18 imagine, when you have a very strong immune
19 response, as you do in these cases with
20 mucosal Leishmaniasis, you want to make sure
21 that your vaccine doesn't exacerbate or have
22 any toxicity, and we did find that in the Peru

1 trial.

2 We don't know yet about long term
3 follow-up whether there will be a lower amount
4 of relapse in the vaccine individuals yet, but
5 as in the Brazil study we did see a tendency
6 again toward a faster rate of cure that
7 excited the doctors that were working on this.
8 It was a blinded study, and they were very
9 happy, because they rarely see people curing
10 clinically before three months, and here we at
11 day 84, a slightly higher number of people
12 curing as compared to placebo alone.

13 Rhea Coler in the lab did some
14 nice immunological studies, and this is just
15 an example of a flow cytometry in a patient
16 that did very well, a cured patient, with
17 immunochemotherapy.

18 These are looking at CD4
19 responses, interferon gamma, TNF and IL-2. So
20 as Bob Seder pointed out recently, these are
21 the three cytokines that are most closely
22 correlated with correlate of protection in

1 Leishmaniasis, and we see this individual
2 making good responses to all these three
3 cytokines after immunization but not before.
4 So again, quite interesting. Strong immune
5 response to Leishmania as a whole, but no
6 immune response to the vaccine antigen, which
7 could explain why some of these people just
8 aren't doing well.

9 This is a similar assay from an
10 individual who did not cure, and here either
11 before immunization or after we see no
12 increase in the cytokine responses.

13 This is the kind of exam they have
14 to do. This is a subjective exam, but it is
15 the lesion of mucosal Leishmaniasis, and again
16 why the individual investigator is very
17 excited, because we see some people responding
18 as early as four weeks after the beginning of
19 immunization, which he had really never seen
20 before. That was a vaccine and drug treated
21 individual.

22 So in summary, with all these

1 trials it is good to point out that the
2 vaccine was safe and well tolerated, quite
3 immunogenic even in a patient with an active
4 immune response. Did not exacerbate disease
5 which, of course, you always want, but I think
6 that that is not a given; and we have seen, by
7 the way, safety and efficacy in mouse models
8 at therapy as well as in dogs, dogs that have
9 visceral Leishmaniasis, which is a problem in
10 the Mediterranean area and Brazil.

11 So we really think that the
12 ability to reverse active disease with a
13 therapeutic vaccine may be possible and that
14 Leishmaniasis may be one of the models in
15 which that is achievable.

16 Several other trials are ongoing
17 or about to start, including visceral
18 Leishmaniasis in India and Sudan, post-kala-
19 azar dermal Leishmania in Sudan. This one is
20 ongoing now, a diffuse cutaneous Leishmaniasis
21 in Venezuela.

22 These are patients that are like

1 the Balb/c of the Leishmania world. They do
2 not respond with a Th1 response. They have a
3 lot of antibody, and they cure with drug, but
4 then they relapse. These are very pathetic
5 kids, because they just keep going their whole
6 life with recurring Leishmaniasis. Our goal
7 here is to use drug plus vaccine and convert
8 their response so that they will have durable
9 response to drug.

10 Then, of course, we are doing
11 another CL trial in Brazil.

12 A special thanks: Thank you very
13 much, Rhea Coler who is here in the audience,
14 for all the preclinical studies in the
15 clinical immunology. Anna Marie Beckman is
16 also here, head of regulatory, that made these
17 all possible, and our clinical investigators,
18 Alejandra Lianos and Evaldo Mascemento.

19 Funding has been going on from NIH
20 for many years and the Bill and Melinda Gates
21 Foundation. Thank you very much.

22 (Applause.)

1 MODERATOR SLATER: Thank you, Dr.
2 Reed. Are there any questions for Dr. Reed?

3 DR. ALVING: This is Carl Alving.
4 When you -- In the military, there are a lot
5 of cases of cutaneous Leishmaniasis that
6 occur, particular in the Middle East and South
7 America and so forth.

8 When they get treated with
9 antimonial drugs, my understanding is that the
10 lesion disappears, but the organism is still
11 there. Is it still there after you find what
12 you call cure?

13 DR. REED: Carl, the antibody
14 levels decrease to the point where it is very
15 difficult to say. The individuals, however,
16 will persist with a positive skin test. So
17 like latent tuberculosis, I would expect the
18 answer is probably yes, but that is a very
19 interesting question, and it is relevant to
20 whether we can use such an approach to reduce
21 the skin parasites so the humans won't act as
22 a reservoir.

1 By the way, one of our goals is
2 working with Allen McGill and the military to
3 replace Pentostam with a vaccine, because as
4 he tells you and you know -- he tells us and
5 you know that this is not a pleasant treatment
6 for the soldiers.

7 PARTICIPANT: Steve, when you are
8 doing these trials on several different forms
9 of Leishmaniasis, you are dealing with
10 patients that have preexisting both antibody
11 and T-cell levels of a variety of sorts. For
12 example, particularly in the DCL patients you
13 will have, as you know, Th2 polarized
14 response.

15 Are you seeing any evidence of
16 skin reactivity, let's say allergic
17 sensitization or anaphylaxis, in the DCL
18 patients or other forms of skin reactivity
19 reflecting recall responses to the
20 vaccination?

21 DR. REED: Yes, that's a great
22 question. Thanks. I should have pointed this

1 out. Both in DCL -- We haven't seen that in
2 DCL, but I will say the trial has only been
3 going on for six weeks. But mucosal
4 Leishmaniasis also is somewhat related to
5 allergy.

6 These patients have IgE, and they
7 have more of a Th2 response. It's a mixed
8 response, but what I am thinking of in this
9 particular setting, that our therapy,
10 especially in that setting of mucosal
11 Leishmaniasis, is more akin to a
12 desensitization for allergy.

13 We are seeing a shift away from
14 Th2 response. The Th1 doesn't necessarily go
15 up much, because they are already very strong,
16 but we do see a decrease in IgE, IL4, IL5. So
17 I think that is what we are really doing, is
18 down-regulating this Th2 response, and it
19 makes a lot of sense that MPL would do that,
20 because MPL is used in allergy desensitization
21 in Europe. So that is why, I think, our
22 choice of the adjuvant was very good.

1 Hi, Carter.

2 DR. DIGGS: Hi, Steve. If I read
3 the slide right, it looked like that in your
4 adjuvant alone trial, you had a higher
5 instance of AEs that you thought were probably
6 vaccine related.

7 So this reflects back to this
8 morning's roundtable and the issue of testing
9 adjuvants alone. Could you comment on that,
10 and particularly with respect to the
11 association of antigen and your emulsion.

12 DR. REED: Right. So in the
13 adjuvant alone arm that we did in Peru, the
14 AEs -- There were no SAEs. The AEs were not
15 significantly different with vaccine or with
16 adjuvant alone.

17 We thought it was important to
18 include an adjuvant alone, because the
19 patients already have organisms. So it is --
20 If you want to see efficacy in the long run,
21 it's nice to have the adjuvant alone. Maybe
22 you don't need the vaccine.

1 What we did not see in that group,
2 and I didn't show the immunology, is any
3 conversion to a Th1 response to the parasite.
4 So we expect that that group won't do as well,
5 but as far as the AEs, there is no really
6 statistical significantly different level.

7 Those are mainly injection site
8 reactions on the second or third immunization,
9 a slightly sore arm. It's just how we put in
10 the reporting.

11 By the way, I should mention this.
12 We gave our vaccine subcutaneously, and we are
13 thinking of switching over to intramuscularly,
14 the intramuscular injections, which we think
15 might help a little bit with the local
16 reactivity.

17 MODERATOR SLATER: Well, thank you
18 very much. I would like to ask Dr. Heather
19 Davis to come up. Dr. Davis is from Pfizer
20 Global Research and Development and Coley
21 Pharmaceutical, a Pfizer company.

22 DR. DAVIS: Thank you very much.

1 I greatly appreciate the opportunity to speak
2 to you today.

3 I will be summarizing the clinical
4 experience with CpG 7909 as the vaccine
5 adjuvant in studies that were carried by Coley
6 Pharmaceutical Group, which is now part of
7 Pfizer, as well as by some of Coley's
8 partners.

9 First of all, what is CpG 7909?

10 It is an agonist for TLR9 which is found
11 within the endosome of human B cells and
12 plasmacytoid dendritic cells. TLR9 normally
13 recognizes molecular patterns that are found
14 in viral and bacterial DNA and not mammalian
15 DNA; hence, it is recognized as a pathogen
16 associated molecular pattern, and these are
17 known as CpG motifs.

18 TLR9 can also be activated by
19 synthetic oligonucleotides that contain such
20 CpG motifs.

21 The desirable features that CpG
22 oligonucleotides offer as a vaccine adjuvant -

1 - first of all, with respect to chemistry and
2 manufacturing, they are fully synthetic. They
3 are easily characterized, at least the ones we
4 have taken into clinic, and they are very
5 stable. Bulk drugs can last for decades, and
6 finished drugs, certainly, for years.

7 With respect to pharmacology, TLR9
8 has the most restricted distribution of all
9 the TLRs in humans, just on the B cells and
10 plasmacytoid dendritic cells. So as long as
11 it works, then this could be a highly
12 desirable feature, since there is no need to
13 activate more than you require. In animal
14 studies it is shown to enhance both antibody
15 and T-cells with Th1 biased responses.

16 CpG 7909, which was also known as
17 Vaximmune when it was used by Coley is a 2 20
18 former oligonucleotide. It contains three
19 copies of the CpG motif, the GT-CG-TT, that we
20 had found to be highly effective in humans,
21 and it is effective in virtually all species.
22 One notable exception is rabbit, which seems

1 to be TLR9 deficient. So it is not just this
2 oligo it doesn't respond to well. It is all
3 CpG oligos.

4 It is a B class, which means it is
5 monomeric and remains linear, no higher
6 ordered structures, which makes it very easy
7 to do the QC, and it is synthesized with a
8 wholly phosphorothioate backbone, which makes
9 it nuclease resistant. So it doesn't have to
10 be encapsulated in any way for protection.

11 This slide summarizes the clinic
12 development history of CpG 7909 as a vaccine
13 adjuvant. There have been a total of 37
14 vaccine clinical trials since the year 2000.
15 The first ones were carried out by Coley, and
16 the approach was to add mix but with an
17 approved vaccine just for proof of concept.

18 Three trials were carried out, two
19 with Engerix-B Hepatitis B vaccine, one in
20 normal, healthy volunteers, one in HIV
21 infected patients, and another trial with a
22 trivalent split flu vaccine in healthy

1 volunteers.

2 A number of trials have been
3 carried out by our commercial partners under
4 license. Emergent, which was BioPort at the
5 time, conducted a trial with their anthrax
6 vaccine. GSK and Novartis -- at that time,
7 Chiron -- have also carried out a number of
8 trials in either the infectious disease space
9 for both of them or oncology for GSK.

10 As well, Lou Miller's group at the
11 NIAID, the Malaria Vaccine Development Branch,
12 has conducted four Phase I trials in U.S. and
13 Mali in adults. The Ludwig Institute has used
14 CpG 7909 with their tumor antigens, and they
15 have conducted a total of 10 Phase I or Phase
16 I/II trials, and an additional 10 trials have
17 been conducted by academic investigators,
18 either in the infectious disease or oncology
19 space.

20 I will now summarize the
21 immunogenicity and safety findings for the
22 Coley studies, as well as some of our partner

1 studies where we have access to all of their
2 data, and I will start with the immunogenicity
3 findings.

4 In Coley's very first trial, we
5 added CpG 7909 to Engerix-B Hepatitis B
6 vaccine and found that it greatly enhanced
7 both the kinetics and the magnitude of the
8 antibody response.

9 This graph shows, with the blue
10 bars being the groups receiving CpG, that the
11 proportion of subjects which achieved a
12 seroprotective titer of 10 million
13 International Units per mil or higher at two
14 and four weeks after a single dose was 58
15 percent and 75 percent respectively, and this
16 is in contrast to zero percent and eight
17 percent for the commercial control vaccine.

18 The actual antibody titers after
19 the first and second doses were ten to
20 fiftyfold higher with the CpG added. The
21 responses at the lowest dose, which is shown
22 in green, the 125 micrograms, were suboptimal

1 but still highly effective; whereas, the .5
2 and 1 milligram doses gave equal
3 immunogenicity and efficacy.

4 A second trial was carried out,
5 also adding CpG 7909 to Engerix-B. In this
6 case, it was conducted in HIV infected
7 patients, half of whom had previously failed
8 to respond to a normal course of vaccination
9 with the commercial vaccine.

10 The subjects received three doses
11 of vaccine which were given at zero, four and
12 eight weeks, thus an accelerated schedule. As
13 in the healthy volunteers, both the kinetics
14 and the magnitude of the antibody response was
15 enhanced, and in the CpG group, which is shown
16 here as pink bars, you can see that the
17 proportion of the subjects which attained and
18 sustained seroprotective titers remained
19 significantly higher all the way up to five
20 years after vaccination.

21 In these same subjects
22 lymphoproliferative responses were evaluated.

1 This is a rather crude assay for T-cell, but
2 that is what was done at the time, and you can
3 see that the CpG groups have had significantly
4 enhanced proliferative responses all the way
5 out to four years after vaccination.

6 In another study that was carried
7 out by Coley and Emergent with DARPA funding,
8 CpG 7909 was added to the commercial anthrax
9 vaccine. The antibody response, both the
10 total IgG as well as its neutralization
11 activity, had enhanced kinetics as well as
12 magnitude with the CpG added. That is shown
13 in green, and is very similar to what I just
14 showed you with the Hepatitis B surface
15 antigen trial.

16 As well, the Malaria Vaccine
17 Development Branch has carried out four Phase
18 I trials which are outlined here. They have
19 had a total of 11 volunteers -- or, sorry, 111
20 volunteers who have received CpG 7909 with one
21 of two different malaria antigens adsorbed
22 alum, the AMA-1C1 or the MSP-1.

1 The adult subjects were located
2 either in the U.S. or in Mali, and they
3 received two or three doses of either the CpG
4 adjuvanted vaccine or the control vaccine,
5 which was the same minus CpG, as indicated in
6 the table.

7 The next slide summarizes their
8 immunogenicity results. With the AMA trials,
9 of which there were three, in the U.S. adults
10 they found an 11 to 14-fold higher titer in
11 the CpG groups after the second vaccination,
12 and a five to sixfold higher after the third
13 vaccination, all highly significant and
14 virtually identical to what we saw with the
15 Hepatitis B surface antigen.

16 In the Malian adults, the
17 responses were significantly less. They were
18 only about twofold higher in the CpG group.

19 For the MSP trial, which was
20 carried out on U.S. adults, there was about
21 tenfold higher titers which were significantly
22 higher with CpG than without, and the figure

1 that is in the lower right shows that data.
2 So they tested two different antigen doses at
3 the low antigen dose, a 40 microgram, compare
4 black with no CpG to red with CpG, or the
5 higher dose, 160 micrograms of antigen,
6 compare blue, no CpG, to green, with CpG.

7 In a trial that was carried out by
8 Daniel Speiser of the Ludwig Institute, T-cell
9 responses to a Melan-A peptide vaccine was
10 tested in melanoma patients, and he found that
11 the T-cell responses were enhanced in the CpG
12 group but not in the group where the peptide
13 had only been combined with incomplete
14 Freund's and adjuvant, incomplete Freund's in
15 both groups.

16 So I am going to show you a single
17 mouse data slide to help put this in context
18 with the next data I am going to show you.

19 This shows that we have found
20 strong synergy between CpG and other
21 adjuvants, especially those that have a
22 delivery or depot type function, and this is

1 presumably because they keep the CpG together
2 with the antigen and ensure delivery of the
3 CpG to the same sites in the node, same cells,
4 presumably.

5 All of the previous clinical data
6 I have shown you had either alum -- that was
7 in every one of the infectious disease
8 vaccines -- or incomplete Freund's. That was
9 in the Ludwig oncology vaccine. So the
10 question is: What happens in humans when CpG
11 is used on its own, and two such studies have
12 been carried out.

13 In the first study, which was a
14 Coley study, CpG was added to a single dose of
15 a trivalent split influenza vaccine, and in
16 this case the enhancement of the antibody that
17 could be attributed to the CpG was only seen
18 in subjects who already had some preexisting
19 immunity. In this case, they had been
20 screened this way, and it was for A/Sydney,
21 and you can see that on the left.

22 On the other hand, the subjects --

1 all of the subjects were negative for
2 A/Beijing and B/Harbin, and in that case there
3 was no effect of the CpG on the antibody
4 titers.

5 Nevertheless, when we looked at
6 interferon gamma secretion from PBMCs that had
7 been restimulated ex vivo, an increase in
8 interferon gamma was noted for all three
9 serotypes regardless of whether or not the
10 subjects had preexisting immunity.

11 The second trial was conducted by
12 GSK, and in this case they added CpG 7909 to
13 Hepatitis B surface antigen without the alum
14 that is normally found in the commercial
15 vaccines.

16 In the upper right, you can see
17 that the antibody level was enhanced over what
18 the antigen would have done alone, but it was
19 not as strong as what we had seen in our
20 earlier study where we had alum present, nor
21 was it as strong as the three other
22 formulations that they tested. But it is

1 noted that these are all adjuvant
2 combinations. The three top lines are not
3 single adjuvants.

4 In the bottom right you can see
5 that the CTL assay was not detected with the
6 CpG on its own with no further formulation,
7 but it was with the other three adjuvant
8 combinations.

9 Moving on to clinical safety: As
10 an overview for all the trials where we have
11 tested CpG either as a sole adjuvant or
12 combined with alum -- I am leaving out the
13 incomplete Freund one, because it has quite a
14 few AEs associated just with the incomplete
15 Freund's, and we also -- because we had not
16 done those trials, we don't have all of the
17 data.

18 In these sets of trials, there has
19 been no serious adverse events related to
20 vaccination. The common adverse events that
21 were seen are similar to those seen with
22 vaccines in general, largely local and

1 systemic reactogenicity, local adverse events
2 being pain, erythema and induration, systemic
3 largely falling under the flu-type symptom
4 category, namely, headache, body ache and
5 fatigue. These are generally of mild to
6 moderate severity, and of short duration,
7 namely, one to two days.

8 This table summarizes the effects
9 of the safety of CpG 7909 in four different
10 vaccine trials. I've introduced all of these
11 to you earlier. So you should recognize them
12 from the left column.

13 In some cases, the frequency and
14 severity of either the local and/or the
15 systemic adverse events was exactly the same
16 as with the control vaccine, and these I have
17 highlighted in green.

18 In other cases, the adverse events
19 were of the same intensity but more frequent,
20 and that is shown in yellow; and in the
21 anthrax vaccine, both local and systemic
22 adverse events were more frequent and more

1 intense.

2 So I am going to show you a single
3 example. That is the second one down or the
4 Engerix-B in the healthy volunteers, to give
5 you some idea of what that data looks like
6 when we make these general conclusions.

7 First of all, local tolerability:

8 You can see that in this case the -- this is
9 the Engerix-B tested in healthy volunteers.

10 In this case, local adverse events were of
11 increased incidence for the two highest dose
12 groups. That is pink and green. But the
13 severity was not increased. They were all in
14 the mild to low moderate level.

15 It should be noted that all of
16 those three doses had been highly effective
17 from an immunogenicity point of view. So this
18 shows that it isn't necessary to have enhanced
19 reactogenicity in order to obtain enhanced
20 immunogenicity.

21 The systemic adverse events were
22 not more severe, and there is no clear pattern

1 for incidence. The two lowest groups of CpG
2 appear to have a higher frequency, but the
3 highest dose group didn't. So it is very hard
4 to make any conclusion from this one, but
5 definitely not clear evidence of increased
6 systemic adverse events.

7 Other safety issues that we have
8 seen or considered: Neutropenia, a transient
9 grade 1 or 2 neutropenia is frequently noted
10 on the second or third days after vaccination,
11 and this returns to baseline by Day Three.

12 We carried out extensive animal
13 studies, and the results from those studies
14 suggest that this is due to cellular
15 redistribution to the periphery and the lymph
16 nodes rather than a true neutropenia. In the
17 other words, the cells were out seeking the
18 danger signal that we have injected in the
19 intramuscular space.

20 The second is more of a
21 hypothetical risk that we have been acutely
22 aware of, because we are injecting as DNA, and

1 that is the presence of anti-DNA antibodies,
2 and whether or not those might induce
3 autoimmune disease.

4 Anti-single stranded DNA is a very
5 common observation in the vaccine studies,
6 more in the 50 percent of the subjects,
7 especially if there is more than one vaccine
8 dose, will present with anti-single stranded
9 DNA antibodies, and these are transient.

10 It is very similar to what can
11 occur after any infection. We have anti-
12 single stranded DNA antibodies that elevate
13 under different circumstances in our life,
14 including infections, and these are considered
15 to have no clinical significance.

16 Anti-double stranded DNA moves
17 more into an area where you might say is there
18 a concern. These were rare. Less than one
19 percent of the subjects in these trials
20 presented with anti-double stranded DNA, again
21 were transient.

22 In these cases, these few cases,

1 they were never associated with an elevated
2 ANA, which would be perhaps a true danger
3 signal, and there was no evidence of any
4 clinical autoimmunity.

5 So to summarize, CpG 7909 has been
6 administered in 37 vaccine clinical trials,
7 and it is for immunogenicity. The best
8 adjuvant effects are clearly when it is
9 combined with a delivery system type adjuvant,
10 and Derek O'Hagan spoke about some of the
11 reasons behind that yesterday.

12 Antibody -- I have shown you some
13 but not all of this data -- shows enhanced
14 kinetics magnitude as well as avidity and
15 duration, T-cell responses, enhanced magnitude
16 and duration.

17 The safety profile is similar to
18 vaccine alone, generally well tolerated with
19 no SAEs. Mild injection site reactions and
20 flu-type symptoms are frequent. In some
21 cases, these are of increased incidence or
22 severity to the AEs seen with the control

1 vaccine, but they still remain in that mild to
2 moderate category.

3 I am just going to end on this
4 last slide which responds to a question that
5 was raised yesterday about oligonucleotides
6 being biologics. So this shows why
7 oligonucleotides on their own -- obviously, a
8 vaccine is a biologic, but on their own are
9 not.

10 They are, first of all, very small
11 compared to plasma DNA which is, I think,
12 where the thoughts came from. They don't code
13 for anything. They are totally synthetic.
14 They bind to a receptor in the body, and
15 signaling through that receptor then they
16 activate a normal cellular function; and
17 contrary to what was reported yesterday, they
18 cannot integrate. They are too short.

19 In contrast, plasmas which are
20 used in DNA vaccines are very large. They are
21 double stranded DNA. They do encode a foreign
22 gene. They are manufactured in a biological

1 system. They are expressing that foreign gene
2 in the nucleus of one of your cells, and
3 integration is theoretically possible.

4 So they are very, very different,
5 even though they are both DNA, and that is why
6 when they are used alone, they fall under
7 drugs. Thank you.

8 (Applause.)

9 MODERATOR SLATER: Thank you, Dr.
10 Davis. Any questions?

11 DR. PETROVSKY: Heather, you
12 mentioned 37 studies. Can you comment on the
13 total number of subjects in those studies in
14 total?

15 DR. DAVIS: I wish I had the total
16 number, but I don't. I think the maximum in
17 one study would have been 60, but some of the
18 oncology ones are as few as five or six
19 subjects. So I'm sorry, I don't have the
20 total number, Nikolai.

21 DR. PETROVSKY: And also we heard
22 this morning with a meta analysis. Have you

1 ever sort of contemplated trying to do a meta
2 analysis by combining the different study
3 results together?

4 DR. DAVIS: It is something we are
5 starting to work on, but we sort of have to
6 group them by the other adjuvants that might
7 be there. So we will be doing that, certainly
8 from a safety point of view, and I have given
9 you a high level summary of that. We will do
10 that with more granularity.

11 For immunogenicity, when it is an
12 alum CpG, very, very similar results have been
13 shown with five different antigens now. And
14 interestingly enough, it is almost the same
15 degree of enhancement seen in mice, even
16 though they have a different TLR9
17 distribution.

18 PARTICIPANT: Yes. The anti-
19 single stranded DNA antibodies that you saw --
20 were they directed against phosphorothioates
21 or normal phosphodiester linked?

22 DR. DAVIS: They would recognize

1 any DNA. We tested them against calf thymus
2 DNA as well as the oligo of our sequence,
3 oligos of other sequences. It was equal rate
4 across the board.

5 PARTICIPANT: Thank you.

6 DR. MALONE: What is your working
7 hypothesis for the decreased responsiveness in
8 Mali population?

9 DR. DAVIS: I am going to -- I
10 know the group from the Malaria Vaccine group
11 is here. Can one of you perhaps answer that
12 question? Ruth?

13 DR. ELLIS: Hi. I am Ruth Ellis
14 from MVDB. There may be some down-regulation
15 of TLR9, particularly in Mali in adults, due
16 to all the cumulative particular malaria
17 exposure.

18 We are hoping to go to Mali in
19 children and look for immunogenicity there.
20 That is our target population.

21 MODERATOR SLATER: We will take
22 one more quick question.

1 PARTICIPANT: I thought that one
2 of the points that you were making in your
3 general slide was that there were more --
4 there was more reactogenicity in the anthrax
5 study, for example, than in the Engerix.

6 I wasn't able to really quite
7 deceive why that was, whether there was a
8 difference in dose or whether you feel that
9 there is a difference in the antigen CpG
10 interaction. I wonder if you could comment on
11 that.

12 DR. DAVIS: It is a more
13 reactogenic vaccine, to begin with, than the
14 other ones that were tested, and that is one
15 of the reasons that emergent is working with
16 CpG as a way to try to be able to reduce
17 antigen dose and reduce number of doses that
18 are required for that.

19 So possibly under those
20 circumstances, adding the CpG tipped it up a
21 little bit more than the other, because that
22 was the only one where we did see both

1 increased frequency and increased severity.

2 That is the best I can come up with.

3 The dose of CpG was the same as
4 used in the other trials. The alum was
5 alhydrogel, the same. So I think it has to be
6 an antigen related situation, and perhaps with
7 dropping that dose of antigen, that wouldn't
8 have happened.

9 MODERATOR SLATER: Thank you.

10 Next is Dr. Gary Dubin from the Prophylactic
11 Vaccine's Clinical Development at GSK. Dr.
12 Dubin.

13 DR. DUBIN: Good morning,
14 everyone.

15 Yesterday many of the presenters
16 in the first session talked about the benefits
17 of using adjuvants and adjuvant systems in
18 terms of factors linked to target populations
19 or targeted pathogens. So I won't cover this
20 slide, which I think was already reviewed
21 yesterday.

22 What I would like to do in the

1 next few minutes is use some concrete examples
2 of clinical development programs for vaccines
3 where we at GSK Biologicals have actually
4 taken different adjuvant systems into the
5 clinic and used these to illustrate some
6 points about clinical development of
7 adjuvanted vaccines.

8 Now yesterday we also reviewed
9 what we mean when we refer to adjuvant
10 systems, and the design principle that we have
11 used at GSK is to combine a vaccine antigen
12 with an adjuvant system. An adjuvant system
13 is defined as a combination of a classical
14 adjuvant -- for example, aluminum salts,
15 emulsions or liposomes -- and an
16 immunomodulatory molecule like MPL, QS-21, CpG
17 or alpha-tocopherol.

18 The goal of using an adjuvant
19 system is to try to induce a tailored immune
20 response to achieve sustained and enhanced
21 protection.

22 So the three examples of clinical

1 development programs that I will describe in
2 the next few minutes are programs that are
3 either supporting vaccines that are licensed
4 in some countries or large development
5 programs where we have accrued a fair amount
6 of clinical data.

7 So the first example I would like
8 to cover is pandemic influenza. I think, as
9 known to this audience, in an influenza
10 pandemic the global population will be largely
11 naive toward the pandemic strain that
12 ultimately emerges, and this will necessitate
13 a high hemagglutinin content and a two-dose
14 vaccine regimen, largely because non-
15 adjuvanted inactivated H5N1 vaccines are
16 poorly immunogenic, even when used at high
17 hemagglutinin content.

18 So this is one of the challenges,
19 I think, which we believe use of an adjuvant
20 system can help overcome.

21 Now a pre-pandemic strategy has
22 several potential advantages in terms of being

1 able to induce protection before a pandemic is
2 declared and ensuring the population is at
3 least immunized, because as I think is also
4 known to this audience, the time window
5 between declaration of a pandemic and
6 significant morbidity/mortality would really
7 be too short to fully protect the entire
8 population. But there are a few requirements
9 that we think a pre-pandemic vaccine needs to
10 have.

11 One is that it should elicit
12 immunity to drifted strains, and the second is
13 that it should be antigen sparing, because
14 potentially the population that might be
15 targeted with a pre-pandemic vaccine would be
16 broad.

17 Now the formulation that we have
18 evaluated is a pandemic vaccine and is a pre-
19 pandemic vaccine, as shown on the slide. It
20 essentially combines H5N1 hemagglutinin in
21 antigen with an adjuvant system that we refer
22 to as AS03, which is a combination of an

1 immunomodulator, alpha-tocopherol and oil-in-
2 water emulsion.

3 So this is actually data from a
4 Phase II study conducted in adults 18 to 60
5 years of age, and I think Dr. Fauci referred
6 to this data yesterday in his opening session.

7 In this study, adults were
8 immunized with H5N1 antigen, either adjuvanted
9 with AS03 or unadjuvanted, and there was a
10 dose range used in the study which included a
11 lowest dose of 3.8 micrograms of the H5
12 antigen and the highest dose of 30 micrograms.

13 As you can see on this slide, when
14 the adjuvanted vaccine was administered even
15 at the lowest dose, the 3.8 microgram dose,
16 after completing a two-dose series, shown
17 here, the immune response induced -- in this
18 case, as indicated by seroprotection rates --
19 achieved the criteria that had been
20 established by CBER and by CHMP; while the
21 highest dose of the unadjuvanted vaccine
22 failed to achieve that same criteria.

1 The same results apply to actual
2 quantification of hemagglutinin inhibition
3 titers, geometric mean antibody titers. So I
4 think this really helped establish proof of
5 principle, indicating that the use of an
6 adjuvant system in this case could convert
7 what is regarded as a relatively poorly
8 immunogenic antigen into one that is highly
9 immunogenic, and it can be used in a lower
10 dose to achieve acceptable levels of
11 seroprotection and geometric mean antibody
12 titers.

13 Now in this same study, a subset
14 of subjects were evaluated for induction of
15 heterologous neutralizing antibody, and I
16 think this is one of the other important
17 criteria that we think that is important in
18 terms of consideration for a pre-pandemic
19 vaccine.

20 So you can see in this graph that
21 shows reciprocal neutralizing geometric mean
22 antibody titers individuals that received

1 adjuvanted vaccine, and these lines each show
2 the subset of subjects receiving the lowest
3 dose, the 3.8 microgram dose, of the
4 adjuvanted vaccine achieved increases in
5 neutralizing activity, not only to the
6 homologous virus, which was A/Vietnam, but
7 also to drift variants which were clade 2.

8 Seroconversion rates for these
9 drift variance range from 75 to 86 percent.
10 Now it is not shown on the graph, but it is
11 indicated here at the bottom. The
12 unadjuvanted vaccine groups for all clade 2
13 viruses failed to have -- or failed to induce
14 responses. So these individuals that were
15 vaccinated with unadjuvanted vaccine did not
16 have detectable neutralizing responses to
17 drift variant virus.

18 Now the next example I would like
19 to turn to is the GSK HPV vaccine. This is a
20 vaccine that has been in development for the
21 last 10 years, and by way of background, I
22 wanted to say a few things about the natural

1 history of HPV.

2 So HPV is now clearly identified
3 as the necessary cause of cervical cancer, and
4 there are two genotypes of HPV, HPV-16 and 18,
5 which are responsible for the majority of
6 cervical cancers. About 70 percent of
7 cervical cancers are caused by these two HPV
8 types, but we believe protection is important
9 beyond HPV-16 and 18, because, obviously,
10 there is a full 30 percent of cervical cancers
11 that are not caused by these types.

12 The target of universal
13 vaccination programs in countries that have
14 introduced HPV vaccination is primarily pre-
15 teenage girls. So we believe it is important
16 that vaccination also induce long-lasting
17 protection, because girls are likely to be at
18 risk of acquiring HPV infection throughout
19 their sexually active life.

20 The composition of the HPV vaccine
21 that we have developed includes virus-like
22 particles, VLPs from HPV-16 and 18, combined

1 with another adjuvant system, AS04. AS04 is
2 a combination of monophosphoryl lipid A, MPL,
3 combined with aluminum hydroxide.

4 In our early development program
5 of this vaccine, we conducted Phase II studies
6 looking at different adjuvant formulations,
7 and this is a summary of some of the Phase II
8 data that emerged from those early studies.

9 In this study, individuals were
10 vaccinated with three doses of HPV vaccine,
11 either containing the AS04 adjuvant that is
12 shown in pink or aluminum hydroxide adjuvant,
13 same antigens, different adjuvant. That is
14 shown in green.

15 Then individuals were followed for
16 48 months, and neutralizing antibody titers
17 were assessed against each of the two VLP
18 components. What you can see here is that for
19 both HPV types, HPV-16 and 18, we saw
20 consistent differences in the level of
21 neutralizing antibody induced, with higher
22 titers observed in the subjects receiving

1 ASO4.

2 I would also like to point out
3 that the peak response, which was seen one
4 month after completion of the three-dose
5 series, predicted what we saw when we looked
6 at the long term follow-up four years out. So
7 higher titers at month seven predicted higher
8 titers at month 48.

9 Now based on the results from
10 those early studies, we initiated a large
11 Phase II-B and Phase III study using the ASO4
12 adjuvanted HPV vaccine. The results that I
13 show on this slide are results from our first
14 efficacy study. So this is human efficacy
15 data.

16 In this study, we vaccinated 1100
17 subjects with the ASO4 adjuvanted vaccine
18 compared to an aluminum hydroxide control, and
19 have followed these subjects out through 6.4
20 years. These are efficacy results for a
21 number of HPV-16 and 18 endpoints over that
22 extended follow-up period.

1 You will see that we measure as
2 endpoints protection against incident
3 infection -- that's detection of HPV-16 or 18
4 -- in previously uninfected individuals at a
5 single time point. We also assessed
6 protection against persistent infection that
7 is consecutive detection, the same virus type,
8 either at a six-month interval -- that's six-
9 month persistence -- or 12-month persistence
10 was another endpoint.

11 Then we have also assessed the
12 efficacy of the vaccine in protection against
13 some of the histologic consequences of
14 persistent HPV infection, cervical
15 intraepithelial neoplasia Grade 1 or worse or
16 Grade 2 or worse. These are recognized as
17 surrogates for cervical cancer.

18 So what you will see in this study
19 is that we observed a high level of protection
20 against the majority of these endpoints out
21 through the entire 6.4 year follow-up period.
22 In fact, in this study there were no

1 breakthrough cases of persistent infection,
2 CIN1+ or 2+ in subjects receiving the HPV
3 vaccine.

4 The follow-up in this study
5 continues. We have now entered another
6 extension phase to this study. So we hope to
7 be able to continue to demonstrate the
8 duration of protection through another three
9 years at least in this longer term follow-up.

10 Now in this study we also assessed
11 the ability of the vaccine to induce
12 protection against infection with
13 phylogenetically related HPV types, at least
14 types that are phylogenetically related to the
15 vaccine types.

16 So HPV-45 is the third most common
17 HPV type associated with cervical cancer and
18 is phylogenetically related to HPV-18, and
19 HPV-31, the fourth most common type globally
20 associated with cervical cancer, is
21 phylogenetically related to HPV-16.

22 Over the six and a half-year

1 follow-up period, we assessed protection
2 against incident infection with HPV-45 and 31,
3 and observed significant protection against
4 each of these two types.

5 Now this is using incident
6 infection as an endpoint, which is not a very
7 robust correlate of cervical cancer, but we
8 have extended these results with recent
9 publication of a Phase III study which has
10 shown protection against six-month persistent
11 infection with these two types.

12 In fact, the recently published
13 Phase III data coming from a large efficacy
14 study that has enrolled about 18,000 subjects
15 confirms the high level of efficacy against
16 HPV-16 and 18, CIN2+ as well.

17 So we think the ASO4 adjuvant used
18 in this vaccine is an important determinant of
19 immunogenicity. That is very clear from our
20 early studies, and we think or at least hope
21 that this will translate into long term
22 protection to be demonstrated with longer term

1 follow-up in our ongoing studies.

2 The third example that I would
3 like to turn to is the example of a malaria
4 candidate vaccine. Malaria is a very serious
5 medical problem, especially in Sub-Saharan
6 Africa. There are about 300-500 million cases
7 of malaria each year and about 1-3 million
8 deaths attributed to malaria. Most of these
9 occur in young children.

10 Although there are currently
11 available interventions, these are not highly
12 effective. They have effectiveness, but they
13 are not highly effective. So that there is
14 clearly a need for malaria vaccine.

15 The vaccine candidate that has
16 been under development combines an antigen
17 which we refer to as RTS, S. So this is a
18 circumsporozoite protein, a proportion of that
19 protein, fused to Hepatitis B surface antigen,
20 combined with another adjuvant system which we
21 refer to as AS02.

22 This is a combination of

1 immunomodulators, MPL and QS21, in an oil and
2 water emulsion.

3 Now the malaria program has
4 actually been a relatively longstanding
5 program in collaboration with Walter Reed Army
6 Institute of Research, and I think research on
7 this vaccine goes back at least 20 years. But
8 in 1996, there was publication of what I
9 consider a very important study, at least at
10 establishing the proof of principle of the
11 difference adjuvants can make.

12 In this study, three doses of the
13 adjuvanted RTS,S antigen were administered
14 with three different adjuvant systems. Two
15 weeks following the third dose, adults were
16 challenged with infectious mosquitos, and then
17 the readout here was protection against
18 malaria.

19 So the three different adjuvant
20 systems that were used in this study were the
21 ASO4 adjuvant, the one that I just talked
22 about used in cervix, the ASO3, the one that

1 I spoke about a few minutes ago used in the
2 pandemic flu, and ASO2.

3 You will see here that this column
4 represents the number of subjects protected in
5 each of the groups receiving the different
6 adjuvant formulations. Now control recipients
7 were completely unprotected. That is how the
8 model is set up.

9 You will see that there was
10 partial protection in subjects receiving RTS,S
11 with ASO4 or ASO3, one out of eight and two
12 out of seven individuals, respectively. But
13 the highest level of protection was observed
14 in individuals receiving the vaccine
15 formulated with the ASO2 adjuvant, and that
16 correlated to about an 86 percent efficacy for
17 the ASO2 formulation.

18 Now there were additional
19 immunologic evaluations done in these
20 individuals, which included evaluation of
21 antibody responses to the RTS,S protein, and
22 then also some mediated immune responses were

1 evaluated, in this case interferon gamma
2 secretion measured by ELISPOT in CD4 and CD8
3 lymphocytes.

4 What is interesting to note is
5 that, if you look at the antibody response in
6 subjects receiving the adjuvant systems that
7 contained the oil and water emulsion -- so
8 that is ASO3 and ASO2 -- there was good
9 induction of antibody responses, didn't differ
10 significantly between those two groups. ASO4
11 induced antigen-specific responses, but at a
12 lower level than the oil and water emulsions.
13 But if you look at the gamma interferon
14 secretion profile, this was different and did
15 differentiate the two oil and water emulsions.

16 So you can see here, with ASO2
17 individuals that were protected -- and that is
18 shown by the black bars -- tended to have
19 higher levels of interferon gamma secreting
20 lymphocytes than individuals receiving the
21 other formulation. So there was a good
22 correlation between the cellular response

1 induced and protective efficacy.

2 Now based on these results, a
3 number of efficacy studies were initiated, and
4 this slide summarizes some of the key efficacy
5 data that has been generated in infants and
6 children in Africa.

7 What you will note is that in
8 separate studies vaccine efficacy against
9 malaria infection, clinical malaria, severe
10 malaria, hospitalized malaria was demonstrated
11 in young children one to four years of age,
12 with long term follow-up showing sustained
13 protection; and efficacy has been evaluated in
14 infants as young as 10 weeks of age in a
15 separate study.

16 So these results, I think, are
17 very promising, and as a result of these very
18 promising results, a large Phase III program
19 will be initiated in the very near future.

20 So those were just some selected
21 examples of vaccine efficacy, immunogenicity
22 linked to different adjuvant systems. I would

1 now like to spend the last few minutes talking
2 a little bit about safety evaluations and some
3 of the considerations that come from what we
4 learned in our clinical development
5 experience.

6 So, clearly, the safety
7 evaluations of any new vaccine, including
8 vaccines containing adjuvant systems, must
9 include traditional safety evaluations, and
10 you have heard a lot about these kinds of
11 evaluations this morning: Solicited local and
12 general symptoms, unsolicited symptoms
13 including serious adverse events and, if the
14 vaccine is being used in women of childbearing
15 potential, pregnancy outcomes.

16 There are additional categories of
17 events which, we believe, need to be
18 considered, depending on the target population
19 for the vaccine and other factors. So adverse
20 events of special interest need to be defined,
21 depending on preclinical data, what
22 information might be available from related

1 products, and again the target population.

2 We also believe it is important to
3 collect information on medically significant
4 adverse events. So these studies are defined
5 of events that prompt physician interactions.
6 These are important, because they generate
7 health care costs but also might be important
8 indicators of important adverse pathology.

9 Then also new onset chronic
10 diseases with a focus on autoimmune diseases
11 are events that we have tried to routinely
12 capture in our adjuvanted vaccine development
13 programs.

14 In addition to these traditional
15 evaluations and the additional categories of
16 events of special interest, we think it is
17 important to consider pooled analyses or meta
18 analyses for rare events -- we heard a little
19 bit about that this morning, and I will come
20 back to that in a minute -- and also in some
21 situations, it might be important to use
22 expert review panels to evaluate certain

1 events or categories of events, depending on
2 data that emerges in clinical studies.

3 I would like to emphasize that
4 these considerations apply not only to
5 vaccines that use new adjuvants or adjuvant
6 systems but to any new vaccine, in fact.

7 So coming back to the example of
8 HPV, this is our largest clinical development
9 program, and I wanted to show you the kind of
10 data that we have collected in our development
11 program, and then show a few examples of
12 clinical data that have come from this
13 development.

14 So in all of our HPV clinical
15 studies, which go back now to our first study
16 beginning about nine years ago, we tried to
17 collect our safety data using relatively
18 consistent methodology, and we collected
19 traditional safety information, solicited
20 symptoms, usually over a seven-day period
21 post-vaccination. Unsolicited symptoms are
22 typically collected for 30 days after each

1 dose of vaccine is administered.

2 Typically, we have collected
3 serious adverse events and pregnancy outcomes
4 over the entire duration of our studies, and
5 in all of our HPV studies we have also
6 collected information on medically significant
7 events and new onset chronic diseases.

8 Now the HPV program is a very
9 large development program most driven by the
10 fact that the clinical outcomes to assess
11 efficacy, CIN2+, are infrequent and, as a
12 result, we have had to do very large studies
13 and, in fact, long term follow-up in these
14 studies to generate enough clinical endpoints
15 to evaluate vaccine efficacy.

16 So this has given us the
17 opportunity to collect a lot of safety data in
18 the course of a development program like this.
19 We have up to 6.4 years of follow-up with an
20 average duration of follow-up in this
21 development program of about two years.

22 So one of the analyses that was

1 done with the HPV program was what I would
2 consider a traditional pooled safety analysis,
3 taking all of the subjects that have
4 participated in this program through the data
5 lock point of this analysis, and looking at a
6 range of adverse events.

7 This large pooled safety analysis
8 which we have conducted includes about 30,000
9 females, 16,000 of which have received active
10 vaccine, and the others have received control.
11 This pooled safety database represents a
12 pretty broad age range as well.

13 Some of the general observations
14 that we have made with this kind of standard
15 pooled safety analysis approach are that the
16 vaccine appears to be generally well tolerated
17 across all age groups. We have not seen any
18 differences in rates of unsolicited adverse
19 events, serious adverse events, medically
20 significant events, autoimmune diseases. I'll
21 come back to that in a minute.

22 We have seen a comparable safety

1 profile in women who had prior exposure to HPV
2 compared to those who were previously
3 uninfected, and overall similar rates of
4 pregnancy outcomes in vaccine and control
5 groups.

6 So these standard evaluations, I
7 think, can be done using the pooled analysis
8 approach, but there are some events that are
9 infrequent enough that you have to use even
10 broader approaches.

11 This is an example of a meta
12 analysis which was conducted recently and, in
13 fact, just published in the last month or so.
14 So it is now available as an electronic
15 publication. It should be in print in the
16 next month or two in the journal Vaccine.

17 In this meta analysis, we have
18 done two things. So first, we have taken all
19 subjects that have been included in the HPV
20 development program and looked specifically at
21 autoimmune diseases.

22 Now I mentioned that we were

1 soliciting physicians, investigators in our
2 studies to report any signs or symptoms that
3 would potentially lead to a diagnosis of an
4 autoimmune condition in the development
5 program, and so there was proactive
6 solicitation.

7 What you will see here is
8 essentially what I showed you in the pooled
9 analysis. When we look at relative risks of
10 any autoimmune disease for individual
11 categories of events -- this is comparing
12 subjects receiving the HPV vaccine over
13 subjects receiving unadjuvanted controls -- we
14 see relative risks that are all very close to
15 one, confidence intervals that overlap one.

16 You will notice that there's a
17 large number of events. So in this analysis,
18 which is restricted to the HPV program, we
19 have about 100 autoimmune events in each of
20 the groups. So that might sound like a lot,
21 but that is because we have done long term
22 follow-up with active surveillance and, I

1 think, good data capture.

2 Now I think even more important is
3 this additional analysis which now expands the
4 meta analysis beyond the HPV program to
5 include subjects that have received any AS04
6 adjuvanted vaccine in one of any of the three
7 largest AS03 adjuvanted programs that we have.
8 So this includes subjects receiving HPV
9 vaccine, adjuvanted HSV, general herpes
10 vaccine, and an adjuvanted Hepatitis B
11 vaccine.

12 What you will notice here is that
13 this analysis includes about 68,000 subjects,
14 36,000 receiving AS04 adjuvant, 31,000
15 receiving control, and the mean duration of
16 follow-up in this study is about 2.1 years.
17 So it is relatively long term follow-up in a
18 very large population of individuals.

19 If we now look at the relative
20 risks for autoimmune diseases, either any
21 autoimmune disease or individual categories of
22 events, you will see again the relative risks

1 are very close to one in all categories.
2 Confidence intervals tend to be relatively
3 narrow, narrower with the broad analysis than
4 with the analysis which includes only the HPV
5 program.

6 We think this kind of data is very
7 reassuring in terms of looking at risk of
8 induction of autoimmunity over the course of
9 very large development programs.

10 So in closing, a few lessons that
11 we have learned about safety evaluations
12 coming from these experiences and other
13 experiences with other vaccines that have been
14 through clinical development.

15 We believe that beyond traditional
16 safety evaluations, it is important to
17 determine events of interest relatively early
18 on in the development program, based on either
19 preclinical data, early clinical data, related
20 products, target population or, in some cases,
21 biological considerations, and use that
22 information to define in advance what you need

1 to collect prospectively to make sure that you
2 have good data to do these kinds of analyses.

3 We think it is also important to
4 define a relevant time period for follow-up,
5 based on biological considerations. So you
6 might think that just collecting more for
7 longer is better. There are, actually, some
8 downsides to having so much data that you
9 might actually have events that occurred,
10 background rates diluting out a potential
11 safety signal.

12 So trying to define the relevant
13 time period does become important in making
14 sure you don't lose specificity in your
15 detection. Then, of course, make sure that
16 you capture the events of interest.

17 The other thing that we think is
18 very important is to use consistent data
19 collection methodology, not only across
20 individual studies in programs but across
21 programs using similar adjuvant systems, to
22 allow pooling of data or the conduct of meta

1 analyses.

2 So in conclusion, we think new
3 adjuvant systems offer considerable promise in
4 helping address important unmet medical needs.
5 The selection of the adjuvant system, of
6 course, needs to be appropriate for the
7 specific need, and I gave you a few examples.

8 The development program should
9 generate data allowing a robust benefit/risk
10 assessment. The studies clearly should
11 demonstrate the value of adjuvant systems but,
12 very importantly, need to include thorough
13 assessment of safety, including appropriate
14 evaluation of events of interest that go
15 beyond what might be considered traditional
16 safety outcomes.

17 Again, to emphasize, these
18 criteria could apply to any new vaccine, not
19 only vaccines using new adjuvant systems.

20 Thank you.

21 (Applause.)

22 MODERATOR SLATER Thank you, Dr.

1 Dubin. Actually, I think we are going to hold
2 the questions until the roundtable discussion,
3 because we went a little bit long.

4 The next speaker is Dr. Greg
5 Glenn, Chief Scientific Officer at Intercell
6 USA, and Dr. Glenn will take us to lunch.

7 DR. GLENN: Well, thank you very
8 much for this opportunity to speak to this
9 audience, and I am very privileged to be with
10 many friends, and I appreciate this chance to
11 talk about Intercell.

12 As you may know, I was formerly of
13 IMI, and Intercell recently acquired IMI. So
14 I am now the Chief Scientific Officer of
15 Intercell USA.

16 I have been interested in
17 listening to some of the previous discussion,
18 specifically about LT and some of the themes
19 of using novel adjuvants and knowing a lot
20 about the adjuvants.

21 So what I am going to talk to you
22 today about is the LT adjuvant patch, which is

1 a potent and safe and, I believe, very
2 flexible adjuvant strategy that can be added
3 to existing vaccines.

4 By the way, I think I will point
5 to the left, if you want to watch the pointer.

6 So the LT, as we all know or many
7 of us are very familiar with this adjuvant,
8 has really -- in a way, was the original novel
9 historical adjuvant, and there has been 30
10 years of tremendous amount of research and
11 understanding about what LT does and how it
12 works.

13 It comes with baggage, and we had
14 some of that discussed earlier. It has safety
15 issues. However, it is a -- In some ways, it
16 is a very safe adjuvant in the sense that it
17 is not very novel. It is a bacterial product.
18 It is well known. There is extensive human
19 exposure in the sense that it is the key
20 pathogenic factor in enterotoxigenic E. coli
21 with hundreds of millions of cases of
22 exposure.

1 So I think it makes for a very
2 interesting discussion to see how one might
3 use a product that is potent, has extensive
4 human exposure, has previous safety issues
5 that could be solved by putting this into a
6 skin patch and providing some of the benefits
7 of immune stimulation at the level of the skin
8 and as well of safety, because it is now a
9 highly sequestered immune stimulation.

10 I think what I will try to do is
11 walk you through the merits of this and some
12 of the thinking we have done in terms of how
13 to develop a patch.

14 Just very briefly, as I mentioned,
15 LT is a potent bacterial product. It is
16 normal -- In the natural setting, it is given
17 off by the E. coli, enterotoxigenic E. coli,
18 and it induces massive fluid secretion.

19 This, by the way, is a profound
20 but transient event. When you look -- This is
21 now looking here at the mucosa. When you look
22 at mucosa post-infectious cholera in ETEC,

1 normally the mucosa is not effaced and looks
2 normal. So a profound effect in the natural
3 setting without sequelae.

4 It is known how it works. It is
5 an avid binder, as Carl Alving mentioned,
6 almost a covalent binding to the GM1
7 gangliocyte, which is a ubiquitous cell
8 membrane component.

9 In the case of the enterocyte, it
10 is found in the lipid raft. It binds, forms
11 a structure that is taken into the Golgi
12 through the ER. There's signals that allow it
13 to get into the cytosol. It causes a rise in
14 cyclic AMP and causes fluid secretion.

15 So I think pathways of how LT is
16 activating in cells have been studied and are
17 pretty well known. In the context of antigen
18 presenting cells, we know that LT induces
19 things that you would hope an adjuvant would
20 do, migration of dendritic cells, of draining
21 lymph nodes which is really a straightforward
22 thing to study in the context of the skin,

1 increased antigen presentation, up regulation
2 of co-stimulatory molecules, etcetera.

3 So this long history and
4 understanding of this adjuvant makes it quite
5 an interesting topic, as far as a potential
6 adjuvant for human use, but it is certainly
7 book-ended by safety issues that have been
8 historically understood as problems that would
9 not allow development by certain routes.

10 So originally LT was thought to be
11 an ideal adjuvant for oral immunization, but
12 it is hard to find a therapeutic window
13 between adjuvanticity and diarrhea caused by
14 the toxin. The same -- We have discussed
15 earlier, nasal use of LT has caused Bell's
16 Palsy.

17 So one of the rationales for
18 targeting the skin would be to provide a
19 potent signal in an ideal biological milieu.
20 Now this is a biopsy of human skin. You can
21 see the three layers, the dermis, epidermis,
22 the stratum corneum, and you can see this very

1 dense population of antigen presenting cells
2 called Langerhans cells in the skin.

3 They make, in my view, an ideal
4 target for immune stimulation, but the skin
5 also represents a significant barrier to
6 penetration, and as GM on ganglioside is a
7 ubiquitous cell membrane component, we have LT
8 arriving in the skin and being taken into the
9 body essentially by the antigen presenting
10 cells.

11 I also would point out that,
12 unlike the nasal passage, the skin, at least
13 in the deltoid, has no vital anatomic
14 structures.

15 I like this picture. This shows
16 the network barrier of immune cells looking
17 down on it. You can see, the pathogen is
18 passing through that. It would have to
19 encounter antigen presenting cells.

20 So in a way, by adjuvanting at
21 this level, we are recapitulating the normal
22 immune process where these antigen presenting

1 cells are activated.

2 Now these are Langerhans cells
3 crawling out of the skin. You see these very
4 nice photomicrographs, and we are just really
5 replicating a normal process that happens on
6 possibly a daily basis where there is immune
7 stimulation at the level of skin. The
8 antigens are picked up by these antigen
9 presenting cells where they crawl out of the
10 skin, migrate to the draining lymph node, and
11 elicit immune response.

12 The we have been working with this
13 concept some, and what I would like to focus
14 on is somewhat of a twist to this, where now
15 we are engaging the skin immune system. We
16 are taking a very potent adjuvant, LT, and we
17 are adding this to an already formulated
18 vaccine -- for example, influenza or pandemic
19 influenza.

20 Now what we are doing is this has
21 to be done in the same draining lymph node
22 site. The APCs are activated, and they arrive

1 at the same draining lymph node, and they have
2 a bystander effect on antigen presentation,
3 immunity, T-cell and antibodies, as I will
4 show you.

5 I think one of the practical
6 merits of this is that you can avoid --
7 Formulation is key. You can avoid formulation
8 issues. You can add this to existing
9 formulations, and it makes a very practical
10 way to adjuvant a vaccine.

11 Now this activation, as I
12 mentioned, is quite regional. Now this is
13 from a mouse where we have immunized it on the
14 back, on the dorsal on the back. The
15 dendritic cells will travel down to the
16 inguinal lymph nodes.

17 What this shows here is simply
18 that, when you add LT to FITC labeled
19 dendritic cells, you increase the number that
20 arrive at the draining lymph node, and you
21 increase their activation state.

22 What I wanted to point out is that

1 it is also a very regional effect. So it is
2 very hard to detect activated antigen
3 presenting cells anywhere but in the draining
4 lymph nodes of the site at which you have
5 applied the patch.

6 This manifests itself in terms of
7 the regionality. So this is, again, a mouse
8 patch here. You can see, at immunization --
9 I believe this was with flu and different
10 doses of LT patches added. So you can see
11 very nice enhancement of the immune response
12 by adding the patch, but when you put it
13 elsewhere, you really get no adjuvant effects.
14 That has been a very key finding for us.

15 So this is a very potent strategy.
16 I am going to show a little bit of animal
17 data. This is a no-patch. This is tetanus
18 toxoid. We actually used this to some degree
19 to look at the potency of the adjuvant patch,
20 because in one dose we have this very profound
21 enhancement of the immune response by adding
22 the LT patch on top of an injection of tetanus

1 toxoid.

2 So these are serum IgG antibodies
3 on this scale, and you can see the individual
4 mice, a very profound adjuvant by adding the
5 patch at the time of injection.

6 it also enhances T-cell immunity.

7 I won't go into too much detail. This is a
8 flu study where we see increased IL4,
9 interferon gamma spots by adding the patch
10 after an injection, and similarly with the
11 mucosal responses which is one of the
12 interesting aspects of skin immunization. You
13 can see, these are enhanced mucosal responses
14 based on adding the patch to an immunization.

15 Then finally,. just to make the
16 point that this adjuvant patch strategy, at
17 least pre-clinically, has been tried in many
18 different antigens, and it is a very effective
19 strategy. Again, this is a trivalent flu.
20 Here is no patch. Here is the patch with the
21 adjuvant, and very big enhancement of the
22 immune response.

1 So what has been unique for us as
2 a company to develop a patch strategy is to
3 find a place where we can do all the
4 development work that relates to delivery,
5 coming up with a commercial format, and yet
6 have something that could really be a product.

7 So we had early success with the
8 delivery of LT as a heat labeled tox with E.
9 coli, and we have done a tremendous number of
10 studies now to focus on this application in
11 terms of optimization.

12 We have to have something that,
13 when you put a patch on and you immunize with
14 this, is a very reliable system, and certainly
15 as good as pushing the plunger and injecting.

16 So I would say today after -- this
17 is actually, I think, a little low. It may be
18 something on the order of 37 trials, many
19 trials of optimization where it generated, I
20 think, a very good system for delivery of LT
21 in a reliable manner. I will show you some
22 data, and I think we understand the safety

1 profile very well.

2 So here the extensive data has
3 helped us understand what the issues are, and
4 I think it will validate what I have been
5 saying, that the skin is a safe route to
6 immunization.

7 Now what is unique here is LT is
8 the key pathogenic factor for traveler's
9 diarrhea or ETEC diarrhea, as I mentioned
10 earlier, and this is actually -- we are just
11 closing the door on the Phase II program and
12 looking to enter Phase III shortly.

13 So we have a lot of data. We have
14 a formulated LT patch with reliable delivery,
15 and this same formulation, the same system,
16 has then been applied as an adjuvant patch and
17 maybe with some differences in the doses. So
18 today we have this two-step system where we
19 have a pre-treatment, and I will talk about
20 that in a little bit, and then a patch
21 application.

22 So what is important for skin

1 delivery? The skin is a formidable barrier.
2 Normally, the stratum corneum, the outer dead
3 layer of skin, is very difficult for things to
4 get through, for compounds, molecules,
5 especially large molecules like LT. But if
6 you do some modest disruption -- and we have
7 published this, by the way. This represents -
8 - This step represented about 25 percent
9 removal of the stratum corneum with a medical
10 grade sandpaper.

11 You can see, in terms of immune
12 response -- this is anti-LT IgG now -- if you
13 don't pre-treat, you see very little response.
14 If you pre-treat, you have a very nice
15 antibody response.

16 So we knew that early on. We took
17 that into a design engineering setting, and
18 now what we have is -- This is a strip. On
19 the other side is a small piece of medical
20 grade sandpaper. On the other side of this
21 push button is a little aperture. So this
22 thing slides across the aperture as you push

1 the button down. It is a highly controlled
2 process. It is very easy to use, and I will
3 show you some data from that, and from the
4 patient standpoint, it is really a non-event.

5 Then we have also then, in
6 concert, developed this patch. What we have
7 tried to do is make the matrix of the patch
8 minimal. It has dry stabilizing incipient
9 formulation. It is a very thin little layer,
10 and essentially it dissolves in contact with
11 water, and I will show you some data on that
12 in just a second.

13 The merits of the dry patch -- it
14 allows you to provide a very stable
15 formulation. I won't go into details, but
16 these are thermal cycling studies where you
17 expose the patches to harsh conditions, and we
18 have a great deal of data.

19 The dry patch is a very good
20 format for stabilizing it, but how do you make
21 the patch work? You have to add water. We
22 rely on what is called transepidermal water

1 loss. So all of us here have some level of
2 transepidermal water loss going through the
3 stratum corneum. When we disrupt the skin,
4 this is greatly enhanced. In fact, it allowed
5 us to optimize the pre-treatment system.

6 Once that happens, the patch
7 becomes very quickly hydrated, and that allows
8 the LT to diffuse passively into the skin
9 where it is then take up by the antigen
10 presenting cells.

11 So this is quite a convenient
12 factor. Many dry vaccine preparations require
13 some logistics for adding water. I just
14 wanted to show you very quickly. This is a
15 dissolution profile form the patch.

16 This is done in the lab. So this
17 is put into buffer, and we simply can't
18 measure how quickly the patch fully dissolves.
19 The LT is fully able to dissolve in our assays
20 in vitro.

21 There is another advantage to the
22 dry patch. It provides an enhanced delivery,

1 and that is because, as you hydrate this
2 patch, you have a high concentration of the
3 antigen forming, super-saturated in a way, and
4 that forces delivery.

5 We have evaluated that. This is a
6 wet, which is simply pipe-headed onto the
7 gauze matrix versus the dry patch, and you can
8 see enhanced antibody responses to LT in that
9 setting.

10 So as I was showing you, we have
11 used the anti-LT IgG in the serum as a way of
12 a marker for delivery. It has helped us
13 optimize the traveler's diarrhea patch, and
14 you can see here, this is now a study, a
15 recent study using the patch system in various
16 permutations.

17 We were entertaining a self-
18 administration format for the traveler's
19 diarrhea, and we have various patches either
20 put on the arm, the arm and the thigh as a
21 prime and boost regimen, put on by clinicians
22 or put on by self.

1 All I wanted to make the point is,
2 even through there are various conditions in
3 various anatomies, the end result, the
4 antibody response is very, very tight between
5 these four groups, and I think it represents
6 an indication that the delivery system is
7 really robust and solved.

8 So now just turning back to how we
9 have tried to show that the adjuvant patch is
10 useful, again we are injecting the vaccine.
11 We are putting the patch over the same
12 draining -- essentially over the site. It is
13 somewhat like adding a Band-Aid. You do the
14 pretreatment step. You do the injection.
15 This pretreatment step leaves some marks here
16 which allow you to register the patch, and you
17 put the patch on instead of a Band-Aid.

18 This is one of the early studies
19 we did. It was a proof of principle of
20 influenza in the elderly. Here we vaccinated
21 56 subjects per group, either with young,
22 elderly or elderly who had a patch. Even in

1 this unpowered study, we are able to see the
2 effects of the adjuvant patch in this setting.

3 Recently, we have been in
4 collaboration with Solvay Biologicals, who
5 makes a H5N1 egg-based vaccine candidate, and
6 under an HHS contract we have been evaluating
7 the adjuvant patch as a strategy for enhancing
8 the immune response to the H5N1 vaccine.

9 So I am going to briefly show you
10 some results from the fairly large trial.

11 This is 500 subjects. It was quite
12 complicated. We did different doses of flu.
13 We did different applications of the patch,
14 and basically we were looking at one versus
15 two doses of the LT patch.

16 Again, a fairly complicated slide
17 here, but I think that the highlights are that
18 we saw our best effects at the higher doses of
19 flu, and they were quite profound, as I will
20 detail in just a second, and you can see very
21 high responses in the groups receiving two
22 adjuvant patches to the H5N1 vaccine.

1 What was most interesting about
2 this data was that the single dose data was at
3 Day 21. First of all, we could measure
4 significant adjuvant effects. What you are
5 looking at here is the percent of subjects
6 achieving seroconversion, which is a fourfold
7 rise, and you can see, we had significant
8 adjuvant effects.

9 At the high dose adjuvant group,
10 we had a very nice adjuvant effect, which
11 plays into a high level of seroprotection. I
12 would note that our assays -- when they did
13 the assays, the subjects were almost entirely
14 naive at Day Zero, and by Day 21 we had a 73
15 percent seroprotection rate which, if we had
16 confidence intervals to expand that, as
17 mentioned earlier, would be a license-able
18 vaccine.

19 So it is a very attractive concept
20 that you could take a single dose pandemic
21 vaccine into a pandemic and decrease the
22 logistics. If you could achieve high levels

1 of seroprotection, and maybe -- Also, I would
2 point out that we have a very high rate of
3 priming in these subjects as well.

4 So the adjuvanted patch seems to
5 allow us to move in the direction of a single
6 dose, and I just throw these pictures up to
7 note how important I think it would be to have
8 a single dose in a pandemic situation.

9 So just a few words on safety. We
10 have done a lot of work here -- I think north
11 of 35 trials. We have been -- It has been
12 important to us to do randomized, double
13 blind, placebo controlled trials.

14 I should mention, most of this
15 work is done with the LT patch for traveler's
16 diarrhea, and we recognize that in the
17 adjuvant patch we are early in the dataset,
18 but I think we have a very characteristic
19 picture.

20 First of all, we don't see
21 systemic signals, as you might expect. The
22 patch is placed on the skin. The adjuvant is

1 taken in by the antigen presenting cells, and
2 so you would expect to see no significant
3 differences between the systemic AEs and
4 placebos in vaccinees.

5 We do see generally mild local
6 site reactions, including rash, pruritus and
7 some post-inflammatory hyperpigmentation.

8 So we are moving ahead with the
9 evaluation of the adjuvant patch with pandemic
10 influenza, trying to improve on the results
11 that we saw. But we are also interested as a
12 company to have a single dose, Japanese
13 encephalitis virus vaccine, also to add this
14 to some of the important vaccines that are
15 used in the context of the elderly and
16 possibly for HPV compliance and multi-dose
17 pediatric vaccines.

18 So just to end, I think that LT is
19 a very interesting adjuvant. It has a unique
20 safety profile, and there is extensive human
21 exposure. But it is also a potent activator
22 of the immune system that we can use in a safe

1 manner and a flexible manner in a patch.

2 For example, for H5N1 pandemic
3 vaccine, this patch can be made well in
4 advance, and if the strain of flue comes
5 through and it is not the same as the vaccine
6 strain, we will not have to remanufacture the
7 patch. So it is a flexible strategy for that
8 setting.

9 I think we are at a place now
10 where the patch has got a good proof of
11 concept. We have a mature product, because of
12 the traveler's diarrhea program, and I think
13 it certainly has borne out the hypothesis that
14 the skin immune system is worth targeting for
15 immune stimulation.

16 So with that, I will end and take
17 questions. Thank you very much.

18 (Applause.)

19 MODERATOR SLATER: So let's go
20 ahead and break for lunch. We will come back
21 in one hour at 20 after one.

22 One final little housekeeping

1 issue. Many of you are going to be leaving
2 for the airports later this afternoon. You
3 can certainly arrange your own taxis or cars
4 on your own, but if you wish, the good people
5 at the registration desk will help you
6 coordinate that.

7 So if you want to go over there
8 during the lunch break and talk to them, they
9 might be able to help you.

10 We will see you at 1:20.

11 (Whereupon, the foregoing matter
12 went off the record at 12:23 p.m.)

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1 guess it was very logical to use as an
2 introduction a few words about the clinical
3 aspects of the EMEA guideline on adjuvants.
4 So there is a guideline that came into force
5 in the middle of 2005, and so that is relevant
6 to the work we perform in Europe.

7 This guideline is not very
8 different as compared to what we discussed so
9 far, and the general principles or general
10 objective that is described in terms of
11 clinical development, we will again refer to
12 that balance we want to have in terms of
13 improving the immune response with the
14 adjuvanted vaccine while avoiding unacceptable
15 increase in local or systemic reactions.

16 So interestingly, this guideline
17 identifies two different scenarios where the
18 recommendations would apply, the first one
19 being the situation of a novel vaccine.

20 So that would be novel adjuvanted
21 vaccines corresponding to a disease for which
22 there was no product existing today, as it

1 would be the case for HIV, CMV vaccines, for
2 instance, or a second situation where we would
3 somehow modify a license or established
4 vaccine, and this could consist either of the
5 addition of an adjuvant or vaccine, removal of
6 an adjuvant or other changes to the
7 composition.

8 Interestingly now, this guideline
9 classifies clinical studies in two different
10 ways. So the first type of studies consists
11 of preliminary studies; second part consists
12 of confirmatory studies. So there is no very
13 detailed specific indication as to what a
14 Phase I, II, III or IV trial should consist of.

15 It is more, I think, logical,
16 general guidance provided. So in terms of
17 preliminary studies, you would be expected
18 there to just have defined what should be your
19 vaccine composition.

20 So one aspect would be to
21 demonstrate the effect of the adjuvant on the
22 immune response, and that could be done in

1 healthy adults. There is no indication in the
2 guideline on what should be exactly the assay
3 to be used. This will depend on the nature of
4 the antigen that you work with, but the
5 guideline, interestingly, mentions the
6 importance of evaluating functional antibodies
7 and also describes cell mediated immunity, and
8 I will come back to that later on.

9 Also, this preliminary phase of
10 development will include those dose-finding
11 studies, and so not only for evaluating the
12 amount of antigen in the vaccine but also the
13 amount of adjuvant.

14 Now the second step of the
15 development will consist of these confirmatory
16 studies. So this would be normally
17 randomized, double blind controlled trials
18 performed in the final population, final
19 target population for the vaccine.

20 While, interestingly, in this part
21 of the development these new adjuvanted
22 vaccines will be considered just as any other

1 new vaccine, and so the same kind of principle
2 for development would have to apply.

3 Then having said this, I guess you
4 understood that one key characteristic while
5 developing an adjuvanted vaccine is that we
6 have multiple objectives at the early stage of
7 development of the vaccine. So we mentioned
8 we want to justify the need for adjuvant, the
9 dose, select the antigen dose. We also want
10 to establish the long term effects of the
11 vaccine, so multiple endpoints.

12 I think having these multiple
13 endpoints doesn't necessarily mean that we
14 could compromise on the statistical
15 considerations, and I here would like to
16 illustrate the way we organize and manage a
17 Phase I trial, a recent Phase I trial at
18 Sanofi Pasteur.

19 So that was a trial of an H5N1
20 vaccine combined to another oil and water
21 adjuvant. So that trial was organized in the
22 population that may look surprisingly big for

1 you, so a total of 265 subjects.

2 The reason why we could do that
3 was that we organized this trial in a
4 staggered fashion. So we started with a small
5 group of subjects receiving the vaccine,
6 waiting until the two doses of the vaccine had
7 been administered, conducted a safety
8 evaluation at that time before enrolling the
9 rest of the cohorts.

10 Of course, the reason why we were
11 able to do that was that, while maybe this was
12 the first administration to man of this type
13 of adjuvant, but at least the antigen was not
14 novel, as this consisted of H5N1 split and
15 activated antigen. But anyway, this design
16 helped us generate very meaningful, useful
17 data to the rest of the development of the
18 vaccine. Even very low dose was as low as 1.9
19 microgram of antigen were sufficient for
20 inducing the type of response that we needed.

21 Also interestingly, so this trial
22 had a long duration, and so had to generate

1 the results that we needed. Finally, I would
2 have to say that we needed to organize a
3 second study to evaluate the dose ranging of
4 the adjuvant itself.

5 Then another topic I would like to
6 cover relates to the way we control our
7 clinical trials when dealing with an
8 adjuvanted vaccine.

9 Of course, we may like to use
10 saline as a control. That is a well known
11 type of control for evaluating baseline
12 reactivity, and it is used regularly in Phase
13 I trials. But personally, I have to say I
14 believe that this type of control has serious
15 limitations.

16 In particular, we saw in that
17 trial I was just referring to before that this
18 may actually compromise the study blind,
19 especially in this type of situation where the
20 adjuvanted vaccine increases a high level of
21 reactogenicity, so high level of pain which
22 would not be the case, of course, with the

1 saline control.

2 Another type of control we may see
3 is commercially available vaccine. That would
4 be, of course, very useful especially for
5 benchmarking of safety and reactogenicity, and
6 especially at late stage of development.
7 However, this one is not always practical and,
8 therefore, cannot apply to all types of
9 programs that we have.

10 A further option -- actually, this
11 is one that was mentioned earlier while we
12 were discussing the preclinical evaluation of
13 adjuvanted vaccines -- is the use of an
14 adjuvant-only control.

15 I have to mention here that this
16 type of control is not recommended by the EMEA
17 guidelines or not recommended for use in
18 clinical studies.

19 Well, you may say that, anyway,
20 this type of control will not induce an immune
21 response and, therefore, if your hypothesis is
22 that the immune response actually is part of

1 the explanation to the type of reactogenicity
2 that you will measure, maybe this type of
3 control doesn't make a lot of sense and would
4 just result in data that are difficult to
5 interpret.

6 I would just like to say that this
7 is not necessarily the case, and here I am
8 illustrating that point with a result we
9 obtained sometime ago with an adjuvanted HIV
10 vaccine at Sanofi Pasteur where we actually
11 observed that the type of reactogenicity --
12 and here I am only showing the results in
13 terms of incidence of pain. So the type of
14 reactogenicity we had with the adjuvant in the
15 adjuvant-only group was as high as that that
16 we had measured in the adjuvant plus antigen
17 group.

18 Then a fourth option in terms of
19 control is, of course, the unadjuvanted
20 antigen. And as you understood before, this
21 is the most useful control to use, especially
22 in early trials where we try to evaluate the

1 impact of adding the adjuvant to the safety,
2 reactogenicity and immunogenicity of the
3 vaccine. But before I conclude on that part,
4 I would just like to remind you that, when we
5 develop -- when we perform clinical trials of
6 a product, we always have to take into account
7 very practical and logistical aspects.

8 To illustrate, this is just a
9 picture of what an adjuvanted vaccine and for
10 this milky emulsion that you heard of -- one
11 of these milky emulsions that you heard of
12 before. So what this may look like as
13 compared to a non-adjuvanted control.
14 Obviously, in this type of situation, the
15 feasibility of a double-blind design may not
16 be -- may be compromised.

17 So this being said, I can now turn
18 on to a couple of points related to the
19 administration of safety, and I will start
20 here, obviously, with a short description of
21 the type of results we may obtain when
22 assessing the safety of an adjuvanted vaccine.

1 So this is just the type of
2 classical evaluation that anybody would
3 perform while evaluating this type of vaccine.
4 So the results presented here again correspond
5 to the situation of this H5N1 vaccine where we
6 monitored both injection site reactions and
7 systemic reactions after our first and second
8 vaccination.

9 Obviously, in this example we had
10 a very high rate of pain induced, especially
11 after the first vaccination. Well, the
12 question we may ask now is to what extent this
13 is relevant to the true vaccine safety. So I
14 think we mentioned before that it is very
15 important to make sure people do not mix up
16 what is reactogenicity compared to the safety
17 of the vaccine.

18 I don't think that with this type
19 of profile, especially taking into
20 consideration the fact that this pain was
21 mild, of short duration and resolved
22 spontaneously, so this was naturally a real

1 source of concern. So overall, I think our
2 interpretations should, in general, remain
3 very cautious and take into account also all
4 the data that may be available such as
5 nonclinical safety, for instance.

6 So this brings me to another topic
7 that we considered before, and that related to
8 the type of adverse events that we may be
9 interested in while developing adjuvanted
10 vaccines. So what kind of safety issue can we
11 foresee at the beginning of such a program?

12 So we discussed a lot yesterday,
13 the type of in vitro data that are available
14 today on the mode of action of adjuvants. I
15 am sure it is very reassuring to all of us to
16 see all the progress that has been made over
17 the last years in terms of understanding
18 better how our adjuvants function. However,
19 I may sound provocative here, but I think that
20 there is still a huge gap between what kind of
21 information we obtain and what understanding
22 we have gained, and to what extent this can

1 impact in practice the organization or the
2 design of our clinical trials, as all of this
3 information that has been generated so far
4 doesn't necessarily result in any specific
5 event that we may like to address or like to
6 evaluate in our clinical trials.

7 I think at the moment, we are
8 still left with this general assumption that
9 probably, as these adjuvants help improve the
10 immune response, probably we have to pay
11 attention to autoimmune diseases.

12 Of course, there are other types
13 of data that may be taken into account, like
14 nonclinical safety data, also signals that may
15 have been obtained from other clinical trials,
16 even from other vaccines, as one of these
17 examples occurred this year.

18 So with this in mind, probably we
19 have to significantly revise this contention
20 that a sample size of several thousand is
21 probably enough to allow detection of adverse
22 events in the course of developing a novel

1 adjuvanted vaccine, so probably this very
2 simplistic view.

3 You heard before that we have a
4 number of additional limits to take into
5 account. Of course, it is important to think
6 of the amount of information we will obtain
7 from randomized controlled trials. So that is
8 to ensure the quality of the data.

9 It is also important to take into
10 account the fact that we may have predefined
11 hypotheses when calculating -- well, to
12 synthesize the safety trial. So you have seen
13 that, when considering the increase in the
14 baseline frequency of a specific event, then
15 instead of just looking at your occurrence of
16 an event in a population, so we will end up
17 with a number of subjects much higher than was
18 the case before.

19 Also, of course, we have to take
20 into account the fact that supportive data may
21 be available, and also ask questions whether
22 or not all of the data need to be made

1 available before registration of the vaccine.

2 Overall, I would think that in any
3 case we will need a case by case evaluation of
4 the needs for a novel adjuvanted vaccine.
5 However, I think an important area to take
6 into account in terms of safety is everything
7 related to the addition investigations that we
8 have the possibility to initiate.

9 I think anyone who would start
10 today a new program, including an adjuvant
11 containing squalene, would be aware of the
12 association that has been proposed between
13 anti-squalene antibodies and the Gulf War
14 Syndrome. So I guess in every case we would
15 be interested in evaluating the induction of
16 such antibodies in our clinical development.

17 So that is just an example. I
18 think, in general, we may have other types of
19 reasons to consider such additional
20 investigations. So that may come either from
21 clinical or preclinical data, and may have
22 been generated on the product we have in

1 development or any other related product.

2 Also, the question may be related either to
3 the pathogen, antigen itself or to the
4 adjuvant.

5 So I will just illustrate here two
6 examples or two examples of the investigations
7 that were conducted at Sanofi Pasteur. So the
8 first one relates to a cytomegalovirus where
9 we had obtained information that an
10 adenovirus-gB recombinant was able to induce
11 autoantibodies in certain mice strains.

12 So this triggered an investigation
13 in the context of development of a vaccine,
14 and here I am referring to a clinical trial.
15 So the gB vaccine produced at Sanofi and
16 combined with MF59 from Novartis was used in
17 that clinical trial.

18 So as illustrated here, so we
19 performed a number of investigations to
20 evaluate, actually, the induction of
21 autoantibodies in humans. As you can see, the
22 results were quite reassuring.

1 Another example is a more recent
2 one and occurred in the context of development
3 of an H5N1 vaccine where, at least
4 hypothetical risk of disease exacerbation had
5 been raised and linked to this observation of
6 the Sixties of an RSV vaccine, so forming
7 inactivated RSV vaccine, so inducing such
8 exacerbation of disease in children.

9 So part of our investigations to
10 respond to that kind of concern included an
11 animal model, and so data were generated in a
12 monkey challenge model of H5N1, but we also
13 conducted some investigations in our clinical
14 trials, and I am here showing the results we
15 obtained in terms of Th1, Th2 balance, also
16 cytokine response after vaccination of
17 infants.

18 So these children received either
19 adjuvanted or unadjuvanted vaccines, and we
20 looked at both the induction of interferon
21 gamma, IL-5 and a number of other cytokines.
22 So with this type of data, we are able to

1 identify the evidence of the similar bias of
2 the response in subjects that received the
3 adjuvanted vaccine as compared to non-
4 adjuvanted control, and again felt that this
5 information was very reassuring.

6 So this brings me to the last part
7 of the presentation. So what about efficacy?
8 Now I don't think I need to go very much into
9 the details of what an adjuvant can bring in
10 terms of improvement of the immune response,
11 and I think you have seen over these two days
12 already a number of examples where the
13 adjuvant was able to improve significantly the
14 profile of the vaccine.

15 Obviously, in terms of antibodies,
16 a number of parameters can be identified, so
17 whether in terms of magnitude of the response,
18 cross-reactivity of the response, also
19 persistence of immunity.

20 I would just like to stop on the
21 last example here, so related to some mediated
22 immune responses. I think that in a number of

1 vaccine, adjuvanted vaccines in development
2 now, we are facing a situation where the
3 disease relates to a situation where we expect
4 some mediated immunity to play a significant
5 role in the protection against the disease
6 and, therefore, these are all situations where
7 generating some mediated immune data is very
8 important.

9 Of course, we have all the tools
10 needed to generate these results today. So
11 science has made significant progress over the
12 last years, and all of these methods allow
13 generation of, certainly, very useful,
14 interesting data. But the question today is,
15 I think, to what extent we can really benefit
16 from these results in the course of developing
17 a vaccine.

18 I think, when looking at the
19 package inserts of all registered vaccines
20 today, we never find any indication in the
21 evidence of CMI data proving essential to
22 registration of the vaccine.

1 Well, obviously, there are a
2 number of challenges to overcome to make this
3 feasible. So for instance, sample management
4 is much more complex when dealing with some
5 mediated immunity as compared to antibodies.
6 Also, there is need for RSV validation that is
7 not as easy to reach as compared to antibody
8 assays.

9 Also, in many situations we know
10 that there is increased, let's say,
11 variability with this type of assay as
12 compared to serology. But while these are all
13 challenges, they can be overcome, and at least
14 there is significant progress being made in
15 just considering the efforts made in terms of
16 HIV or cancer, CMI assay.

17 So in terms of standardization, I
18 think we can be quite positive in terms of
19 what we can expect. So this is just an
20 illustration of the type of CMI data that we
21 have generated so far at Sanofi Pasteur. So
22 in different areas, HIV vaccine, H5N1 vaccine

1 or metastatic carcinoma vaccines are all
2 situations where we were able to detect a
3 significant improvement with the adjuvanted
4 version of the vaccine as compared to
5 nonadjuvanted.

6 So this brings me to a conclusion.
7 Here, I actually thought back to a paper, a
8 title of a paper I had read sometime ago.
9 When looking at this, I am sure that we all
10 want adjuvants to remain our friends in the
11 future.

12 I think for this to be feasible in
13 the future, it will be very important that we
14 pay specific attention to the way we design
15 and analyze our clinical trials. I am sure
16 all the knowledge that we exchange over these
17 two days will contribute to that. Thank you.

18 (Applause.)

19 MODERATOR SLATER: Thank you very
20 much, Dr. Denis. I think we will hold the
21 questions until the roundtable discussion,
22 please.

1 Our next speaker is Dr. Ofer Levy,
2 and we are going to have a little platform
3 change. It will take about 30 seconds to do
4 that. Let me just introduce this section.

5 When we were planning out this
6 session, there was interest among many of us
7 in having some discussion of age related
8 issues, and it was correctly pointed out that
9 we actually could have planned a two-day
10 workshop addressing only age related issues.

11 Nonetheless, we felt it was
12 important to at least introduce this in some
13 way, and Dr. Ofer Levy from Boston Children's
14 Hospital is going to address some of the
15 issues regarding the neonatal immune response,
16 to start off this last section of Session 4
17 before the roundtable discussion.

18 DR. LEVY: All right. Thank you
19 for the opportunity to speak. So the title of
20 my talk today is Distinct Innate Immunity of
21 Human Newborns, Implications for Development
22 of Neonatal and Infant Vaccine Adjuvants.

1 This is work carried out in my
2 laboratory at Childrens Hospital, Boston, in
3 the Enders Building.

4 Just by way of introduction,
5 newborns and young infants have an increased
6 risk of invasive microbial infection, and a
7 statistic that brings that very clearly into
8 focus is that, according to the World Health
9 Organization last year, globally more than 2
10 million infectious disease deaths in those
11 less than six month of age.

12 Common bacterial pathogens include
13 gram-positive bacteria such as Group B
14 Streptococcus. Streptococcus pneumoniae is
15 still responsible for nearly 1 million deaths
16 globally per year. It is worth noting that
17 the Prevnar and other vaccines in the pipeline
18 have been a big win in the West, but they
19 don't cover a lot of the serotypes that are
20 prevalent in other countries.

21 Gram-negative pathogens in this
22 age group include Haemophilus and E. coli, but

1 also Bordetella pertussis, the causative agent
2 of whooping cough. Viral infections in this
3 age group include Herpes simplex virus.

4 Respiratory syncytial virus is the leading
5 cause of infant hospitalization in the United
6 States, and diarrheal diseases are still a
7 prominent player. Rotavirus alone is
8 responsible for several hundred thousand
9 deaths per year in infants and newborns.

10 So, clearly, there is an unmet
11 medical need for prevention of microbial
12 infection early in life.

13 So our lab has been trying to
14 understand the roles of the fetal and neonatal
15 immune system, and particularly the innate
16 immune system, with the underlying hypothesis
17 that, if we understand it better, we might be
18 able to manipulate it to come up with better
19 vaccine adjuvants.

20 So as with any immune system, the
21 role of the fetal or neonatal immune system is
22 to protect against infection, but it is also

1 to avoid potentially harmful pro-inflammatory
2 or Th1 polarizing reactions.

3 It is well known that pregnancies
4 that end up in spontaneous abortion or pre-
5 term delivery are characterized by high
6 peripheral blood concentrations of interferon
7 gamma and other Th1 polarizing cytokines in
8 maternal blood.

9 The fetal and neonatal immune
10 system also mediate the transition from a
11 normally sterile intrauterine environment to
12 a foreign antigen-rich outside world. If you
13 think about it, the first few days of life are
14 quite remarkable.

15 It is the initial colonization of
16 the skin with fluorides, the initial
17 colonization of the intestinal tract with
18 bacteria, and early host-microbe interactions
19 affect the risk of the newborn for infection,
20 and we will remember that pre-term newborns
21 are particularly susceptible to infection, but
22 even full term newborns after a normal birth

1 have a pretty high susceptibility to
2 infection.

3 Then also, of course, immune
4 system polarization is affected, and we are
5 all aware of the hygiene hypothesis that, in
6 a nutshell, exposure to infection and
7 infectious agents early in life is correlated
8 with less autoimmunity and less auto-
9 inflammatory disease.

10 So in the past 10 years there has
11 been tremendous progress in defining the
12 pathways by which the innate immune system
13 recognizes danger signals, both endogenous
14 danger signals and also microbial products.

15 This kind projects weird here.
16 Some of the molecules look radioactive, but
17 nevertheless, this is supposed to represent
18 lipopolysaccharide or endotoxin, which is
19 found on the outer leaflet of the gram
20 negative bacterial outer membrane, and as we
21 know, that signals through toll-like receptor
22 four.

1 This is supposed to the surface of
2 a monocyte, macrophage or antigen presenting
3 cell and bacterial lipo-peptides derived from
4 gram positive and gram negative bacteria
5 activate through toll-like receptor 2, and
6 there are signaling cascades that are
7 activated that culminate in NF-kappa B
8 activation.

9 We know these pathways are
10 important in humans, not just in mice, because
11 human patients who are defective in this
12 interleukin receptor associated kinase-4 or
13 IRAK-4 -- these children present to our
14 clinics with recurrent staphylococcal and
15 streptococcal infections.

16 I follow a child with recurrent
17 staphylococcal meningitis, and when we
18 sequence the IRAK-4 gene, it is a deficient
19 IRAK-4. This observation was initially made
20 by Jean-Laurent Casanova in Paris. He is now
21 at the Rockefeller.

22 So we know these pathways are

1 relevant in humans, number one. Number two,
2 we know that children with IRAK-4 deficiency
3 grow out of their immunodeficiency. So if
4 they make it to their teen years and beyond,
5 their susceptibility to infection drops, and
6 that indicates that these pathways are
7 particularly important in newborns, infants
8 and young children.

9 There was recently a paper in the
10 journal Science about MyD88, the adaptor
11 molecule in the Toll pathway, and certain
12 alleles of Myd88 and certain hypomorphic
13 alleles.

14 You end up with recurrent
15 Streptococcal infections, and once again in
16 that paper by Luke O'Neill and many other co-
17 authors, the children grow out of this
18 susceptibility, so once again indicating this
19 pathway is important in humans, and it is
20 particularly important early in life.

21 So part 1 of my talk is
22 characterizing the mechanism for polarized

1 neonatal monocyte responses. There is a vast
2 literature about neonatal immunity, and it
3 mostly says that neonatal leukocytes don't
4 function as well as adult leukocytes when you
5 test them in vitro. That sums up about 1,000
6 papers, and it is most of what those papers
7 will say.

8 Then the question is -- and I
9 don't want to be too dismissive, but I am
10 trying to quickly give you the background.
11 But we decided to take a whole blood screen
12 comparing neonatal cord blood and adult
13 peripheral blood, probing TLR agonists,
14 because when we started this project a few
15 years ago, the pure agonist for various TLRs
16 were just being described.

17 We measured TLR induced production
18 of tumor necrosis factor alpha, which is pro-
19 inflammatory but, as you know also, Th1
20 polarizing, and interleukin-6. It is
21 underappreciated fact that interleukin-6 has
22 anti-inflammatory properties. It actually

1 inhibits neutrophil migration. It also is Th2
2 polarizing, unlike TNF, and is regulated very
3 differently.

4 So cutting to the chase, if you
5 take human adult peripheral blood, and if you
6 take human newborn cord blood, and you
7 incubate them in vitro with Toll agonists and
8 then you measure in the extracellular phase
9 TNF and IL-6 by ELISA, and you plot TNF on the
10 Y axis against IL-6 on the X axis, you find
11 that the adults and the newborns segregate to
12 two completely different groups.

13 The adults make a lot of TNF and
14 very little IL-6. The newborns make a lot of
15 IL-6 and very little TNF. This is something
16 we published in Journal of Immunology a couple
17 of years ago.

18 It turns out, as we tried to break
19 apart the mechanism, that human neonatal blood
20 plasma reduces TNF alpha production in
21 response to agonists of Toll-like receptors 1
22 through 7.

1 What we did was we took human
2 neonatal cells, and we spun them down, and we
3 washed extensively with a pyrogen-free buffer,
4 and then we resuspended the neonatal cells in
5 adult plasma, and we did, conversely, adult
6 cells in neonatal plasma, a mix and match
7 experiment, if you will, and then stimulate
8 with different Toll agonists and look at
9 whether TNF production is enhanced or
10 inhibited.

11 These big black bars shooting up
12 indicate that, if you take human newborn cells
13 and culture them in adult plasma, you
14 dramatically enhance the amount of this Th1
15 polarizing cytokine, that you make TNF.
16 Conversely, if you take adult cells and put
17 them in newborn plasma, you inhibit production
18 of TNF.

19 There was an exception to this
20 rule, and we will talk about that exception a
21 little later. But we tried to target here:
22 Let's understand why Toll-like receptor-1

1 agonists, these bacterial lipo-peptides, are
2 so inhibited by neonatal plasma.

3 We did a large study that was
4 published in JI, but to cut to the chase, we
5 found that there is a soluble low molecular
6 weight factor in human newborn cord blood that
7 turned out to be adenosine.

8 Adenosine is an endogenous purine
9 metabolite made by all the cells in our body,
10 that acts through cognate adenosine receptors.
11 It is an anti-inflammatory factor. It is a
12 counter-regulatory factor that is elevated by
13 hypoxia and stress.

14 If anybody has been present at the
15 birth of a baby, you see how the baby comes
16 out blue and purple until it takes its first
17 breaths, and we were able to show that
18 adenosine is at very high levels by HPLC
19 measurement in human neonatal plasma, and it
20 acts through seven transmembrane adenosine
21 receptors.

22 If you block those receptors

1 pharmacologically, you can dramatically
2 enhance TNF production, here on the Y axis, in
3 response to a Toll-2 agonist, with no effect
4 on adult TNF production and no effect on IL-6
5 production. So this adenosine factor
6 selectively inhibits TNF production in
7 newborns.

8 We think the mechanism is through
9 inducing cyclic AMP. So there is ATP, and
10 under the aegis of the enzyme adenylate
11 cyclase, ATP gets converted to cyclic AMP.
12 That is the key second messenger that earned
13 Dr. Sutherland his Nobel prize and is induced
14 by ligands via 7-trans-membrane receptors like
15 epinephrine, norepinephrine, etcetera, and
16 these are G-coupled.

17 It is very important to know that
18 in PubMed, if you look at the literature,
19 study after study shows that cells that have
20 a lot of cyclic AMP in their cytosol are
21 unable to produce Th1 polarizing cytokines,
22 but they preserve production of IL-6 and other

1 cytokines.

2 So we took neonatal cord blood
3 mononuclear cells, and we lysed them, and we
4 measured cyclic AMP by competitive immuno-
5 assay, and it turns out that at birth the
6 mononuclear cells in the cord blood of
7 newborns have more than 20-fold more cyclic
8 AMP per cell than adult peripheral blood
9 mononuclear cells.

10 So the physiology of the neonatal
11 leukocytes is profoundly different from that
12 of adults, and serum confers this. If you
13 culture the cells in newborn serum, you detect
14 cyclic AMP, but if you culture them in adult
15 plasma or serum, you don't detect cyclic AMP.
16 Conversely, neonatal serum when placed on
17 adult cells, will induce cyclic AMP.

18 So this low molecular weight
19 adenosine factor induces cyclic AMP in these
20 cells. And now we hypothesize that cyclic AMP
21 may be a general regulator of neonatal
22 cytokine production, and we hypothesize that,

1 because it is known that newborns don't make
2 TNF alpha very well or interferon alpha very
3 well or interferon gamma or IL-12 or IL-1.

4 Guess what? The world literature
5 suggests that cyclic AMP inhibits all of
6 these. Conversely, newborns make IL-6. They
7 make the anti-inflammatory counter-regulatory
8 IL-10 well, and they make IL-23 well. In all
9 three of these cases, cyclic AMP either
10 enhances or does not inhibit.

11 So that is a hypothesis I have put
12 forward recently in a review article I wrote
13 for Nature Review's Immunology, and this is
14 also from that review article, looking at
15 mechanisms that polarize the cytokine
16 responses of human neonatal antigen presenting
17 cells.

18 There is the extra cellular
19 adenosine binding its adenosine receptor,
20 inducing cyclic AMP production, which through
21 protein kinase-A dependent and independent
22 manner inhibits production of TNF and other

1 Th1 polarizing cytokines.

2 Now part 2 of my talk is the
3 discovery of a Toll-like receptor pathway that
4 is refractory to this inhibition, and here I
5 very much have to acknowledge the work of
6 Eugene Suter and Victoria Philbin in my lab,
7 and we believe that the preservation of this
8 pathway suggests novel neonatal vaccine
9 adjuvants.

10 I want to emphasize again that
11 vaccines at birth, it has been argued, could
12 be a key to global health. We talked about
13 greater than 2 million deaths per year due to
14 infection in those less than six months.

15 According to World Health
16 Organization, birth is the most reliable point
17 of health care contact in resource poor
18 settings. If anybody -- if a child is going
19 to see a health care provider at all during
20 their life, it is on the day they are born,
21 whether it is a midwife or a nurse or a
22 doctor.

1 So early life immunization, such
2 as with BCG vaccine, is associated with higher
3 vaccine coverage. It is a practical point.
4 However, vaccines effective in adults and
5 infants may be poorly protective at birth, and
6 that includes the conjugate vaccines.

7 Impaired neonatal AMP responses
8 have been described to most adjuvants. There
9 is, therefore, an unmet medical need for
10 vaccine adjuvants that are effective at birth.

11 This is the general diagram of the
12 antigen presenting cell, expressing Toll-like
13 receptors and other pattern recognition
14 receptors, and that activation through these
15 receptors can enhance the second signal needed
16 to enhance APC function and lead to long
17 lasting immunity.

18 This is a figure that was recently
19 made by Victoria Philbin in our lab for a
20 review article that will be coming out soon in
21 the journal Pediatric Research, and it reviews
22 vaccine adjuvants and how they engage innate

1 immune pathways.

2 Incomplete Freund's adjuvant, it
3 turns out, activates through these nucleotide
4 oligomerization domain proteins that act
5 through MF-kappa B. Hemophilus influenza Type
6 B vaccine, the one that is conjugated to OB-C,
7 actually is a TLR-2 agonist because of the OB-
8 C portion, and that was shown by Schreiber and
9 Eike Latz at U. Mass.

10 BCG or Bacillus Calmette-Guerin
11 expresses Toll-like receptor 2 and Toll-like
12 receptor 4 agonists. Attenuated live viruses
13 engage the RIG pathway that culminates in
14 production of Type-1 interferons, important
15 for cross-presentation.

16 Then alum, which is the most
17 commonly used vaccine, as you know, through
18 work from Fabio Re and other groups, Gabriel
19 Nunez, engages the inflammasome. So this
20 adjuvant that we have been using a very long
21 time with limited understand -- now we
22 understand the pathways involved, and this

1 will trigger IL-1 production through caspase
2 activation.

3 I am going to tell you a bit about
4 the imidazoquinolines, a family of compounds
5 that activate through Toll-7 and 8, but also
6 engage the inflammasome.

7 So viz a viz imidazoquinolines,
8 they are synthetic, low molecular weight
9 immune response modifiers developed by Dr.
10 Richard Miller at 3M Pharmaceuticals. This is
11 adenosine, by the way, and you could see the
12 resemblance there.

13 This is a first FDA approved
14 stand-alone TLR agonist, imiquimod or a Toll-7
15 agonist. As you know, it is FDA approved as
16 a topical therapy that will induce antiviral
17 interferon in the context of human papilloma
18 virus or warts, and it is safe and efficacious
19 for that indication. Turns out to be a Toll-7
20 agonist.

21 Of course, there are a variety of
22 congeners. R-848 which has these ethoxyl and

1 hydroxyl groups is more polar, more soluble
2 and also engages Toll-like receptor 8.

3 We found some very interesting
4 effects when we started to explore these
5 compounds. We are calling the Toll-like
6 receptor 7 as expressed on B cells and
7 plasmacytoid DCs, whereas Toll-like receptor
8 8 is on monocytes and myeloid DCs. So 7 and
9 8 are both located in endosomes.

10 So when we tested the ability of
11 human newborns to respond to imiquimod or a
12 Toll-7 agonist, it was very much impaired,
13 much like that of the other Toll agonists we
14 discussed. However, we did find a Toll
15 agonists that was refractory to the inhibitory
16 effect of plasma adenosine, and that turned
17 out to be R-848, which is one of the
18 imidazoquinoline congeners.

19 There is the structure of it
20 again. This is TNF production on the Y axis,
21 increasing concentration of this R-848
22 compound. This is in whole blood in vitro

1 assay of cord blood and adult peripheral
2 blood.

3 This is the congener from
4 imiquimod with enhanced solubility. It has
5 been in Phase III human trials as a topical
6 against Herpes simplex virus, and did reduce
7 HSV reactivation and shedding, but it did give
8 a local irritation that was unacceptable as a
9 side effect profile for that indication.

10 Now TLR-8 agonists turns out can
11 induce up-regulation of CD40 on neonatal
12 myeloid DCs. In the world of newborn
13 immunology, that is a pretty big deal, because
14 turning on neonatal antigen presenting cells
15 has not been an easy thing to do.

16 Most of the literature, again, in
17 this field is how a variety of stimuli fail to
18 adequately up-regulate co-stimulatory
19 molecules on neonatal cells.

20 Here, we took human neonatal cord
21 blood and, by flow cytometry, gated on myeloid
22 DCs and measured CD40 up-regulation, and of

1 all the Toll agonists -- these are Toll-7
2 agonists -- the Toll 8 and Toll 7/8 agonists
3 gave stronger CD40 up-regulation, both in
4 adults, in black bars, and newborns, in white
5 bars, that exceeded that by lipopolysaccharide
6 and Toll-2 agonists.

7 Here, we worked with monocyte-
8 derived dendritic cells, culturing monocytes
9 in vitro, and then differentiating them to
10 dendritic cells, and showing up-regulation of
11 CD80 and CD40 and production of IL-12p70,
12 recalling that it is the p70 form of IL-12
13 that is Th1 polarizing.

14 It is a good marker for good
15 vaccine adjuvant activity, and R-848 and the
16 3M002, which are imidazoquinolines activating
17 through Toll-8 were superior to the Toll-7 in
18 inducing IL-12p70 in newborns.

19 Now there may be some interest in
20 engaging the Toll-7 pathway, because
21 interferon alpha production is an important
22 feature of some adjuvants and induces a cross-

1 presentation. So here we looked at interferon
2 alpha production.

3 Again, the world literature would
4 suggest that human newborn cells are not very
5 good at making interferon alpha, but when we
6 took the Toll-7 and 7/8 agonists, we were able
7 to induce interferon alpha from human neonatal
8 cord blood and up-regulation of CD40 on plasma
9 cytooid DCs. So a combined 7/8 agonist might
10 afford the advantages of both a 7 and 8
11 pathway.

12 Here we have used a bioinformatic
13 approach to look at mRNA production in human
14 neonatal monocytes isolated to purity and
15 cultured in vitro in autologous plasma, and
16 compared it to a Toll-4 endotoxin stimulation,
17 and we plotted the LPS response against the
18 imidazoquinoline Toll-8 response.

19 The dots that you see above the
20 line of equivalence indicate that the Toll-8
21 agonist gave a superior induction of mRNA
22 transcript for these cytokines, and at the

1 protein level by a multi-analyte B platform,
2 we were able to show that the Toll-8 agonist
3 gave a stronger cytokine induction than the
4 Toll-4 agonist with respect to newborn
5 monocytes.

6 A question I often get when I
7 present this work is you are showing us a lot
8 of work with cord blood; how about peripheral
9 blood from older infants? So we do have some
10 limited data here.

11 Here is an infant from the United
12 States who was tested, a healthy infant, at
13 two months of age and 15 months of age, the
14 same child. We stimulate in vitro for TNF
15 alpha production in whole blood in comparison
16 to a Toll-2, Toll-4 or Toll-7 agonist.

17 It is only the Toll-8 agonist that
18 gives a robust TNF production, both at two
19 months of age and at 15 months of age.

20 Similarly, through a collaboration
21 with the Medical Research Council in the
22 Gambia with Sarah Burle and Katie Fitzgerald

1 there, we have blood from a nine-month-old
2 Gambian infant, and again the 7/8 and 8
3 agonists give the most robust response.

4 So we know these effects are not
5 evident just in cord blood, but also
6 peripheral blood of human infants.

7 By what mechanisms do the Toll-8
8 agonists activate human monocytes? They lead
9 to superior p38 MAP kinase phosphorylation,
10 which is important for TNF production.

11 So by flow cytometry we are able
12 to show that, when you add these Toll-8
13 compounds, you get stronger phosphorylation of
14 p38 MAP kinase with a 8 agonist versus the 7
15 agonist, also a more profound and prolonged
16 degradation of NF-kappa B. So these correlate
17 with the enhanced efficacy, and we published
18 in the journal Blood a number of years ago.

19 We also have recently showed --
20 and this is unpublished information -- that
21 the Toll-8 agonists are relatively refractory
22 to inhibition by cyclic AMP. That is the

1 intracellular factor that we posit is
2 polarizing the neonatal response.

3 Here is increasing amounts of
4 dibutyryl cyclic AMP. This is a cell
5 permeable cyclic AMP analog. It is a
6 pharmacologic manipulation to enhance cyclic
7 AMP in the cytosol. As you increase cyclic
8 AMP, you inhibit TNF production as a percent.
9 That is 100 percent with no enhancement of
10 cyclic AMP, and the Toll-8 agonist is
11 relatively refractory to that inhibition.

12 If we want to develop an animal
13 model for this compound as a neonatal vaccine
14 adjuvant, as discussed, the Rhesus macaque
15 becomes very important as a primate model for
16 Toll-like receptor 8 studies.

17 There are the protein alignments
18 for mouse TLR-8, human TLR-8 and the monkey
19 TLR-8, and these are the leucine rich repeats
20 that are characteristics of the extracellular
21 domain of the TLRs and, as you could see just
22 by glancing on it, the human and monkey

1 structure, the leucine rich repeats are much
2 more similar to one another, and the mouse is
3 divergent; and as you know, the mice express
4 Toll-8, but they don't respond to all the same
5 Toll-8 agonists that the human does.

6 Also very important work done by
7 Wille-Reece and Seder who are here at the
8 meeting is a Toll-like receptor 7/8 agonist
9 enhanced vaccine responses in adult rhesus
10 macaques in vivo.

11 They did studies with HIV GAG
12 protein, and also covalent linkage of Toll-
13 like receptor 7/8 agonists to GAG protein,
14 enhanced both the magnitude of the Th1
15 response, enhanced both antibody responses and
16 cellular immunity. These are published in
17 PNAS and JX MED a few years ago.

18 We have looked at cord blood from
19 rhesus macaques and peripheral blood from
20 infant macaques in vitro in collaboration with
21 Keith Mansfield at the New England Primate
22 Research Institute, and we show robust TNF

1 alpha production from rhesus macaque blood
2 stimulated in vitro with Toll-like receptor
3 7/8 or 8 agonists.

4 What you could see here is that
5 Toll-2 agonist in the cord gives very little
6 TNF, much like our human data, the Toll-7 not
7 much, but the Toll-7/8 and the Toll-8 give
8 superior TNF induction, and that is not just
9 in the cord. It is throughout infancy. This
10 is blood collected every week from the same
11 monkey. We follow them as they mature. So
12 that suggests that the macaque is a realistic
13 model for us.

14 The Toll-7/8 agonist also induces
15 CD40 up-regulation on infant rhesus macaques.
16 So if we take blood from infant macaques and
17 stimulate and then do flow cytometry in vitro,
18 gating for CD40 expression on myeloid DCs,
19 here are the infant macaques. If anything,
20 you get a stronger response in the adult.

21 Finally, what we have done most
22 recently is take a photoactivatable agonist

1 and link it to a model antigen, CRM197, and we
2 can show that that confers Th1 polarizing
3 activity on newborns.

4 So here is a compound we worked
5 with courtesy of 3M Pharmaceuticals. There is
6 imidazoquinoline backbone, and there is the
7 aryl azide that has been added that will
8 confer photoactivatable conjugation.

9 Here we could show that this
10 compound in human newborn blood -- and this is
11 adult's response curve -- as you increase the
12 concentration of the compound, you induce TNF.
13 These are the newborns. These are the adults.
14 The newborns give at least as strong a
15 response as the adults.

16 There is the chem draw reaction
17 for post-reaction mechanism upon ultraviolet
18 light for the conjugation. This is gel
19 filtration, and the pooled fractions by silver
20 staining. So we have CRM physically
21 conjugated to this imidazoquinoline.

22 Then when we take the conjugate

1 into newborn and adult blood, we get a robust
2 TNF induction in a way that the CRM alone did
3 not induce.

4 It is also important to note a
5 paper by Peng and co-workers that, of all the
6 Toll pathways, Toll-like receptor 8 agonists
7 reverse the suppressive activity of human T-
8 REG cells. That is a paper in Science in
9 2004. Synthetic and natural Toll-8 agonists
10 reversed T-REG mediated suppression in vitro
11 and in vivo through a MyD88 pathway, and did
12 an adoptive transfer of Toll-8 agonist
13 stimulated T-regs to tumor bearing mice,
14 enhancing anti-tumor immunity.

15 So TLR-8 plays a key role in
16 enhancing adaptive immune responses. As you
17 know, T-REG cells are very important, and they
18 are there for a reason, but they can also
19 serve to limit adaptive immune responses, and
20 they are particularly plentiful and
21 suppressive at birth.

22 So this is our current cartoon on

1 how these agonists might work. They act
2 through Toll-8, and we have some SI-RNA data
3 showing that, but they also may act by
4 blocking at the adenosine receptor. I haven't
5 shown you that data.

6 They act on T-REG cells. This is
7 Peng's work to reverse T-REG mediated
8 suppression, and by all these pathways then,
9 enhancing a Th1 type response.

10 Of course, safety will be a
11 primary concern in developing these, as with
12 any new compound, but there are some reasons
13 that local and transient engagement of TLR-8
14 might be safe.

15 Conjugation might localize the
16 adjuvant effect, as discussed earlier. A TLR-
17 7 adjuvant is apparently safe and efficacious
18 in adult non-human primates, at least in those
19 primates studied in the Wille-Reece papers.

20 A TLR-7 agonist, imiquimod, is FDA
21 approved for human use, and has been used in
22 pediatric indications such as Mollusca pox.

1 A TLR-7/8 and 8 agonist also induced counter-
2 regulatory IL10, and systemic mechanisms that
3 keep Th1 responses in check will remain intact
4 if you have a covalently modified local depot
5 effect, the adenosine mechanism described in
6 the rest of the T-REG cells on the body.

7 So conclusions and future
8 directions: Neonatal immune responses to
9 agonists of Tolls-1 through 7 are skewed
10 toward a low TNF to IL6 ratio by the adenosine
11 system. Impaired Th1 responses of newborns to
12 Toll agonists may help avoid allo-immune
13 reactions, but contribute to infection
14 susceptibility and impaired neonatal vaccine
15 responses.

16 TLR-8 agonists activate robust Th1
17 polarizing responses from adult APCs,
18 exceeding responses to other TLR agonists,
19 even setting aside the neonatal data, and TLR-
20 8 agonists are refractory to the inhibitory
21 effect of neonatal plasma adenosine, and
22 induced robust adult-like Th1 responses from

1 neonatal APCs. They activate through p38, NF-
2 kappa B, and I haven't shown you this, BTK
3 kinase, and they are refractory to the cyclic
4 AMP inhibition.

5 So our hypothesis is that Toll-8
6 agonists conjugated vaccines will induce
7 protective neonatal CD4 positive T-Cell and
8 antibody responses, and our approach will be
9 to assess vaccine adjuvant potential of Toll-
10 7/8 agonist in neonatal rhesus macaque model.

11 That has potentially great public
12 health relevance, and will require appropriate
13 partners and resources, and there is my e-mail
14 for any who are interested in helping us in
15 that journey.

16 Finally, I have a long list of
17 acknowledgments, but just to go through
18 briefly: Victoria Philbin and Eugenie Suter
19 in my lab spearheaded a lot of the Toll-like
20 receptor work. Dr. Michael Wessels is our
21 Division Chief. Dr. Raife Jehine, immunology,
22 has been a mentor, Dr. Zach Bohane in the

1 bioinformatic realm, Dr. Keith Mansfield at
2 the New England Primate Research Center, Dick
3 Miller and Mark Tomai at 3M Pharmaceuticals,
4 and our funding, we should acknowledge,
5 through NIH, RO1, NIAID on the adenosine work,
6 and Dana Human Immunology Award, and we have
7 received funding from XOMA and reagents and
8 support from 3M Pharmaceuticals. Thank you.

9 (Applause.)

10 MODERATOR SLATER: Thank you. I
11 think we have another platform change. I'm
12 sure there will be questions for Dr. Levy at
13 the roundtable, which we will be starting
14 quite soon.

15 I would like to invite Dr. Rino
16 Rappuoli to come to speak. He is the global
17 head of vaccine research for Novartis. Dr.
18 Rappuoli.

19 DR. RAPPUOLI: Well, while the
20 computer goes up, I want to start. My focus
21 is going to be about using adjuvants,
22 especially MF59, in different age groups and

1 somehow practice of the best science that has
2 been just described in the previous talk.

3 I will be talking mainly about
4 immunogenicity, because the safety has been
5 described in the previous talk by Giovanni
6 della Cioppa. So all the data I am going to
7 talk about the safety, you have already seen.

8 So I am going to talk about the
9 MF59, and I will talk about basically
10 immunogenicity in children, in adults, in the
11 elderly, how the adjuvant broadened the cross-
12 reactivity across different age groups, and
13 finally a couple of slides on pandemic
14 influenza.

15 You heard a lot about MF59. I
16 will not go into it. I think the only thing
17 I can add is MF59 was born Chiron, and was
18 developed originally by Gary VanNest, who is
19 sitting over there, and was the only adjuvant
20 other than alum licensed the past century.
21 This century just started. We will see how it
22 goes.

1 The great merit so far of this
2 adjuvant is having been in 40 million people.
3 We have very robust confidence on the safety,
4 and we are starting to work a lot on the
5 molecular mechanism of adjuvantation, how it
6 works, and there have been a number of papers
7 published.

8 I think the best way to describe
9 and summarize the way we believe it works is
10 it basically creates a micro environment which
11 is optimal for antigen presentation by
12 recruiting all the cells, optimal like an
13 artificial lymph node or whatever, where
14 things happen optimally. That is all I wanted
15 to say about it.

16 What about different age groups?
17 MF59 a few years ago has gone into newborn
18 kids in a trial where, basically, the adjuvant
19 was used with GP-120 in newborn infants from
20 mothers which were infected by HIV. So 72
21 hours after the birth, people were vaccinated
22 with -- children were vaccinated with MF59,

1 and three doses followed.

2 There was one study to find the
3 schedule. The second one just to look at
4 immunogenicity. It was found that the optimal
5 immunogenicity, one dose at birth was able to
6 induce good response, antibody response, to
7 GP-120, and it was found the safety was fine.

8 So, basically, this was a small
9 study, under 54 newborns, but basically MF59
10 has gone safely in three doses into newborns,
11 and for three consecutive doses. So this to
12 say that adjuvants as MF59 can be used even at
13 birth.

14 The second study I want to talk
15 about in infants is on influenza. This is a
16 number reference that tell you that the
17 influenza vaccines that we have for infants
18 are not optimal or they are pretty lousy, and
19 there is a way to improve them.

20 So we have been using the licensed
21 vaccines for influenza in six-month-old kids.
22 Basically, we need to use two doses, and you

1 still get a lousy -- a pretty bad response.

2 So there is room for improvement.

3 Here we compare in kids from six
4 months to three years the immunogenicity of a
5 licensed vaccine against an MF59 adjuvanted
6 influenza vaccine, the three cell types. The
7 story is the same, one , two, three. They are
8 basically much better immunogenicity. This is
9 a log scale. So you can see the difference,
10 if you use MF59 in infants.

11 This is a detail about what
12 happens with the B strain of influenza. In
13 yellow, licensed, non-adjuvanted vaccine.
14 Basically, this is six months. You see
15 increasing with age the adjuvant -- The non-
16 adjuvanted vaccine basically at six months is
17 absolutely not effective, and it goes up with
18 age, and when you get to three years,
19 basically you get seroconversion across 50
20 percent of the population.

21 With MF59, you get 100 percent
22 from the very beginning. That gives you an

1 idea. It looks like the adjuvant basically
2 accelerates the young immune system to work
3 extremely well from the very beginning,
4 independently of the age.

5 Basically, this is another slide
6 showing a year later, you can revaccinate
7 those kids, and basically the influenza you
8 still see statistically significant difference
9 when you revaccinate them.

10 So MF59 can be used and works in
11 newborns, the HIV, works and can be used in
12 infants and children from six months to three
13 years, and induces optimal immune response.

14 This is for infants and children.
15 I want to move now to people -- categories of
16 people that are at risk, some kind of diseases
17 that basically compromise their response to
18 vaccines. So this is chronic diseases.
19 Again, it is still influenza, and the three
20 vaccine strains. Always, the MF59 is much
21 better in immunogenicity than the control
22 vaccine.

1 These are basically HIV patients,
2 similar story. MF59 is always better than the
3 control vaccine. MF59 is in red, and the
4 yellow is the control vaccine, and this is
5 people, transplant recipients, same story.
6 MF59 is much better.

7 In the elderly, which also have a
8 kind of compromised immune system, there is a
9 need for adjuvanticity. You see a similar
10 story. MF59, much better against the three
11 influenza strains, and this is a story that
12 repeats in many, many trials. You always see
13 these kind of things.

14 We did a meta analysis to see
15 whether in all the trials that we have done in
16 the elderly the MF59 will induce superior
17 immunogenicity, and again here is the ratio.
18 One will be that they are equal immunogenic.
19 Below one will be the conventional vaccine is
20 more immunogenic. Above one means that the
21 MF59 adjuvanted vaccine is more immunogenic.

22 So for all the three strains in

1 this meta analysis of many studies, the MF59
2 is always consistently more immunogenic.

3 So this is about immunogenicity in
4 infants, in people with chronic diseases, and
5 in the elderly. What about coverage of
6 strains which are antigenically equal to these
7 vaccine strains, still in the case of
8 influenza?

9 We know that, when there is a
10 mismatch between the vaccine strain and the
11 circulating strain of influenza, the vaccine
12 efficacy, which is usually in the 60-80
13 percent, drops down to 50 or 40 percent. So
14 can MF59 broaden the immune response so that,
15 even with a mismatched strain, you can still
16 cover things?

17 The first data are in children.
18 Here is pre-vaccination, post-vaccination, and
19 against the mismatched strain. With MF59 you
20 get seroconversion in more than 90 percent.
21 With a conventional vaccine you are in the 50
22 percent or less, similar for -- This is for

1 H1N1.

2 So in adults at risk, a similar
3 story. Against mismatched strains, MF59 is
4 able to cover seroconversion in most of the
5 people, conventional vaccine much less.
6 Elderly, similar story.

7 So, basically, the MF59 not only
8 improves the immune response in children and
9 infants, in elderly adults at risk, but also
10 in the same populations. It broadens the
11 immune response so you can cover strains that
12 will not cover without an adjuvant.

13 Now the last couple of slides are
14 about using MF59 for a pandemic, and here is
15 a study, part of which has been just published
16 in the New England Journal of Medicine as a
17 letter.

18 Basically, this goes back to --
19 The first immunization was in 1999 when we
20 immunized people with and without adjuvant
21 with a vaccine with a H5N3 vaccine, which
22 today we call clade zero. This was the 1997

1 Hong Kong strain.

2 Then a year ago we went back and
3 we boosted the same people with a clade one
4 2004 Vietnam vaccine. Basically, here is what
5 happens. The first experience was 1999. We
6 vaccinated with a vaccine without an adjuvant,
7 and we basically got no response. This is the
8 protected level.

9 In the same study we used MF59,
10 and we got basically more than 80 percent
11 protective responses. We published this in
12 the Lancet 2001. In the meantime, I think
13 there have been many, many other papers
14 confirming this data. With no adjuvant, you
15 don't get a response. With adjuvant, you do
16 get a response.

17 Then as I said, a year ago we went
18 back. We got the same people, and we gave
19 them two doses of H5N1 clade one, and priming
20 had been done with clade zero; and we asked,
21 do we get immune response?

22 Here is what we got. This is a

1 log scale. This is the protective level.
2 Basically, Day Seven after the first dose,
3 seven-eight years later, you get -- Day Seven
4 you get antibody responses that are one, two
5 logs above the protected level.

6 We are proud, very proud, of these
7 responses here. Look at this, and this is
8 against the strain used for boosting. What
9 about the other one, clade two, clade three,
10 all the other ones. Here they are.

11 Basically, by Day Seven you get incredibly --
12 I mean two logs, 1.5-2 logs more antibodies,
13 protected level of antibodies, levels of
14 antibodies above the protected level.

15 This is what you get. That
16 doesn't really matter. Basically, you prime
17 with clade zero. You boost with clade one,
18 and in three days you are covered against any
19 strain. That means that we can prime with an
20 adjuvanted vaccine. Forget the things for a
21 while, and then when there is a danger, come
22 back and one dose. In three days, five days,

1 seven days, you will be protected against any
2 strain, independently of this thing you used
3 to prime or to boost.

4 That will take away all the
5 questions, which strain or H5N1 do we put in
6 the vaccine. You don't care.

7 So these are the data. Only
8 another slide, which says what is the
9 mechanism. We are trying to investigate the
10 mechanism of what is going on here. So people
11 will be mentioning several responses. What
12 happens? Which are the things beyond
13 antibodies that we can measure?

14 Well, the only thing that we can
15 measure, really, that makes a difference here
16 is after the dose of priming, what we see is
17 the memory T cells, they go up with the
18 adjuvanted vaccine. Non-adjuvanted, they
19 don't go up.

20 Basically, so the first thing that
21 the adjuvant does is to generate a pool of
22 memory T cells after the first dose. All the

1 action starts here.

2 What is the consequence of that?

3 The consequence of that is that, when you get
4 down here, you boost. The people that had not
5 been primed have no memory B cells. The
6 people that had been primed have huge numbers
7 of memory B cells, and these memory B cells
8 guaranty long term protection.

9 So this, I think, is a solution
10 for a pandemic influenza. This is starting to
11 understand the mechanism, how it works, and
12 with that I want to just summarize what I
13 think I tried to tell you, that the adjuvant
14 MF59 works for different age groups, is a
15 solution for pandemic influenza, and is safe,
16 and we start to understand the mechanism of
17 action. Thank you.

18 (Applause.)

19 MODERATOR SLATER: Thank you very
20 much. We have time for one or two questions
21 before the break, if there are any.

22 DR. SUTCLIFFE: Hi. Joyce

1 Sutcliffe. Just a clarification. On the last
2 study you told us about, was the boost with
3 H5N1 without adjuvant?

4 DR. RAPPUOLI: No. The boost was
5 with adjuvant.

6 DR. SUTCLIFFE: Was also with
7 adjuvant?

8 DR. RAPPUOLI: Yes.

9 DR. SUTCLIFFE: Thank you.

10 \ PARTICIPANT: Along those same
11 lines, do you know that adjuvant was required
12 in the prime? If you gave the prime without
13 adjuvant, would the boost have worked?

14 DR. RAPPUOLI: We did have a
15 little show for simplicity here. We did have
16 a group which was primed without adjuvant.
17 They also responded when we boosted, but the
18 magnitude was lower, and the cross-protection
19 was lower.

20 PARTICIPANT: Is there any direct
21 interaction of the adjuvant with the antigen?

22 DR. RAPPUOLI: Do you ask whether

1 there is a direct interaction of the adjuvant
2 to the antigen?

3 PARTICIPANT: Yes.

4 DR. RAPPUOLI: Well, in the case
5 MF59, no, we cannot measure that, because MF59
6 is an emulsion. We can spin it down, and the
7 antigen remains in the supernatant. So it is
8 no measurable interaction that we can see,
9 basically.

10 MODERATOR SLATER: Thank you very
11 much. We are going to take a 20-minute break,
12 our last coffee break of the meeting. We will
13 regroup at 10 minutes to three.

14 (Whereupon, the foregoing matter
15 went off the record at 2:29 p.m. and went back
16 on the record at 2:55 p.m.)

17 MODERATOR SLATER: Welcome back.
18 We are going to begin the roundtable
19 discussion.

20 First of all, I would like to
21 acknowledge individuals who are participating
22 in both this roundtable and this morning's

1 roundtable who actually had never been
2 introduced, because although most of the
3 roundtable discussants are either co-chairs or
4 speakers and all the speakers have been
5 introduced, Dr. Emmanuel Hanon from GSK, Dr.
6 Geert Van den Bossche from the Gates
7 Foundation participated this morning. I would
8 like to thank them.

9 In addition, Dr. Martin Friede
10 participated this morning, and he is
11 participating this afternoon. Dr. Friede from
12 the World Health Organization actually has
13 the distinction of being the only person to
14 participate in both roundtable discussions
15 today. So thank you very much.

16 Dr. Thomas Holdich from ATL is
17 joining us now. Dr. Thomas Verstraeten from
18 GSK is joining us as well, and finally through
19 an oversight, Dr. Florian Schodel from Merck
20 is not indicated on your program as a
21 roundtable discussant, although he is, and is
22 sitting two places to my right.

1 Dr. Ballou this morning discussed
2 briefly the roundtable 2 questions. I did cut
3 off some people who were interested in asking
4 questions of specific speakers. So if you
5 have specific questions that you would like to
6 raise, by all means, write those down, and at
7 some point where it is appropriate, you can
8 certainly raise those with specific speakers,
9 but I am now going to turn the proceedings
10 over to Dr. Ballou who will conduct our
11 discussion.

12 DR. BALLOU: Thanks, Jay. The
13 questions that we have posed for the
14 roundtable here were discussed by the
15 organizers of the meeting, and without talking
16 out of school, I think when we developed these
17 questions, one of the first questions was
18 should we design, and this was thought to be
19 too incomplete of an approach.

20 So we would like to -- We wanted
21 to rephrase these to how can we, because we
22 felt that we actually did need to discuss and

1 think about how studies should be designed
2 more to provide better information, more
3 complete information around some of the issues
4 that we have heard presentations on today.

5 I think that one of the first
6 bullets on here is detecting age specific
7 differences in adjuvant responses. This
8 builds very nicely on the last two
9 presentations.

10 So I would like to perhaps start
11 with this, and to first of all, invite anybody
12 who had questions of the last two presenters
13 that might be in this area of age specific
14 responses, particularly in neonates, to also
15 please participate.

16 So is there anyone on the panel
17 that would like to make an opening statement
18 of opinion regarding this issue of design
19 around age specific differences in adjuvant
20 responses?

21 DR. DAVIS: One easy place to
22 start -- it is not the full answer -- is that

1 if you can pick up innate immune activation in
2 immune cells, which is PBMCs or cord blood
3 that you can test from different ages. That
4 is a very quick way to start to see if you get
5 a similar level of activation.

6 DR. LEVY: Hi. This is Ofer Levy.
7 One thought that came to mind immediately was
8 vis a vis animal models. Believe it or not,
9 if you go to newborn immunology meetings,
10 which aren't that frequent and aren't that
11 large, because it is not that large a
12 community of people doing that work, but when
13 we have those meetings, there is actually
14 discussion about what is a newborn.

15 In the human medical literature, a
16 newborn is defined as birth to 28 days of age.
17 So if you are searching PubMed, that is more
18 or less how a newborn is going to be defined
19 for humans.

20 Now when you look at other animals
21 that have a different lifespan and a different
22 rate of maturation of their immune system,

1 that number might change and is open to some
2 debate among immunologists and veterinarians,
3 etcetera. So that is an interesting
4 dimension.

5 I think you have to keep in mind
6 what your goals are. One element that I
7 tended to emphasize in my talk, although it is
8 not the only venue to use those kind of
9 discoveries, would be to vaccinate on the day
10 that a baby is born. I think, from a global
11 health perspective, that is a practical
12 advantage, although it is not the only way to
13 go, and we believe that some of the adjuvant
14 effects we have shown are relevant also later
15 in life throughout infancy.

16 If that is a goal of a particular
17 vaccine development program, then a lot of the
18 mouse, the newborn mouse, literature will look
19 at mice that are a week old or rats that are
20 one week old.

21 We saw some impairments in
22 immunity, but it might not be the same level

1 of impairment as one sees in the first 24
2 hours of life, and people tend not to look at
3 the first 24 hours of life, because the mouse
4 is very small and harder to work with, but
5 that is something that we are doing with our
6 murine program; because we believe that some
7 of the adenosine and other effects may be
8 acute and particularly relevant in the first
9 few days of life.

10 So those are interesting elements
11 and dimensions to consider.

12 DR. BALLOU: Could I ask you just
13 to elaborate a little bit more on this issue
14 around the timing of this first dose. As you
15 know, although BCG is recommended to be given
16 from the day of birth, in practice probably
17 the majority of children in the developing
18 world do not receive it as a birth dose,
19 because they are not -- most of these births
20 are not attended, and frequently receive it in
21 the first month to two months of life; if they
22 haven't gotten it by their first EPI visit,

1 will get it then.

2 I wonder, it was not clear from
3 the data that you presented whether there
4 really is a fundamental difference in terms of
5 this first two-month window when you can have
6 the impacts that you are seeing on neonatal
7 immune responses, or is it really critical to
8 get in these first few days?

9 DR. LEVY: I think, to turn it
10 around a bit, we see a severe impairment in
11 the first days of life, and then there is a
12 gradual age-dependent maturation. So if you
13 wanted to choose a pathway to stimulate to
14 give you optimal efficacy, if efficacy is
15 defined as co-stimulatory activity as measured
16 by CD40 up-regulation, production of IL-12-
17 p70, a TNF alpha, etcetera, then the Toll-8
18 pathway appears in our hands, both in humans
19 and non-human primates, at least within the
20 confines of what we have done, to be the
21 pathway that will give you the most
22 efficacious response from the get-go, from the

1 first hours of life.

2 When you look later on, there is
3 maturation, and the infants start to catch up
4 to the adults in terms of the magnitude of
5 responses. What remains true in our hands is
6 a Toll-7/8 or Toll-8 agonist have superior
7 bioactivity with respect to these endpoints
8 than the other Toll agonists that we evaluated
9 in our assays.

10 We looked at Toll-2 agonists and
11 LPS, and we looked at a pure Toll-7 agonist,
12 etcetera. So in fact, one element of our
13 work, which we tend not to focus on because we
14 are focused on newborn and infant immunology,
15 but if you just look at our adult data, set
16 aside the pediatric data for a moment, in our
17 hands within the limitations of the assays
18 that we do, the Toll-7/8 and 8 agonists are
19 giving the most robust response as compared to
20 the other agonists we evaluated, even with
21 adult cells.

22 DR. SCHODEL: The other antigen

1 that is generally given at birth in many
2 countries, and that wasn't mentioned,
3 surprisingly, is actually Hepatitis B, which
4 is just a good old alum adjuvanted vaccine.

5 Could you comment briefly on why
6 that works so well, in spite of it not being
7 on any of these adjuvants?

8 DR. LEVY: So we have an emerging
9 body of data on the bioactivity of alum in an
10 age-dependent way, and that is something that
11 we are working on now and is not yet ripe for
12 public consumption. But suffice to say that
13 there is some bioactivity of alum at birth,
14 which shouldn't be surprising, because the
15 clinical experiment is there.

16 You get some responses. One
17 dimension is that, if we build a better
18 adjuvant, will we get a more effective
19 response that would require fewer doses and/or
20 provide a higher level of protection with
21 fewer doses or faster, in which case then you
22 close a window of vulnerability.

1 DR. GLENN: I just found your talk
2 fascinating, but I have to say I am skeptical.
3 There is a big gap between the data points in
4 the neonates and adults.

5 I know, with the GI tract and the
6 mucosal immune system, once there is, say,
7 contamination or there were microflora
8 involved, you get rapid development of pairs,
9 patches, etcetera. I would imagine -- and we
10 talked about this at lunch a little bit --
11 that maybe also to the skin where you may have
12 underdeveloped immune system.

13 It seems that this picture from
14 cord blood where a lot of your data, and very
15 good data, was generated really needs to be
16 extended to two weeks later or some time
17 period when there has been significant antigen
18 exposure, so a chance to see how differently
19 oriented the immune system is.

20 As mentioned, that is a more
21 likely time when infants would be receiving
22 these agents.

1 DR. LEVY: I went through the talk
2 very quickly, because I had too many slides.
3 As I told somebody, you know, one person tells
4 another: I wrote you a long letter, because
5 I didn't have time to write you a short one.

6 The bottom line there is I did
7 quickly go through a slide that showed that,
8 if you take peripheral blood from a U.S. born
9 infant at, I think it was, two months of age
10 and then follow that same infant at 15 months
11 of age, the Toll-7/8 and 8 gave the superior
12 efficacy of TNF alpha at that readout.

13 Then we do have some limited data
14 from the Gambia of an African infant at nine
15 months of age where the Toll-7/8 agonist gave
16 the expected or hypothesized superior
17 activity.

18 Now there is a limited dataset in
19 the infants, but we are starting to develop
20 some experience with infant blood as well.

21 DR. GLENN: But that is precisely
22 the point. I think you need a lot more data

1 points to make those conclusions.

2 DR. CHEN: Bob Chen. I would like
3 to follow up on the questions. So as you
4 noted, the first six months of life is a
5 period of very high mortality rate and very
6 high selection pressure evolutionarily,
7 presumably not only for homo sapiens but for
8 all the other species.

9 So why is it, do you think, that
10 the immune system is configured the way it is,
11 and are we doing something potentially
12 disruptive there?

13 DR. LEVY: Right. So, obviously,
14 this is not an accident, and it probably
15 relates to the fact that the system has to be
16 designed so that the maternal immune system
17 and the fetal immune system don't attack one
18 another's tissues. That is why pregnancy is
19 an immunosuppressive state, and that is why we
20 recommend to pregnant women not to eat
21 unpasteurized cheese and end up with
22 intracellular infection with listeria, for

1 example. So that is a reason at that level.

2 Then, of course, after birth one
3 can speculate that it is important in the
4 first few days of life when the newborn is
5 first getting colonized in the skin with their
6 first bacterial flora and getting colonized in
7 the intestinal tract. You can imagine what
8 would happen if the newborn had a very Th1
9 polarized response to that. There would be
10 severe inflammation.

11 So what we know not just from our
12 work -- this is a global literature -- that
13 birth initiates an acute phase response, an
14 IL-6 polarized acute response. Time didn't
15 allow me to get into it, but we have data from
16 infants, not just newborn cord blood but from
17 infants, a European study we did with
18 collaborators in Rome, that IL-6 levels rise
19 after birth.

20 That is suspiciously similar --
21 and TNF levels stay flat. That is
22 suspiciously similar to the pattern of

1 cytokine production I showed you with our cord
2 blood cultures. So we believe that that
3 pattern is relevant not just in vitro but in
4 infants as they are growing up.

5 What we are proposing to do,
6 though, is in a local environment with a
7 conjugated adjuvant locally apply in a
8 reversible way a Th1 polarization that can
9 locally break tolerance so that you can get an
10 adaptive immune response.

11 DR. KENNY: Rick Kenny with GSK.
12 I just wondered. You know, you said that the
13 neonatal immune response essentially is
14 designed to be polarized against the Th1
15 response. What do you see as the long term
16 safety implications of trying to break that
17 right at birth, and how would you go about
18 studying that in a way to be able to get into
19 neonates with novel vaccines?

20 DR. LEVY: Yes. Well, obviously,
21 that is a major regulatory and safety issue
22 for any new drug development and, of course,

1 particularly in pediatric drug development,
2 which has typically lagged behind, and then
3 particularly when you are talking about
4 newborns.

5 For the doubters, you've got to
6 look at the biomedical and public health
7 significance. You have to look at the fact
8 that there are vaccines we give around the
9 world in newborns, Hepatitis B vaccine, BCG.
10 So there are certain proofs of concept.

11 Now, of course, just because those
12 are safe doesn't mean a new one is safe, but
13 it does show that certain vaccines can be
14 given at birth and result in some protective
15 effects.

16 We also use imiquimod, a Toll-7
17 agonist. It has been used and published in
18 pediatric populations as a topical cream for
19 molluscum contagiosum. So local application
20 of imidizoquinolines has been done as a
21 pediatric experience, and some pediatric
22 literature on that.

1 Finally, as with any drug
2 development, there is going to have to be
3 thoughtful safety approach and, obviously,
4 careful endpoints. I would suggest in newborn
5 Rhesus macaques looking not just at efficacy
6 but looking at safety endpoints, and that is
7 where the discussion from this morning becomes
8 relevant.

9 I think it is interesting and
10 important to follow cytokines, to follow
11 lymphocyte patterns, etcetera, but we all, I
12 think, have to agree up front that we don't
13 know at this point in time with our state of
14 knowledge that a level X of cytokine Y
15 definitely proves that you are going to end up
16 with complication Z.

17 I think it is valuable and
18 important to gather that information, but how
19 to interpret it will be interesting.

20 DR. WARREN: Just something to
21 think about: You are highlighting the
22 challenges of the regulatory environment in

1 terms of vaccines for neonates. Should we
2 immunize a neonate or the mother?

3 DR. LEVY: Yes. Well, the
4 question of vaccinating maternal immunization
5 is a whole field and discussion, in and of
6 itself, and there are proofs of concept. You
7 know, influenza vaccination in the mother does
8 result in some protection. There was recently
9 a paper on that The Newborn.

10 From a medical, legal and
11 regulatory perspective, I think that is an
12 even more complicated area. That doesn't mean
13 it shouldn't be pursued.

14 DR. PETROVSKY: Nik Petrovsky,
15 Australia. I am a little bit confused by your
16 claim that the TLR 7/8 agonists were the most
17 effective, because you didn't show any dose
18 response curves, I guess, for all the
19 different agonists that you were comparing.

20 So again, with single doses of
21 different TLR agonists, how do you actually
22 compare relativity where that dose is in the

1 dose response?

2 DR. LEVY: Right. That is a
3 cogent point. So there is a difference, of
4 course, between potency and efficacy, and we
5 will define efficacy as the dose at which we
6 can get a maximal response for any of these
7 biological systems. You max out at some
8 point.

9 We have three publications in this
10 area, two in Journal of Immunology and one in
11 Blood. In each of those, we satisfied the
12 reviewers. We did full dose response curves,
13 and then in the summary plots I showed we
14 selected the concentration of agonists that
15 led to a maximal response.

16 DR. BALLOU: I would just like to
17 comment that in my world, efficacy is defined
18 as protection against a clinically, medically
19 important disease. I would hope that we try
20 to use that as a general description of
21 efficacy.

22 The second bullet point here,

1 providing long term safety information -- We
2 have had a proposal from one of the speakers
3 today that, really, the best way to do this is
4 prospective observational studies. I wonder
5 if people either agree with that or have
6 different views on how one should think about
7 attaining long term safety.

8 DR. SCHODEL: Yes. I would like
9 to make a comment on that and point to an
10 important gap. I think Bob Chen has pointed
11 out the value of the observational studies
12 and, obviously, the efforts of the CDC and the
13 rapid cycle analysis.

14 All these things are great new
15 tools that help discover signals. One thing
16 that I think is severe missing is when we see
17 relatively rare events, it is not always easy
18 to get a clear answer as to whether a signal
19 is not biased by all kinds of different
20 things.

21 What we are lacking is the power
22 of the observational long term analysis and

1 the computerized follow-up to be meshed with
2 a randomized, blinded design with some
3 appropriate control, which we have been into,
4 but we haven't really gotten there with any of
5 our post-licensure or pre-licensure large
6 studies.

7 I think that would be really sort
8 of getting the two worlds together and give
9 you the best answers for not the very, very
10 rare things, because they are just too
11 infrequent, but for the answerable questions.
12 Obviously, both GSK and I have shown -- and
13 Merck -- have shown it with interception for
14 rotavirus with a specific hypothesis that
15 these things can actually be answered in
16 prospective randomized, controlled studies --
17 of course, very expensive, and you can't do
18 this for everything.

19 So what we would need is another
20 public health tool -- and it can't just depend
21 on the companies, I'm afraid, because of the
22 finances involved -- that allow us to mesh the

1 power of randomized and blinded groups with
2 computer follow-up in an automated way to some
3 of the things that Bob and others have so
4 nicely built up at the CDC.

5 DR. VERSTRAETEN: I would like to
6 comment to that as well. I certainly agree
7 that observational studies, Phase IV, have
8 their value and have their place, but there is
9 still the outstanding question of what safety
10 data do you collect in your clinical trials.

11 I think we have talked a lot about
12 immediate reactogenicity. A lot of the
13 presentations yesterday were about that. I
14 don't think anybody has any doubt about that.

15 Now there's a lot of debates
16 between industry and the regulators on how
17 much more and how much longer do you have to
18 follow up in your clinical trials. You cannot
19 push everything to Phase IV. I think that
20 merits some discussion.

21 We, as Gary has shown, have talked
22 to quite a few experts in the field of

1 autoimmune diseases to understand what is the
2 risk area that we really should be looking at
3 or, in other words, how long after vaccination
4 do you expect you could see something as an
5 adverse reaction, a true adverse reaction
6 following your vaccine?

7 When we did that, we usually get
8 the same response in sort of a couple of
9 weeks, a couple of months at most, and very
10 rarely have we had feedback that you should
11 look for five years or 10 years.

12 So our position has been it is
13 more useful to look at that immediate -- if
14 you can call that immediate -- couple of
15 months after vaccination and make sure you
16 capture as good as possible information, and
17 do a proper comparison of that information
18 than just go on and on and on and collect data
19 from which you really don't know anymore what
20 was the cause of that event.

21 So I think, even if we go for
22 large Phase IV trials with electronic

1 databases, we still have to agree for clinical
2 trials what is really the period at risk.

3 There is another comment I would
4 like to make. That is that we should
5 distinguish between the risk period and the
6 follow-up period. A lot of people have these
7 long term diseases in mind, like multiple
8 sclerosis. That may take years to develop.
9 That is true, but that doesn't mean that your
10 vaccine can cause these diseases during all
11 these years.

12 I think what we should agree is
13 what is really the risk period, how many
14 months or years, if you wish, but I think it
15 should be months after vaccination, and then
16 in addition do you want to calculate in your
17 study some additional follow-up time to make
18 sure that you identify those diseases, if they
19 occur on the longer time scale.

20 So I think it would be good to
21 have some debate on this period.

22 DR. DELLA CIOPPA: Well, I think

1 we should maybe borrow from other areas of
2 development to get some ideas as to what kind
3 of studies we could do to realistically assess
4 long term safety.

5 One of these areas that kind of
6 goes in the direction of the previous comment
7 is that of the so called large, simple
8 clinical trials, and I am borrowing this from
9 the cardiovascular area where the key word is
10 simple. Can a company do a study in -- I
11 don't know -- 120,000 subjects, randomized
12 clinical trial, pre-license?

13 In the current setting and with
14 the kind of things that we measure in clinical
15 trials, the answer is, in most cases, no; or
16 even a company like Glaxo or Novartis, you do
17 it once. You cannot do it all the time.
18 However, the reason -- The main reason for
19 this is that we load our clinical trials with
20 too many questions, which is, obviously,
21 understandable.

22 There is another approach, which

1 is a minimalistic approach, and I will give an
2 example. Let's say we are interested in
3 autoimmune disease. A large, simple,
4 randomized clinical trial in autoimmune
5 disease would be as follows. You randomize
6 the subjects to either adjuvanted or non-
7 adjuvanted vaccine, and then two years down
8 the road you ask the one question: Did you
9 get an autoimmune disease or did you get one
10 of these diseases. And the answer is yes/no.
11 The end.

12 This is a simple, large clinical
13 trial. This is a doable trial. Now people
14 laugh, because why not adding some other
15 information? Why not some immunogenicity?
16 Why not this? Why not that? And then the
17 trial implodes, and then the cost becomes
18 impossible.

19 So strong recommendation of how I
20 would spend my money as a company to provide
21 long term safety information before approval
22 through these large, simple, randomized

1 trials. The word simple has to be such that,
2 when you kind of tell it to people for the
3 first time, they have to laugh.

4 The second statement, suggestion,
5 recommendation that I would have, speaking
6 with regulators, is to allow to elevate as
7 pivotal evidence of safety the pooled analysis
8 and the meta analysis, which today are not
9 considered as pivotal evidence.

10 In order to do that, there are two
11 features that are in my mind essential, the
12 first one being pre-definition. You have to,
13 of course, define beforehand what we are going
14 to collect and how. The second is, of course,
15 standardization. But if these two features
16 are met, I don't see why a large, well done,
17 well defined, pre-defined, pooled analysis
18 could not be elevated to pivotal evidence of
19 safety.

20 Now it is intriguing that in a
21 submission we do have to do the integrated
22 summary of safety, but that as such is not

1 used as pivotal evidence like a normal
2 clinical trial.

3 My third point, I think that not
4 everything can be determined pre-approval. I
5 think, more and more, we should bridge -- This
6 concept between pre-approval and post-approval
7 is a little bit artificial, because it is
8 based on the assumption that we will know the
9 story by the time the vaccine gets out, but in
10 most cases that is not the case.

11 So I think proper agreements on
12 post-approval commitments is a third way
13 forward. Then, of course, the company or
14 whoever gets the approval is bound to do the
15 study, to do the study according to the
16 predefined rules, and to submit results and to
17 take action in case the results aren't
18 improving the safety signal.

19 Think of these three methods,
20 large simple studies, a meta analysis, and
21 post-approval commitment which include the
22 prospective observational studies. We can

1 move in the right direction in a way that is
2 sustainable.

3 DR. BALLOU: Thank you for those
4 helpful comments. Let's get some responses
5 from the audience.

6 DR. CHEN: Let me make two
7 comments. First, I would like to propose a
8 different design for large, simple trials that
9 we need to think about. That is, in this era
10 of almost great transition to electronic
11 medical records in large HMO-type national
12 health services, rather than necessarily --
13 and, obviously, for the typical set of
14 numbers, you will want to go kind of solicit
15 adverse events. But for these sets, let's
16 just let the regular health care system run
17 the way it is.

18 Yes, we need to define ahead of
19 time which might be the adverse events we want
20 to analyze, but allow the natural pattern of
21 visits to emerge, similar to how we currently
22 do the post-marketing large linked database

1 studies. But we could do it pre-licensure
2 using, more or less, a similar setup.

3 The second comment relates to a
4 different challenge that we need to face, and
5 that is, as Tom said, that even though we want
6 to get as much answer in the pre-licensure
7 domain, inevitably certain things will need to
8 be addressed in the post-licensure setting,
9 and how can we track these individuals that
10 were exposed pre-licensure as well as folks
11 who are exposed post-licensure in the real
12 world domain where many people may be getting
13 all sorts of different vaccines, different
14 adjuvants, etcetera?

15 At the end of the day, to me, the
16 only way that could happen is if we track the
17 vaccine exposure with the adequate level of
18 specificity down to the lot level. What would
19 be needed is that each vaccine manufacturer,
20 as they produce that lot, would need to report
21 to a centralized database all the different
22 information about what went into that specific

1 lot, be it the adjuvant, be it the other
2 excipients, other adjuvants, etcetera.

3 Then down the road whenever new
4 issues come up or whatever studies we want to
5 do, we would then be able to link it together.
6 One proposal that has been out there is let's
7 get a smaller bar code. The newer sets of bar
8 codes, they are two-dimensional, can collect
9 all sorts of information.

10 So as we produce the new vaccines,
11 let's incorporate that and make sure that
12 information is captured, because in analyzing
13 our safety data, a huge part of the problem is
14 that the nurses that have been giving the
15 shots in the clinics have been used to writing
16 DTP for so long, when there is new DTAP, ITV,
17 Hepatitis B. They only have a certain amount
18 of time to write, and so the amount of error
19 in that information is incredible.

20 So we need to automate all that,
21 and I think perhaps those might be two ideas
22 for the folks to think about.

1 PARTICIPANT: For the gentleman
2 that suggested that the survey for such things
3 as autoimmunity ought to be time limited, I
4 would be curious for you to be a little bit
5 more specific about how limited the time
6 should be, because let's keep in mind here,
7 the idea of the vaccine is that you want to
8 induce life-long or near life-long immunity.

9 If the adverse event that
10 frightens us most is related to the actual
11 mechanism by which you are inducing immunity,
12 then there is no reason to imagine that the
13 risk for the adverse event would be there as
14 long as the actual beneficial effect that you
15 are trying to induce.

16 Now, obviously, that means that
17 you can't withhold licensure until immunity
18 waned in all your Phase III trials, and that
19 does bring to the idea of the post-marketing
20 commitments.

21 I guess the concern with that, and
22 it is a reasonable issue, but in the United

1 States we don't have provisional licensure.
2 Right? I mean, once it is licensed, it is not
3 licensed for five years and then you get to
4 take a look at it again.

5 So, therefore, isn't it true that,
6 in a sense, industry is not as motivated to
7 get that post-marketing data as one would
8 hope, particularly in a country such as the
9 United States that doesn't have national
10 health registries as Europe does?

11 DR. SCHODEL: You've brought up a
12 number of interesting issues. Let me tell you
13 that we are very motivated because, obviously,
14 there is the perception that vaccines might
15 cause adverse effects of long consequence are
16 very detrimental for the public health usage
17 of the vaccines. So all of us who are in this
18 particular field are very, very nervous about
19 these kinds of allegations.

20 So I think both -- I can certainly
21 say that from industry, we are certainly very
22 interested in finding out whether such adverse

1 events might happen and whether they happen in
2 the long run. But I would just like to point
3 out one very simple complication of this kind
4 of a question, which is that what you are
5 painting is a uni-dimensional world in which
6 the only effect is the vaccine.

7 Now even the harshest adjuvants
8 that we use are very similar to things that
9 happen during any infection that you have in
10 the meantime. As you go out -- and I think
11 that is what Thomas was saying as well, in a
12 way. As you go out further, you dilute your
13 effect.

14 It is not so much that it couldn't
15 theoretically happen a lot later, but the
16 likelihood that you would be able to detect it
17 over all the other things that happen becomes
18 increasingly smaller. Besides, in most cases
19 vaccination is actually, from a biological
20 point of view, a very limited exposure to
21 exactly the same thing that happens in a much
22 more dramatic way when you encounter a

1 pathogen.

2 So I think there are practical
3 limitations to this. It is very different
4 from the drug world where we have continuous
5 exposure to the same drug over long periods of
6 time, and we can really look at long term
7 effects. Here, we often have a single shot,
8 sometimes two or three shots, and then you ask
9 us whether there is a consequence five years
10 later.

11 The antibodies stay around, but
12 the original sin, so to speak, is hardly
13 detectable anymore.

14 PARTICIPANT: I appreciate that.

15 DR. DAVIS: I will just follow up
16 on that comment, and I think it really depends
17 on what your putative mechanism of action is
18 for the autoimmunity.

19 So if you are working with an
20 antigen that you expect to have molecular
21 mimicry of a self-antigen, then yes, a
22 longstanding antibody response is something to

1 think about long term, but that is not the
2 case for most of our situations.

3 So in our case with the CpG, the
4 innate immune activation, which potentially
5 could play a role, is largely over within
6 three days or four days, five at the max. If
7 it is the DNA presence itself, it is gone
8 within a few weeks.

9 So, really, you have to think
10 about why you are worried about autoimmunity,
11 and then look at it as to what would be a
12 reasonable time from that point of view.

13 PARTICIPANT: I'm sorry. I agree
14 with you. As a matter of fact, I would even
15 state that in many cases, if you are worried
16 about triggering autoimmunity, my guess would
17 be that you are triggering it in those who are
18 prone to it anyway. But on the other hand, a
19 couple of years without MS is better than a
20 couple of more years with it. But I agree
21 with your point.

22 DR. VERSTRAETEN: Rip, can I just

1 answer that? To answer your first question on
2 that period that we actually established, I'm
3 not the expert in autoimmunity. That is why
4 we went to these folks. They were experts in
5 neurology, rheumatology or autoimmunity in
6 general.

7 We settled on a period of six
8 months after the last dose, and we agreed with
9 the European regulators that we would
10 integrate that in our Phase IV trials as well.

11 DR. GRUBER: I had a question or
12 perhaps wanted some clarification on a comment
13 that was made earlier on, and that is the idea
14 of performing large simple trials. I think
15 this is something that the agency is very
16 interested in.

17 I just wanted to ask you. You had
18 indicated that you could envision a large,
19 simple trial in which you would randomize
20 subjects to either vaccine only or vaccine
21 adjuvanted arms, and then follow them up.

22 I can see that being a possibility

1 where you perhaps have a product that is
2 already licensed and that you now want to
3 combine with an adjuvant, that you can then
4 design these studies. But let's say you have
5 a novel vaccine antigen that you combine with
6 a novel adjuvant. There, I think the idea of
7 randomizing to vaccine only and vaccine
8 adjuvanted arm becomes a little bit more
9 challenging, because you must have a rationale
10 for adding the adjuvant in the first place.

11 So I think it is the idea of then
12 including study arms where you do the vaccine
13 antigen only may become rather challenging,
14 and perhaps even not that feasible. I would
15 like for you to comment on that.

16 DR. DELLA CIOPPA: Well, yes,
17 certainly, the choice of a comparator depends
18 very much on the nature of the vaccine you are
19 testing. In some cases, it is doable when you
20 have an equivalent, as you said, like in flu,
21 for instance, that work without the adjuvant.

22 In other situations where this is

1 not viable or actually not interesting, then
2 the large, simple study trial would be made,
3 carried out, comparing the new adjuvanted
4 vaccine with either no treatment or a placebo
5 or an alternative vaccine of a different kind.

6 I think the value of the large,
7 simple study is still there. Then the nature
8 of the question that you try to answer is
9 slightly different, but the end product is
10 still of value in determining whether the
11 adjuvanted vaccine is detrimental or not.

12 DR. GRUBER: Thank you.

13 DR. BALLOU: I'll put on my Gates
14 Foundation hat here. We are talking about
15 studies and concepts here that can probably
16 only be done in settings such as the United
17 States or Europe or other developed countries
18 that have health systems that can detect these
19 kinds of events.

20 What about the rest of the world
21 where, increasingly, we are seeing even the
22 large manufacturers going for vaccine

1 development programs? What do we do about
2 assessing long term safety in populations in
3 diverse places, some of which have zero to
4 little medical infrastructure that could
5 capture --

6 DR. DELLA CIOPPA: Actually, I
7 would argue the other way around. In my mind
8 -- and maybe I am wrong, of course, but the
9 large simple trial concept is one of the few
10 that actually can be implemented in countries
11 where the medical system is not advanced,
12 because if the -- Again, if the question is
13 simple enough, then most medical systems can
14 answer that question.

15 If the question is were you
16 hospitalized for -- I don't know -- MS or for
17 lupus, I think you can easily do it in Africa
18 or in Asia. It is the more complicated trials
19 that we typically do that cannot be done in
20 less rich health care systems.

21 DR. GLENN: I have a question for
22 the panel. If the adjuvant is a natural

1 compound like MPL, for example, there is
2 historically a lot of exposure to that, and
3 one can expect that these very short events
4 would be somewhat like an infection. But if
5 it becomes a more exotic adjuvant, more
6 synthetic, less like something you would find
7 in the natural setting, it seems to me that it
8 would change your thinking about the long term
9 follow-up, and maybe you need to know more
10 about that or maybe it doesn't play into it.

11 I would be interested in other
12 comments.

13 So if the adjuvant is truly a
14 bacterial product like MPL, for example, it
15 seems to me that historically through years
16 and years or centuries of exposure, we have
17 already sorted out whether there are going to
18 be important long term signals with that. But
19 if it is a new, novel synthetic adjuvant,
20 maybe that is a different track.

21 DR. SCHODEL: I would say that it
22 probably depends on the pharmacokinetics. We

1 should go back -- On these things, we should
2 go back to basic pharmacology.

3 I was a little surprised,
4 actually. I was glad that Ripley said what he
5 said about the value of the preclinical
6 studies, because that is exactly the way I
7 would see them as well.

8 We do look at general toxicity of
9 the compounds. We figure out what the maximum
10 doses are that we can actually test, and it
11 does give guidance as to what we want to even
12 try in people. So I think it is extremely
13 valuable work.

14 What I was saying, the question I
15 was asking from my preclinical colleagues was
16 actually a little different. I was saying,
17 okay, I am quite happy with what you are doing
18 anyway, because that is sort of the
19 prerequisite for doing anything. We have to
20 know whether these things are toxic and so on.

21 So I would comment on your comment
22 a little bit the same way. I would say you

1 just -- If it is a compound that has a very
2 short half-life, very rapid kinetics and it
3 doesn't have any clear -- from all the
4 preclinical work, you haven't any. Of course,
5 you repeat that in your Phase I studies. If
6 it doesn't have any long term consequences,
7 well, then you look mostly on the indirect
8 effects that it might elicit.

9 If it is something that actually
10 does stick around for a long time, well,
11 you've got to figure out what that does,
12 similar to implants or things that are around
13 or depot solutions or pharmcos that have a
14 very long half-life and that stick around.

15 I would try to simplify these
16 things, and if it can't be metabolized and it
17 is an inert compound that stays around, well,
18 you got to look at what that does.

19 DR. MALONE: Thank you. this is
20 exactly the point I wanted to make. It seems
21 like we are reinventing the wheel. All we
22 have to do is turn to our CDER colleagues.

1 Aren't we asking the question,
2 what is different about adjuvants from other
3 vaccines? In a way, all vaccines may be
4 associated with some risk associated with
5 autoimmune response. What is unique about
6 adjuvants is the adjuvant component.

7 How do we assess the duration of
8 risk associated with the adjuvant component?
9 Well, that is a function of metabolism, right?
10 So if we have a CpG that is phosphorothioate
11 that is designed for long life, we should know
12 what that half-life is, its clearance and pK,
13 and that should inform that decision.

14 It seems to me that this remains -
15 - This determination remains in the domain of
16 the dialogue between the competent regulatory
17 authority and the sponsor. I can imagine
18 there would be some appropriate guidance, but
19 my sense is that we are inventing complexity
20 that unnecessary right now in this aspect of
21 the focus.

22 DR. GOLDING: I want to make a

1 comment and then to also pose a question. We
2 keep hearing this comment from different
3 members of the panel.

4 DR. BALLOU: Hana, could you put
5 the microphone toward you? It's a little hard
6 to hear.

7 DR. GOLDING: Yes, sorry. That
8 after all, many of the novel adjuvants are
9 basically derived from bacteria. We have been
10 exposed to bacteria all our lives. Then,
11 really, what is the difference? Why are we
12 worried about them?

13 I think this is kind of a little
14 bit of oversimplification. It is true that we
15 are growing with bacteria on our skin, in our
16 GI tract, and maybe in our mouths, but that is
17 not the same as introducing bacteria and
18 bacterial derived product systemically.

19 Even though most of the vaccines
20 are administered intramuscularly, they clearly
21 have the potential of systemic distribution,
22 and as we know, that is -- If bacteria does

1 get into your blood, you are likely to have
2 very serious consequences, including death due
3 to bacteremia.

4 So I think the sort of concept
5 that we are always living with bacteria,
6 therefore, anything that comes from bacteria
7 is now okay, I think, is a little bit
8 underestimating of the potential.

9 We have seen it, actually, in the
10 clinic, that bacterial derived product when
11 administered as a vaccine product generated
12 responses that were very strong. I don't want
13 to mention any specific examples, but I am
14 sure most of us know about those examples.

15 I do want, though, to ask the
16 panel, since there are other people who are
17 involved with clinical trials and Phase I
18 trials, in particular, should we start
19 thinking of some additional type of
20 measurements of immune parameters that we may
21 have not looked at up to now.

22 The general SS biomarkers, blood

1 chemistries that we are doing may overlook
2 certain signals that can be generated in some
3 of our exploratory preclinical studies, not
4 necessarily in the rabbit but in the mice or
5 in the non-human primate.

6 When do you think it will be
7 justified to bring some of these new
8 parameters, biomarkers -- I don't know -- T-
9 cell subsets, cytokine measurements into the
10 clinic, into the Phase I to really follow up
11 and see whether they will give us additional
12 tools to decide whether to move forward to
13 Phase II or even select the right dose, the
14 maximally tolerated dose, etcetera?

15 DR. BALLOU: My own view is that
16 we are increasingly seeing these kinds of
17 tools being brought into Phase I and early
18 Phase II studies, and trying to make an
19 assessment about whether or not they are
20 actually telling us anything more than we
21 would have known otherwise.

22 Without a doubt, you have a lot

1 more information to look at, but whether it
2 actually allows you to form a different
3 opinion about the way forward or not -- I
4 think that has been, to me, the biggest part
5 of the puzzle, and of course, as we move
6 forward down clinical development, there is,
7 I think, the appropriate attempt to simplify
8 study design so that you focus on the most
9 important endpoints.

10 A lot of times that is not going
11 to be chasing lots of markers and other
12 ancillary readouts. That is my opinion.

13 DR. ROTROSEN: I would add to
14 that, that I think within a few years we may
15 be in a position to draw some reasonable
16 conclusions about immune markers being
17 correlates of immunogenicity and efficacy. I
18 think we are probably far, far away still,
19 though, from immune markers being a signal for
20 safety. I think that might be very useful,
21 again, for efficacy and immunogenicity, but to
22 assign a particular profile to the safety

1 concern, I think we are still years away from
2 that.

3 DR. LEVY: Yes. I would like to
4 amplify on those comments. I think that those
5 markers and those cell types, the new
6 lymphocyte types that we are aware of, the T-
7 REG cells, etcetera, can be very powerful from
8 the standpoint of trying to understand
9 mechanism better, to ask certain questions
10 about how the formulation is interacting with
11 the immune system.

12 I like something that was said
13 earlier this morning, the notion of a safe
14 haven where the information is collected, when
15 possible, when financially feasible, bearing
16 in mind the comments that we load up these
17 studies with so many endpoints, they get very
18 expensive.

19 So that is another element, but to
20 the extent that they are measured, being up
21 front about the fact that they were
22 exploratory, and maybe the long term goal is

1 to find surrogate markers for efficacy and
2 safety, but that we are not there yet, and
3 that they are going to be there to be
4 hypothesis generating or getting better
5 insight onto mechanism, but not to assume that
6 a certain signal there proves either efficacy
7 or safety.

8 DR. SCHODEL: Ripley, I actually
9 want to turn your question back to you a
10 little bit, because I think most of us would
11 agree that simple trial design and the power
12 of appropriately randomized studies with
13 whatever the controls are in populations which
14 are the users of these vaccines and where we
15 particularly want to deploy them would be
16 extremely helpful, and simple is, of course,
17 good.

18 One of the problems with
19 simplicity here is -- and just to exemplify
20 that for those who don't maybe think about
21 this all the time -- is that if you run a very
22 large study and you lose a certain part of the

1 population to follow-up, you don't know what
2 has happened to them.

3 That is the biggest problem with
4 these simple designs and populations that you
5 can't necessarily reach, because you don't
6 know whether there is something hidden
7 underneath or, you know, maybe they have died.
8 Maybe something else has happened.

9 So the question to Ripley is:
10 Then since this is such an important area and
11 not any manufacturer alone could actually
12 really resolve it -- I mean, we are all making
13 some efforts in our own ways, and we all have
14 pretty large studies in developed and in
15 developing countries, but we are struggling
16 with this issue.

17 Is there a plan from the Gates
18 Foundation and associated consortia to build
19 some sort of a network in which these studies
20 could actually be a practicality, could be
21 done?

22 DR. BALLOU: Well, there is

1 certainly not a plan, but I do think that the
2 Foundation does recognize that the whole issue
3 of pharmacovigilance as it relates to issue
4 around in the developing world is a big,
5 important vacuum right now, and one that we
6 are thinking about heavily.

7 I don't think that we are -- We
8 don't have a plan, no. But I think it is an
9 issue that needs to be addressed.

10 I would say, though, that my
11 experience in studies done in the developing
12 world is that we have higher follow-up rates,
13 lower dropout rates in those populations than
14 any of the studies I have done, part-studies,
15 in the developed world, simply because people
16 are just not that noble, and you can usually
17 find somebody who knows where somebody is.

18 DR. CLEMENS: Ralf Clemens from
19 Novartis. I have a bit of a difficulty with
20 the entire discussion. We are talking since
21 an hour about rare events, very rare events.
22 We didn't talk a single minute about the

1 benefits of adjuvants.

2 We heard from Gary that adjuvants
3 are critically important for some vaccines for
4 malaria, vaccine -- vaccine, for example, not
5 adjuvant. There is the malaria vaccine. We
6 heard from Rino that adjuvants are very
7 powerful to make an effective flu vaccine.

8 So why do we only look on the one
9 side of the corner, and we don't talk at all
10 about the benefits. How can we quantify these
11 benefits better? I think, if we don't that,
12 we miss an opportunity here.

13 DR. BALLOU: Well, I think
14 everybody in this room believes that adjuvants
15 are the jewel in the vaccine crown, that they
16 are the thing that is going to make the new
17 vaccines work. So if there is a sense that we
18 are worried about those perceptions or actions
19 that we fail to take to protect this important
20 tool, I think that is reflecting the
21 discussion here, but I think if we didn't
22 believe they were important, we wouldn't be

1 here today.

2 Are there other -- Geert?

3 DR. VAN DEN BOSSCHE: Geert Van
4 den Bossche from Gates Foundation. I am just
5 all the time asking myself the question, if
6 indeed we would be able to prove that we
7 deliver only locally -- and we have had Greg's
8 presentation, for example, on the intradermal
9 delivery -- would this change in any regards
10 the kind of safety concerns we would have for
11 -- and for example, these type of studies
12 could easily be done in animals, right?

13 If we really prove we deliver only
14 locally, would this change the whole
15 discussion or would we still be concerned, as
16 mentioned by all the questions we are
17 discussing?

18 DR. SCHODEL: Well, isn't all
19 immunity local? So in a way, maybe all
20 autoimmunity starts somewhere, too? I think
21 it is an artificial question.

22 You know, any positive and

1 negative immune response has to start
2 somewhere, probably in the lymph node.

3 DR. VAN DEN BOSSCHE: So you
4 wouldn't distinguish from systemic
5 distribution?

6 DR. SCHODEL: No, I would, but
7 from a pharmacology point of view. So in
8 other words, if I have an adjuvant or a drug
9 that has strong systemic effects, obviously,
10 I've got to study them. I've got to look at
11 the maximum tolerated doses and all the
12 classic pharmacology. It's very simple, and
13 we all know how to do that.

14 If I have a much more short acting
15 drug, then I don't have to do as much on that
16 side. So I would agree with you there, but on
17 the other hand, the consequences of a strong
18 local immune response can still be strong
19 consequences, and it is not necessarily
20 because we have circulating interleukins that
21 something bad happens. That is not -- I think
22 it is a juxtaposition that is not quite right.

1 DR. BALLOU: I have done a fairly
2 poor job of going through our questions here,
3 but I would like to actually address the third
4 bullet on this first question, because I
5 haven't seen any data presented here on this
6 question, particularly from the large
7 manufacturers that have fairly fixed
8 formulations.

9 Is there the need, and has there
10 been done but we haven't just seen it, careful
11 dose ranging of adjuvants, the way we
12 typically do for adjuvants -- for antigens?
13 And is this something that -- Is this an
14 opportunity that we are missing to help
15 reassure us on issues around safety?

16 DR. DENIS: Maybe I can take that
17 question, because I think I at least partly
18 addressed it during my presentation. While
19 indeed we evaluated the dose ranging of the
20 adjuvant in our H5N1 program, I didn't present
21 the data today.

22 To me, the question remains to

1 what extent these results can really help. Of
2 course, we can always use the data to make
3 sure that the balance of immunogenicity and
4 reactogenicity that was obtained with a
5 selected dose is better than for the other
6 doses that were evaluated, but that is, of
7 course, limited information that you get from
8 this.

9 In our case, so that was
10 additional information obtained from an
11 additional trial. So it required a doubling
12 of the investment as compared to a single
13 trial, but it was done anyway, as it was
14 considered as required.

15 DR. GITTLESON: I would like to
16 comment as well. So we have done dose ranging
17 work with the adjuvant, which I didn't show
18 today, where we have looked at a number of
19 escalating doses with the adjuvant where the
20 antigen has been held stable.

21 The differences can be very, very
22 subtle. If you are doing it early on in a

1 Phase I study, you actually have to have
2 fairly large patient numbers in each group to
3 be able to tease out the differences. If you
4 take just the standard Phase I study approach
5 with a very small study and small patient
6 numbers, you are going to miss it.

7 What we have seen is that, when we
8 have a look at a humoral response, that when
9 you use very low doses of, for example, the
10 ISCOMATRIX adjuvant compared to higher doses,
11 you will get a higher immune response as you
12 dose range up, but you will get a flattening.

13 Where we have found value is
14 specifically for us, because we are looking at
15 T-cell responses. What we see is that the
16 higher one goes with the adjuvant dose, that
17 you get a broader response, and you can induce
18 CD8 responses with the higher adjuvant dose.

19 Some of that work has been done.
20 When we have a look at safety, in our hands
21 with ISCOMATRIX adjuvant, we have not seen on
22 local reactogenicity a dose response that

1 seems to occur with increasing antigen,
2 because we have done the same. We have held
3 the adjuvant dose stable, and then we have
4 dose escalated on the antigen.

5 There, as you increase antigen, we
6 tend to see greater reactogenicity. Where we
7 have seen a trend toward increased number of
8 AEs is with systemic side effects, such as
9 myalgia and fatigue, if you go to higher
10 adjuvant doses in some patient populations.

11 Perhaps later on I can comment on
12 some of the work we have done with ages,
13 looking at the elderly, because we have not
14 touched on looking at the elderly and the
15 affected immunosenescence, and not all elderly
16 are the same, and how do you tease that out
17 and look at responses. Perhaps we could talk
18 about that afterwards.

19 DR. ROTROSEN: Can we comment on
20 whether animal models, mouse or rodent, other
21 rodent species, were useful in predicting
22 those changes in the human response based on

1 the adjuvant to antigen ratio?

2 DR. GITTLESON: So adjuvant dosing
3 has been done as well as antigen in rodent
4 species. We didn't see increase
5 reactogenicity that we were able to detect.
6 There again, it is very much, when you looking
7 at reactogenicity in the mouse, they don't say
8 "Ah." In our hands, we haven't had animals
9 ending up limping and such like as we have
10 dose escalated.

11 So we needed to go in our Phase I
12 programs and dose escalate with the adjuvant.

13 DR. BALLOU: Can I ask if there is
14 a comment from either Novartis or GSK in
15 regard to dose ranging in adjuvants?

16 DR. DUBIN: Yes. So I think that
17 the situation is potentially even a little bit
18 more complex when you are talking about
19 adjuvants that have more than one component or
20 adjuvant systems, as we define them.

21 The approach that we have
22 generally taken is to do dose ranging of the

1 components in different ratios pre-clinically,
2 but once we enter the clinic, we tend to use
3 a fixed ratio of components of dose ranging of
4 the adjuvant system.

5 The reason for that is that you
6 could argue that, when you change the ratio of
7 the components, you are actually changing the
8 adjuvant system, because in some cases, there
9 are interactions between the components. So
10 that is the approach that we have used, and in
11 clinical trials this is something that is
12 becoming more standard to do dose ranging of
13 the adjuvant system with a fixed ratio.

14 DR. DELLA CIOPPA: Well,
15 personally, I believe that dose ranging of
16 both components is necessary and essential.
17 However, I believe it is only useful if you
18 manage to do it in the same trial. Here, I am
19 going to suggest that there is a
20 methodological tool that allows for this.

21 This is so called factorial design
22 where you can kind of identify two or more

1 factors, and you put them together so that you
2 can dose range in the same trial the level of
3 adjuvant, assuming it is only one, and the
4 level of antigen in various permutations.

5 Of course, I realize that you do
6 introduce another confounder, which is the
7 volume, because you will have to do bedside
8 mixing. Then the volume changes, but still
9 you could have very useful information.

10 I would like to make also a
11 slightly provocative remark. I think we
12 should do much bigger studies in Phase I, and
13 actually much bigger toxicology studies.
14 Either not do them at all or do them big,
15 because the same doubts that people have with
16 very small clinical studies, they have them
17 exact the same when you get three rats, three
18 female, and three male rats. The information
19 you get from that is questionable.

20 So, yes, you have to do it.
21 Actually, I think the balance between the kind
22 of investment we make in Phase III and the

1 kind of investment we make in earlier stages
2 has to be changed a little bit, and the
3 earlier stages have to go toward bigger
4 studies. So some of the studies that were
5 presented, I think, are going in the right
6 direction.

7 DR. BALLOU: Steve, did you have a
8 comment?

9 DR. REED: My only comment was
10 that in our approach where we try to keep the
11 emulsion constant. With TLR-4 agonists, both
12 synthetical and natural, it is easy to find
13 doses that are optimal for rodents and for
14 macaques, and so we have used both of those to
15 help us choose the human dose, and it is very
16 apparent that it is quite easy to use too high
17 a concentration of agonist and actually get a
18 poorer response.

19 So that is something to keep in
20 mind. Certainly, more is not better in our
21 experience, especially in the monkey system.

22 DR. BALLOU: We have five minutes

1 left. Charmaine, I think you raised an
2 important issue, the issue around the
3 adjuvants in the elderly, which is, in fact,
4 one of the populations where we are going to
5 see adjuvants used more heavily in the near
6 term. Could you please comment?

7 DR. GITTLESON: So one of the
8 things that I thought was of interest,
9 typically when we consider the elderly, the
10 data is often presented for patients who are
11 over 60. One of the things that we did in a
12 study was we took that patient population and
13 broke it up to actually have a look and see
14 whether there are different responses and to
15 what degree do patients have immunosenescence.

16 We found, interestingly, that if
17 you have a look at patients who are, say,
18 between the ages of 60 and 74 who are
19 ambulatory and community dwelling, or compare
20 that to patients who are 75 and over who are
21 fairly well and community dwelling, and then
22 have a look at patients who are over 60 who

1 are in long term care facilities and who have
2 a lot of comorbidities, what we were
3 interested to see was, was there a different
4 response in those patients in terms of the
5 ability of an adjuvant to overcome
6 immunosenescence.

7 So we compared it to a licensed
8 vaccine, and we did see that there was,
9 certainly, a trend toward patients who were in
10 long term care facilities, so 60 and over,
11 then compared to those patients who were
12 community dwelling, that they actually seemed
13 to benefit more if we had a look at the fold
14 increase in the GNC titers of interferon
15 gamma, looking at their CD4, CD8 responses, or
16 having a look at their humeral responses.

17 So it was really interesting for
18 us to try and have a look and try and tease
19 out why that might be, and it is a question I
20 would like to put forward just to say that not
21 all elderly are the same.

22 Which are the elderly patients

1 that would benefit more? What are we actually
2 overcoming? Which adjuvants would be better
3 placed to overcome some of the issues of
4 immunosenescence? I don't have the answers,
5 but I think that that needs a lot more teasing
6 out.

7 One of the challenges that we
8 faced in our program is that again patient
9 numbers were fairly small, and I take the
10 comment that I think there does need to be --
11 If we are exploring this from a scientific
12 basis and not so much just trying to get the
13 product registered but really trying to tease
14 out the science, that we do need to be looking
15 at larger patient studies.

16 DR. BALLOU: I know that the
17 elderly population have been looked at fairly
18 extensively by both Novartis and GSK in the
19 development of their pandemic influenza
20 vaccine. So people from either one of those
21 groups want to comment on their views on the
22 elderly?

1 DR. RAPPUOLI: Well, I can try to
2 answer some of this. Well, we have done
3 trials where we have done with pandemic
4 influenza in the elderly and the adults, and
5 you do see that, when you go in the elderly,
6 you get lower responses, but the plans are the
7 same. So we have done that study, separating
8 the two populations.

9 Talking about the elderly, I
10 think, we've got into a fascinating field,
11 because the way you define the elderly, I
12 think, from the immune system point of view
13 may change over time, may change with
14 different populations.

15 Thirty years ago, 30-35 years ago,
16 basically, the people that were hospitalized
17 in Italy were basically mostly -- in internal
18 medicine were mostly 60-75 years old. Today,
19 the same place, you get 75, 85, 90 years old.
20 So which one of the elderly?

21 So you mentioned that when you get
22 75, you do get a different response than you

1 get in the Sixties. There are people that are
2 starting to do studies, what happens to the T-
3 cells. Basically, they do find that in
4 today's population, when you get to 70-75 that
5 both CD4s and CD8s, basically, they basically
6 go down dramatically.

7 So I think we need to do a lot
8 more basic studies about what is the
9 underlying immune system. What are the T-
10 cells, the B-cells, the cytokines. The
11 beautiful things you are doing with the
12 infants need to be done in the elderly, and we
13 need to define the elderly, because maybe the
14 elderly in a population has a life expectancy
15 of 85 years is not the same as the elderly in
16 a population that has a life expectancy of 50
17 or 60 years that they have in some developing
18 countries.

19 So I think you really need to
20 define what elderly means for the immune
21 system.

22 DR. ROTROSEN: Let me just add to

1 that. NIAID has a handful of programs looking
2 specifically at special populations, elderly,
3 transplant recipients, and the like, looking
4 at immune responses. We haven't focused on
5 adjuvanted versus non-adjuvanted vaccines, but
6 if there are manufacturers here who are
7 interested in evaluating products through
8 those clinical research networks, we would be
9 happy to talk to you.

10 DR. DUBIN: And just a quick
11 comment. In the context of pandemic flu, we
12 have seen that different adjuvant systems
13 appear to have different effects on
14 reconstituting immunosenescence or restoring
15 immune responses in the adjuvant system that
16 we are currently using for our pandemic
17 vaccine.

18 The AS03 adjuvant system appears
19 to be one that is particularly good at
20 restoring immune responses in the elderly, in
21 particular.

22 DR. GLENN: May I ask how the AE

1 rate looks? Is it different as you get into
2 the older population?

3 DR. DUBIN: What we have typically
4 seen, comparing the same adjuvant system in
5 younger versus older individuals, we typically
6 see lower AE rates in the elderly. I mean
7 those AEs that are temporally associated with
8 vaccination, reactogenicity, etcetera.

9 Now why that is, I don't know. I
10 think Rip alluded to this this morning as
11 well, but that has been the general pattern
12 across different adjuvant systems, lower rates
13 in older individuals.

14 DR. GITTLESON: So if I can
15 comment on that as well, in the program that
16 we looked at, we had within the same trial
17 younger adults together with our older adults.
18 Yes, when you just compare looking at licensed
19 vaccine or looking with the ISCOMATRIX
20 vaccine, your elderly patients had a lower
21 incidence of reactogenicity.

22 What was really interesting and

1 why we wanted to have a younger adult
2 population and need to compare was what we
3 wanted to see was that if we reconstituted an
4 immune system and were able to overcome that
5 immunosenescence, which we did show, that we
6 were able to get immune responses in the
7 elderly at much the same levels as the young
8 adults with just the licensed vaccine.

9 What we really wanted to see was
10 did you take the AE rate up to the same
11 instance as the reactogenicity seen in the
12 young, and it was reassuring to see that we
13 didn't.

14 So whilst we boosted the immune
15 response in looking at humeral responses as
16 well as interferon gamma responses, we didn't
17 see an increase in the AE rates to the same
18 extent as what one sees in the young with a
19 licensed vaccine.

20 DR. PETROVSKY: Maybe just again a
21 word of caution, that we shouldn't say the
22 elderly as an extension of the young, just as

1 we can't extrapolate to neonates. Therefore,
2 maybe we need to look for a different adverse
3 event profile in the elderly.

4 Certainly, I think it is a general
5 observation that the elderly get less local
6 reactogenicity, but maybe other things start
7 to come into play. I guess one of the
8 potential issues is the data in mice that TLR-
9 4 is important in myocardial infarction and,
10 if you actually look at TLR-4 knockout mice,
11 they actually are protected against
12 atherosclerosis and myocardial infarction.

13 Now, obviously, that is not going
14 to be an issue in a younger population, but in
15 an elderly population in potentially that
16 pathway, if you activated strongly, may result
17 in myocardial infarctions. Again, that is not
18 a typical adverse event of vaccines that are
19 used in younger populations, but maybe we
20 would have to look at that specifically as
21 something unique to an elderly population.

22 So again, it is just this issue of

1 should we be looking at the different
2 pharmacology and the different behavior of the
3 elderly when we start saying whether or not
4 they are going to get more or less side
5 effects.

6 DR. VERSTRAETEN: I absolutely
7 would endorse that. We talked a lot about
8 neonates and potential effect of vaccinating
9 neonates, but when you go to the other end of
10 the spectrum, we are not talking about
11 autoimmune disease anymore. we are really
12 talking about atherosclerotic process or
13 cancers. I think that deserves a special --
14 not a special design, but special attention
15 when collecting serious adverse events.

16 DR. BALLOU: Are there other
17 comments from members of the panel, the
18 roundtable, that have not had a chance to
19 voice and opinion or make a comment?

20 DR. HOLDICH: Yes, I would like to
21 just raise a somewhat different aspect, which
22 is really from the aspect of therapeutic

1 vaccines, and one of the issues that we have
2 is the detection of rare or long term side
3 effects, bearing in mind that is general
4 speaking.

5 The inherent natures of the
6 program are not large in terms of patient
7 numbers. On the other hand, the degree of
8 monitoring and selection of patients is
9 perhaps more intense than with the
10 prophylactic vaccines. Therefore, the issue
11 that we need to deal with is in that context.
12 How can we go about assessing perhaps the
13 longer term or the rare side effects?

14 DR. FRIEDE: Better put my two
15 pennies' worth on this.

16 It is to do with risk management,
17 and the fact that we've got many manufacturers
18 using their own proprietary adjuvants, which
19 work across essentially similar mechanisms.
20 So we've got the oil and water emulsions from
21 most manufacturers. We've got several groups
22 using TLR-4 agonists. You've got several

1 groups using TLR-9 agonists.

2 So when one of these groups with
3 their particular vaccine has an adverse event
4 -- Just take an example of the recently
5 publicized Wegener's syndrome. How does this
6 impact the other manufacturers' products that
7 are working on similar mechanism or similar
8 targets?

9 My feeling is that each vaccine is
10 separate, and we have to view each vaccine as
11 being separate. So we cannot say that an
12 adverse event seen in one manufacturer's study
13 immediately becomes a detraction to other
14 manufacturers' approaches. But the design of
15 the studies subsequent to this, we should
16 perhaps be taking this into account.

17 So this could give us some ideas
18 of at least factors to be included in future
19 clinical studies to say, if that was a real
20 event that was seen, what parameters could we
21 design into the study of those manufacturers
22 that are working in a similar area.

1 This would also then come back to
2 the issues of squalene antibodies. So
3 Novartis has done a lot of work to eliminate
4 those concerns. But I think this risk
5 management issue is of concern to the entire
6 environment.

7 DR. BALLOU: Would someone from
8 the FDA like to comment on how you approach
9 this question? You're brave.

10 DR. GOLDING: I think this is
11 actually a very, very important point, and
12 there is always sort of the balance between
13 proprietary information, that really, we are
14 not at freedom to divulge, yet when a similar
15 product comes in our door, how do you address
16 it?

17 So I think, again, there is no one
18 answer, but clearly, when the problem with the
19 myocardial, pericardial adverse reaction was
20 seen in the case of the smallpox vaccination,
21 that clearly affects the way we started to
22 look at all pox-derived, and our clinical

1 reviewers were asking manufacturers that were
2 using either new Dryvax-like or host in a
3 vaccine as well as MPA-like vaccines and so
4 forth, to looking for any type of signals that
5 related to what was found.

6 So I think there is clearly an
7 influence, and of course, if it is in the
8 public domain, it is much easier to explain to
9 the next manufacturer why it is asked. I
10 really think that this is a very good time to
11 plea to the manufacturers to make these type
12 of adverse reactions, even if they are already
13 part of the public domain, because ultimately
14 it will help the whole field to move forward,
15 and there is nothing wrong with making it
16 public, because rare adverse events are
17 exactly that.

18 Nobody can be blamed from finding
19 them, because we couldn't pick them up at the
20 earlier studies, but once we have seen them,
21 we should be able to now retrench and at least
22 look for these kind of signals in the other

1 trials, because I think ultimately it will
2 benefit the whole field.

3 MODERATOR SLATER: Just to answer
4 that, problems aside, we have to look at the
5 question from both directions. It has been
6 expressed several times today and yesterday
7 that we need to look at antigen-adjuvant
8 units, that we need to look at safety issues
9 for the whole vaccine, for the whole
10 adjuvanted product.

11 That actually cuts both ways. If
12 one consequence of this is the view that,
13 well, if we had an adverse reaction with one
14 particular adjuvanted vaccine, we should not
15 carry over those concerns to all other vaccine
16 candidates that use the same adjuvant.

17 Likewise, there is a limit to how
18 much reassuring data we can accumulate with
19 other adjuvanted vaccines that use the same
20 adjuvant. In other words, if we have an
21 individual product in which we observed an
22 adverse event, there may be limits to how

1 reassured we can be that four or five or six
2 other candidates have been studied using the
3 same adjuvant without reporting that
4 particular adverse event.

5 It is a difficult situation. It
6 is not obvious how you should approach that,
7 but the logic, unfortunately, carries both
8 ways, and we have to be very careful as to how
9 we handle it.

10 DR. SCHODEL: I think we also have
11 to be very careful as to what we consider as
12 a signal. A single event of anything is not
13 necessarily a signal. It is a single event,
14 as Hana said as well.

15 That is why I asked earlier from
16 the preclinical colleagues as to whether there
17 is any approach toward mechanistically
18 thinking, because that is what we would do in
19 any other circumstances. We would try to
20 figure, you know, is there any biologically
21 plausible correlation, if you really think
22 this is a signal.

1 First of all, of course, you would
2 like to know whether it is a signal, but let's
3 assume it is a signal. Then you would try to
4 find out, is it plausible? Then if you had a
5 model in which you could actually study
6 whether the adjuvant in question elicits such
7 a mechanism or has an influence on it, then
8 you could rule out or rule in whether you have
9 to do more.

10 That is somewhat where we are
11 stuck, because we see a single case of
12 something, and we regard it as a signal. Then
13 basically, the observation stops right there.

14 DR. VAN DER LAAN: Yes, I will
15 give some comments from a preclinical point of
16 view. I think you are fully right. Just a
17 single event is only a single event.

18 Toxicology is done with much
19 smaller groups, and that is not a real
20 problem. Toxicology is not the final answer.
21 Toxicology is just preparing the clinical
22 studies, and toxicology is only raising

1 signals or not, and there should be -- There
2 is always the discretion, are the groups big
3 enough in toxicology? Never, but that is not
4 the issue.

5 You are playing with the dose.

6 You are playing with the mechanism of action,
7 and you try to understand what is the
8 biological relevance rather than the
9 statistical relevance. Of course, you have to
10 look at statistical relevance, but the causal
11 relationship and pharmacology is also very
12 important for the interpretation of your
13 toxicology studies.

14 That is what toxicology can offer
15 the clinical experience also with respect to
16 adjuvants.

17 DR. BALLOU: I would like to thank
18 all of my fellow colleagues up here for their
19 willingness to participate in this, and for
20 the very interesting discussion and dialogue
21 we have had with the participants in the
22 audience.

1 Jay, do you have any final
2 comments? If not, thank you very much, and
3 there will be a wrap-up session immediately
4 following with Hana and Chuck.

5 (Applause.)

6 MODERATOR SLATER: The wrap-up
7 session starts immediately.

8 DR. HACKETT: Okay. So it comes
9 down to us. So let us do the wrap-up.

10 What we would like to do, Hana and
11 myself, is to provide a sort of a high level
12 view of some of the points that we pulled out
13 from the earlier sessions, and not go into
14 really details of how things are going to be
15 done, but some of the ideas that we got and
16 some of the things that we wanted to take
17 home, and they can be perhaps titles of future
18 meetings, perhaps ideas for new initiatives
19 ultimately, and new foci of our research.

20 So that will be what we will be
21 doing. We didn't, obviously have enough time
22 to go over the roundtable 2. So you have to

1 kind of treat that as -- You have to digest
2 that yourself, but Hana will start out with
3 the roundtable 1.

4 DR. GOLDING: So first of all, I
5 think that I really want to thank all of the
6 participants for being here. I think this by
7 itself is sort of a success point of this
8 workshop, that we were able to bring into the
9 same room a significant number of
10 representatives from the manufacturing of
11 vaccines and novel adjuvants, of regulatory
12 and NIAID that is supporting a lot of the sort
13 of discovery agenda in this area, and CDC,
14 etcetera.

15 The important thing was not really
16 to come up with answers to all the questions
17 that were posed, either in the roundtable 1 or
18 2, but to agree on the questions, to agree on
19 the gaps, to maybe together -- If any of us
20 went home and then said maybe this is a point
21 that we should start thinking about designing
22 some experiments, either in vitro or in animal

1 model or in our next Phase I trial, that maybe
2 we can start to address, I think we already
3 achieved something.

4 With that, I would like to just
5 sort of summarize what I got out of
6 participating in the first day and the first
7 roundtable.

8 There was a lot of very specific
9 questions about preclinical studies, but what
10 we actually heard from the panel was that the
11 most important word is flexibility.

12 We really have to think about
13 product-specific issues. They may include
14 both the studies that are likely to give us
15 meaningful information, may include both novel
16 in vitro studies as well as in vivo studies in
17 animals; and not all of these studies
18 necessarily have to be conducted with a GMP
19 product, which is required for the pivotal
20 preclinical tox studies.

21 Animal studies may be a
22 progressive process, including post-Phase I,

1 to explore mechanism of an unpredicted AERs,
2 and that has already happened.

3 We need to take into consideration
4 when designing all of these preclinical
5 studies the specie specificity of the adjuvant
6 mode of action, if it is known, of course, and
7 the availability of reagents to fully evaluate
8 biomarkers in a given animal model.

9 That, I consider actually an
10 important gap in the field right now, because
11 I think, as we are trying to understand better
12 both the efficacy and the potential toxicity
13 of novel adjuvants, once we identify the
14 models that are appropriate, we really have to
15 know that we have all the reagents, and that
16 should be an area where I think some both
17 financial and research be addressed.

18 Ultimately, studies with both
19 adjuvant alone and adjuvanted vaccine
20 formulation may be informative during early
21 vaccine development, as well as the GMP tox.
22 This issue was debated. Some of you felt

1 that, really, the final product that goes into
2 the human arm is the one to test in
3 preclinical, but others felt that it was
4 important to try and understand the mechanism
5 of action as well as the underlying mechanism
6 of toxicity associated with a given adjuvant.

7 My personal view is that probably
8 there is definitely a place for both types of
9 studies at this point.

10 I would like to now open the floor
11 to some other comments related to the first
12 day and the first roundtable before we move to
13 the next set of conclusions.

14 DR. HACKETT: Well, yes, there
15 should be enough time to bring up any other
16 points as we move ahead.

17 I wanted to sort of briefly give
18 my take, and again this will also be something
19 we can discuss, on some of the research topics
20 that were highlighted in the workshop. I have
21 a few, and I am actually going to flesh out
22 each one of them, and also I can send

1 everybody all these slides from our sessions.

2 So you don't have to write anything down.

3 Let me go one by one through

4 these, because what I did was try to -- as I

5 listened to people talk about the things they

6 did, the things they wanted to do, especially

7 in the basic studies and some of the

8 preclinical and clinical, I tried to pull out

9 some of the ideas that we were hearing and

10 some of the research foci and needs that we

11 should develop.

12 So under the topic you might call

13 immunological markers of efficacy and

14 toxicity, it seems that one of the really

15 valuable approaches is to have a definition of

16 the relevant immunological profiles according

17 to the adjuvant mechanism.

18 I have put down TLR and non-TLR

19 receptor targeted and APC uptake activation,

20 because it seems to me that what you can see

21 is you can always do gene expression, and that

22 may be very relevant to analyze pathways if

1 you pretty much know the pathway. And that
2 may be true now with the TLR and many of the
3 non-TLR.

4 In some of the other adjuvants
5 which, for example, that might stimulate
6 effective antigen presenting cell uptake and
7 activation, maybe the genes -- I don't know if
8 we know the genes, but maybe the genes are not
9 what you should be looking at, but some other
10 parameters, maybe such things as ways of
11 measuring expression of peptide MHC complexes
12 on APC surfaces, maybe actually kinetics of
13 ingestion. I don't know, but I am saying, I
14 think that if you look at how your adjuvant
15 should be working, probably the next step is
16 to refine those profiles.

17 The other thing is the
18 standardization of reagents, analytical
19 approaches and controls. I think in some of
20 the studies I was thinking of what is the
21 control, actually, and some of them are good,
22 and some of them aren't. I think that is

1 something that we as a group could standardize
2 reagents in particular and looking across
3 different animal models and so on.

4 The in vitro/in vivo correlation
5 is actually very telling. I think Bali
6 Pulendran showed in his paper using systems
7 biology that he was getting -- when he looked
8 in vitro at human cells versus his in vivo
9 studies with the yellow fever, that he was
10 getting quite a high percentage of similarity,
11 but it wasn't 100 percent. I don't know if
12 everyone remembers, but it was in the sixties
13 or so percent.

14 So that is something that is very
15 telling, but we have to know what the actual
16 correlation is.

17 Human and animal model
18 correspondence: There are probably many areas
19 where the correspondence is excellent. A long
20 time ago in immunology, people used to say, if
21 you are looking at a real fundamental process,
22 it is going to be the same in animals and

1 humans, like loading peptides into MHC.

2 It is probably a certain amount
3 true, but that is sort of -- You have to
4 actually quiz yourself as to whether that is
5 going to be true or not, because when you get
6 to the innate immune system, it was pointed
7 out, well, I think that, no, we don't have the
8 same number of Toll-like receptors even as a
9 mouse.

10 So there will be some areas where
11 there will be processes, I am sure, that are
12 reasonably well indicated in the animal model,
13 but tying these together is very important.

14 The profile with and without
15 vaccine antigens, actually, Hana mentioned.
16 I think everyone mentioned that.

17 What I was wondering about is what
18 happens, really, in interpreting already
19 effective vaccines. So if you wanted to study
20 the yellow fever or polio vaccine, that has
21 its adjuvant and its antigen together already.

22 You can say, well, we have the

1 double-stranded RNA already in the vaccines,
2 but you also have the antigen. So I think it
3 would be very instructive to try to figure out
4 what the antigen actually does, because we
5 often think of the antigen as being only the
6 adaptive immune system and the other one being
7 only the innate, but an emerging idea, which
8 is, I guess, not that emerging, is that there
9 is really an enormous amount of interface
10 between the two, and that is probably right
11 where that happens.

12 The other point was the adjuvant
13 mechanisms that drive distinct T and B cell
14 subsets. This is probably one of the real
15 joys of having a pipeline of adjuvants, is
16 that you can probably start to think about
17 driving in the different directions of CTL and
18 so on. But exactly how that drives is a lot
19 less evident to me than I thought it would be.

20 It is not easy to say this is the
21 reason you get a Th2 response with alum,
22 exactly. I think there is a lot of

1 contributors and, certainly, some of that has
2 to do with the dendritic cells, the
3 macrophages, the cytokine profiles, co-
4 stimulatory molecule patterns, but also the
5 type of T and B cell responses that you get.

6 It is particularly important, I
7 think, to understand this cross-protection and
8 the repertoire differences that could be one
9 of the most valuable parts of what we are
10 seeing with adjuvants. So how does that
11 happen? I think -- I believe we don't know.

12 Tools and resources: Certainly,
13 systems biology computational approaches --
14 there is a vast amount of things going on in
15 terms of cellular pathways, different cells
16 and so on.

17 We also heard a lot of talk about
18 clinical samples of interest. That means to
19 me that high and low responders, infants and
20 elderly, serious adverse events -- to have
21 access to samples where you could actually
22 probe and decide what is a normal response,

1 which I would like to know.

2 We saw in some of Bali Pulendran's
3 data that there are people that had a very low
4 CTL response, had a high antibody response,
5 and some had a high of both. I don't know,
6 but I would imagine all those people are
7 protected. They got the vaccine, and they
8 probably are protected.

9 So I think we need to be able to
10 define those, and that will be by studying
11 people who have been profiled, who have shown
12 that they have different responses.

13 Then there is development of a
14 database, and I wonder if Hana could just say
15 a couple of words about maybe why that might
16 be valuable to the community.

17 DR. GOLDING: Actually, this is
18 something that had been presented today by
19 Solvay manufacturer, that I think are really
20 taking the lead. They say we are going to
21 design prospective studies to capture a large
22 amount of follow-up clinical data that

1 ultimately would help us as well as the field,
2 the public health, to look back and detect low
3 frequency adverse events that happen and to
4 maybe identify other types of biomarker or
5 clinical endpoints that predicted or can
6 correlate, or both, either with the efficacy
7 of a given vaccine or possibly with unexpected
8 adverse reactions.

9 It reminds me a little bit of the
10 early days of the gene therapy field. It was
11 very obvious that we are entering a new era,
12 and we need to have some sort of a registry to
13 follow up people that receive gene therapy, so
14 that we can accumulate stepwise, long term
15 safety data to see what happens in five, 10,
16 20 years from this treatment.

17 Arguably, our adjuvants are not as
18 novel as earthbreaking, but nevertheless, as
19 we are starting to introduce these adjuvants
20 into larger numbers of people, I think
21 together with the CDC and there may be a
22 partnership between the manufacturer and the

1 government, that should allow to build a
2 really good database that eventually should be
3 very helpful in terms of meta analysis and
4 identifying the tendency or trends toward a
5 unique type of adverse reaction.

6 Actually, I think there will be --
7 It is important to have everybody at the
8 table, both industry and government, to
9 suggest how best to go forward and build this
10 kind of a database.

11 DR. HACKETT: And, really, the
12 final thing that I wanted to highlight was
13 really the need for new collaborations. I
14 think the field actually has grown to this
15 level in part because -- from some of the
16 earlier stages.

17 Biochemists and developmental
18 biologists, Drosophila biologists, and so on
19 were collaborating with immunologists. I
20 think in the future there will be a lot of
21 room for computational biology and model
22 building to make sense of some of the complex

1 profiles that we see in immune responses.

2 Certainly, biophysical chemistry
3 is an area. Biophysics of these compounds and
4 so on, how they interact with cells and
5 tissues probably holds a lot toward more
6 rational design, a lot of potential.

7 In vivo imaging -- Nobody actually
8 really mentioned that, but it seems like it
9 would make some sense. If you want to know
10 how long is your adjuvant lasting at a certain
11 site, what cells are going there, what are
12 some of the hints that you can get about
13 pathology, that would be something that could
14 be done, could be started now.

15 Another thing is the sample
16 sparing assay development. Several people
17 mentioned, well, you have to make a choice
18 about what cytokines you want to look at and
19 what markers you want to use and so on.
20 Probably in the future, you can do them all,
21 if it was possible to miniaturize and do
22 things in a very small scale where you could

1 get good readouts.

2 So that would probably be the
3 ultimate. If you just try everything that we
4 know about that the immune system can do,
5 ultimately something like that.

6 So I think those are areas of new
7 collaborations that we will see developing,
8 and maybe we should also think about if there
9 are some meetings or ways of sort of
10 catalyzing these reactions, we should really
11 think about that.

12 So that is all I had to say.
13 Certainly, I think we have enough time before
14 the wedding or whatever is supposed to happen
15 in here, to have more input comments. As I
16 say, we can send you our slides, certainly.
17 So you don't have to write down any of these
18 things. Any other feedback, we would
19 certainly -- Feel free.

20 MODERATOR SLATER: Thank you
21 again. I was asked about three more times
22 today about the slides, and I will just say

1 again what is going to happen with the slides.

2 We are going to ask all of the
3 speakers for their permission to put their
4 slides on the website. Once we have secured
5 that permission, we will do so.

6 I think you can be fairly sure
7 that all the government originated slides will
8 be made available on the website. I don't
9 think that is going to be an issue, but we do
10 have concerns about individuals from
11 manufacturers and from academia that they may
12 or may not wish to have their slides on our
13 website, and we will respect that.

14 Give us a few days to sort that
15 out. My suggestion is check back on the
16 website in a week or, better yet, 10 days, and
17 hopefully, we will have a link to all the ones
18 that we will be able to share with you.

19 Aside from that, if there are no
20 comments, thank you all very much for
21 participating. Thanks again to the organizing
22 committee, and have a safe trip home.

1 Thank you.

2 (Applause.)

3 (Whereupon, the foregoing matter

4 went off the record at 4:35 p.m.)

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