Subject: CEPI SAC meeting, COVID-19 response update

Dear SAC members,

The CEPI secretariat have prepared and uploaded the documents that will be presented at the meeting on Monday March 9 at 1600 CET.

Please follow the link to the folder for the documents here!

If you have problems to log in or other technicalities please write to it@cepi.net or just reply to me.

Looking forward to receive your inputs on Monday.

Best wishes
Stig
STIG TOLLEFSEN
Head of Strategic Science

 (+47) 901 50 770
stig.tollefsen@cepi.net

Visiting address: Marcus Thranes gate 2, 0473 Oslo, Norway
Postal address: P.O. BOX 123, Torshov, 0412 Oslo, Norway

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Dear SAC members,

This is the agenda for the upcoming meeting.

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Pre-reads for the meeting will be published on the secure SAC SharePoint site as soon as they are ready. I will forward you a notification when it is all in place with the secure link for you to log in.

Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI New vaccines for a safer world

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Well noted. I replaced the original file with this one in the sharepoint, to which now you should have received the link and granted access. We have invited researchers from the Wuhan institute of virology / Chinese academy of sciences in the TCs on “cross-reactivity” organized by Bill to share information on their viruses and reagents they have and plans to share internationally. Unfortunately, we did not receive much information. I understand that only the missions’s reps, will not be coming in-person to the forum. We hope that they will join via WebEx, as well as China CDC (George Gao has accepted to give a presentation remotely in the plenary, so perhaps we will know more), in the vaccine group to provide more insights about international sharing of samples and sequences.

Kind regards
Pierre

From: Krause, Philip <Philip.Krause@fda.hhs.gov>
Sent: 10 February 2020 15:03
To: GSELL, Pierre <gsellp@who.int>
Subject: RE: Vaccines subgroup updated outline

Hi Pierre, here is a slightly modified document, which may be better for the Sharepoint- Peter Smith pointed out that it might be politically better to include China in the list of countries with virus! Of course, it would be nice if someone from China would participate in these research calls to help figure out how critical reagents can be shared across international boundaries, but maybe we can’t solve everything all at once... PHIL

From: GSELL, Pierre <gsellp@who.int>
Sent: Monday, February 10, 2020 5:23 AM
To: Krause, Philip <Philip.Krause@fda.hhs.gov>; HENAO RESTREPO, Ana Maria <henaorestrepa@who.int>
Subject: RE: Vaccines subgroup updated outline

Hi Phil,
Thanks so much for updating the document. From now on, we will upload any additional documents in a sharepoint for which we will grant access to all participants. We will grant access to the sharepoint later today. Please go ahead with sharing the document with the group.
Kind regards
Pierre

From: Krause, Philip <Philip.Krause@fda.hhs.gov>
Sent: 09 February 2020 04:34
To: GSELL, Pierre <gsellp@who.int>; HENAO RESTREPO, Ana Maria <henaorestrepa@who.int>
Subject: Vaccines subgroup updated outline

Hi Pierre and Ana Maria,

I went ahead and updated the vaccine research outline based on my notes from Friday’s call. There were several places where additional information or links to other material may be useful—if you have any links that you think should be added, or suggested edits, please add them to this version, which I can then share Sunday evening (European time)
which may give participants a chance to take a look before Tuesday, also with invitation to provide updates before the meeting in case I missed anything important.

Thanks! (and see you soon- I’m landing early Monday morning).

Phil
Subject: RE: Cancellation of CEPI SAC meeting Friday February 14

Dear Stanley,

Many thanks for your important point. Indeed we will develop regular updates to the SAC on progress. We will get this developed in the coming week.

Kind regards
Melanie

---

+4475 786 37 304
melanie.saville@cepi.net

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From: Stanley Plotkin <stanley.plotkin@vaxconsult.com>
Sent: 11 February 2020 19:35
To: Stig Tollef森 <stig.tollef森@cepi.net>; Barrett, Alan <abarrett@utmb.edu>; Alash'le Abimiku <aabimiku@ihv.umd.edu>; Allouche, Ali <Ali.allouche@takeda.com>; christian.brechot <christian.brechot@pasteur.fr>; cbrechot@usf.edu; happic <happic@run.edu.ng>; Schmaljohn, Connie (NIH/NIAID) [E] <Connie.schmaljohn@nih.gov>; Daniel Brauseur <(b)(6)@gmail.com>; mimi darko <(b)(6)@yahoo.co.uk>; dongxp238 <dongxp238@sina.com>; hrees <hrees@wrhi.ac.za>; Damon, Inger K. (CDC/OID/NCEZID) <iad7@cdc.gov>; James Robinson <(b)(6)@outlook.com>; Jean Lang <Jean.Lang@sanofipasteur.com>; Van Hoof, Johan [JRDBE] <JHVOOF1@its.nijm.; John Edmunds <John.Edmunds@LSHTM.ac.uk>; Josie Golding <j.golding@wellcome.ac.uk>; kneuzil <kneuzil@som.umaryland.edu>; Jansen, Kathrin <kathrin.jansen@pfizer.com>; Kenji Shibuya <kenji.shibuya@kcl.ac.uk>; Michel De Wilde <(b)(6)@aol.com>; Levine, Myron <Mlevine@som.umaryland.edu>; Bryant, Paula (NIH/NIAID) [E] <paula.bryant@nih.gov>; Penny Heaton <penny.heaton@gatesmri.org>; Peter Smith <Peter-Smith@lshtm.ac.uk>; Phil Krause <philip.krause@fda.hhs.gov>; Ralf Clemens <(b)(6)@outlook.com>; Tom Kariuki <t.kariuki@aaasciences.ace.k; SATHIYAMOORTHY, Vaseeharan <moorthyv@who.int>; yves.levy <yves.levy@inserm.fr>; smrivas <smrivas@utmb.edu>; oumunna <oumunna@ihvnigeria.org>; Ryanto.Ryanto <Ryanto.Ryanto@takeda.com>; graca <graca@health.usf.edu>; <(b)(6)@yahoo.com; <(b)(6)@yahoo.co.uk>; Susie Cornell <scornell@wrhi.ac.za>; fmw1 <fmw1@cdc.gov>; Camille.Bayrat <Camille.Bayrat@sanofi.com>; Van Tulden, Karin [JRDBE] <kvultulden@its.nijm.; DEgorugwu <DEgorugwu@som.umaryland.edu>; markay.hopps <markay.hopps@pfizer.com>; Zottoli, Jessica <Jessica.Zottoli@pfizer.com>; shinoyamaz <shinoyamaz@m.u-tokyo.ac.jp>; Small, Dottie <Dsmall@som.umaryland.edu>; Mary Burke <Mary.burke@gatesmri.org>; admin@vaxconsult.com; Anita Chami <a.chami@aaasciences.ac.ke; bruniquelv <bruniquelv@who.int>; benassiv <benassiv@who.int>
Cc: Raimonda Viburiene <raimona.viburiene@cepi.net>; Melanie Saville <melanie.saville@cepi.net>; Richard Hatchett <richard.hatchett@cepi.net>; Joseph Simmonds-Issler <jsi@cepi.net>; Frederik Kristensen <frederik.kristensen@cepi.net>; Shanni Dhoofe <shanni.dhoofeer@cepi.net>; Rebeka Yasmin <rebeka.yasmin@cepi.net>
Subject: RE: Cancellation of CEPI SAC meeting Friday February 14

Dear Stig:

    I completely understand the need for cancellation of the meeting. However, I think the SAC should be kept informed by brief weekly reports of CEPI activities with regard to nCoV.

    Stanley

From: Stig Tollef森 <mailto:stig.tollef森@cepi.net>
Sent: Tuesday, February 11, 2020 2:30 PM
To: Barrett, Alan; Alash'le Abimiku; Allouche, Ali; christian.brechot; cbrechot@usf.edu; happic; Schmaljohn, Connie (NIH/NIAID) [E]; Daniel Brasseur; mimi darko; dongxp238; hrees; Damon, Inger K. (CDC/OID/NCEZID); James
Robinson; Jean Lang; Van Hoof, Johan [JRDBE]; John Edmunds; Josie Golding; kneuzil; Jansen, Kathrin; Kenji Shibuya; Michel De Wilde; Levine, Myron; Bryant, Paula (NIH/NIAID) [E]; Penny Heaton; Peter Smith; Phil Krause; Ralf Clemens; Stanley Plotkin; Tom Kariuki; SATHIYAMOORTHY, Vaseeharan; yves.levy; smrivas; oumunna; Ryanto.Ryanto; graca; __________@yahoo.com; __________@yahoo.com; Susie Cornell; fmw1; Camille.Bayrat; Van Tulden, Karin [JRDBE]; DEgorugwu; markay.hopps; Zottoli, Jessica; shinoyamaz; Small, Dottie; Mary Burke; admin@vaxconsult.com; Anita Chami; bruniquelv; benassiv
Cc: Raimonda Viburiene; Melanie Saville; Richard Hatchett; Joseph Simmonds-Issler; Frederik Kristensen; Shanni Dhoofe; Rebeka Yasmin
Subject: Cancellation of CEPI SAC meeting Friday February 14

Dear SAC members,

We hope this email reach you well.
Due to the priority activities surrounding the Corona virus outbreak, we need to cancel the planned regular SAC teleconference this coming Friday.
We apologize for the inconvenience.
We will organize a further SAC call as issues relating to the 2019 nCoV (COVID-2019) continue to evolve in the next couple of weeks and continue to plan for the face to face SAC in May.
A calendar cancellation will also be sent.

On behalf of the secretariat
Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI New vaccines for a safer world

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Dear Phil,

Sorry I could not make the call. I think it is not too early to start planning for the design of Phase 1/2 studies – size, target groups, populations. Also some planning for Phase 3/4 evaluations would be appropriate, even when they are a little way away.

There is a TPP for vaccines against disease X. I do not know if this has been modified yet for nCoV but, if not, this would seem an urgent priority.

Peter

Prof Peter Smith, MRC Tropical Epidemiology Group,
London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT. Tel: +44 20 7927 2246
William Dowling <william.dowling@cepi.net>; HENAO RESTREPO, Ana Maria <henaorestrepoa@who.int>; PREZIOSI, Marie-pierre <preziosim@who.int>; (SPmig) ralf wagner <ralf.wagner@pei.de>; alan.embry@nih.gov; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>; Michael.c.kaufmann@pwc.com; COOKE, Emer <cookeee@who.int>; Jean-pierre Amorij <jamorij@unicef.org>; Rene.Gysin@swissmedic.ch; michael.rosu-myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; aportela@aempes.es; alopezn@aempes.es; Lukasz.Montewka@urpl.gov.pl; Levis, Robin <Robin.Levis@fda.hhs.gov>
Cc: madelaione claire____(b)(6)____@yahoo.fr; Alicia Rosello <Alicia.Rosello@lshtm.ac.uk>; Embry, Alan C (NIH) <embrya@niaid.nih.gov>; Stemmy, Erik J (NIH) <erik.stemmy@nih.gov>; PLUUT, Elisabeth <pluute@who.int>; MUBANGIZI, Deusdedit <mubangizid@who.int>; RODRIGUEZ HERNANDEZ, Carmen A. <rodriguezhernandezc@who.int>
Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call

Dear Colleagues,

Thank you for your participation in yesterday's call to discuss nCoV vaccine R&D. In the attached document, I've tried to categorize key discussion points made yesterday, with some embellishments in places where I thought further discussion may be useful. I'd like to use this as a general outline for tomorrow morning's call. In the meantime, if each of you can take a look at this and identify what you think is missing from the outline and let either Ana Maria and me or the entire group know via e-mail, we can improve the outline even before tomorrow's discussion at 1300 CET. Obviously, we'd like to make as much progress as is possible between now and the meeting in Geneva next week, so your rapid input is greatly appreciated!

Thanks,

Phil

-----Original Appointment-----
From: GSELL, Pierre <gsellp@who.int>
Sent: Tuesday, February 4, 2020 7:00 AM
To: GSELL, Pierre; Krause, Philip; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int; b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH); malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmodjarrad@eiresearch.org; ilongini; Peter Smith; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu; Donis, Ruben (OS); richard.hatchett@cepi.net; COSTA, Alejandro Javier; William Dowling; HENAO RESTREPO, Ana Maria; PREZIOSI, Marie-pierre; (SPmig) ralf wagner; alan.embry@nih.gov; Cavaleri Marco; Michael.c.kaufmann@pwc.com; COOKE, Emer; Jean-pierre Amorij; Rene.Gysin@swissmedic.ch; michael.rosu-myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; aportela@aempes.es; alopezn@aempes.es; Lukasz.Montewka@urpl.gov.pl
Cc: madelaione claire; Alicia Rosello; Embry, Alan C (NIH); Stemmy, Erik J (NIH); PLUUT, Elisabeth; MUBANGIZI, Deusdedit; RODRIGUEZ HERNANDEZ, Carmen A.
Subject: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
When: Wednesday, February 5, 2020 1:00 PM-2:00 PM (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where: +41.58.26.20722 / Participant code: (b)(6)

Dear All,

We hope your travel is being safely arranged to Geneva for Feb 11-12.

We are very pleased to invite you to participate to the WG on Vaccine R&D, one of the thematic area of the summit. The aim of this WG is as follow:

1. Overview of state of the art
2. Identification of key knowledge gaps
3. Preliminary list of research priorities
To best prepare the meeting, we would like to convene you to a first teleconference – Tomorrow WEDNESDAY 5 FEBRUARY – 1 pm Geneva time

Dial- in Details
+41.58.26.20722 / Participant code: _{(b)(6)}_.

Kind regards

Pierre on behalf of the Blueprint
KIND REMINDER –  
For those who have not done yet, to be able to participate to the WG on nCoV vaccine prioritization and receive the materials on vaccines, please fill, sign and return the  
- Declaration of Interest  
- Confidentiality Undertaking

The call is planned tomorrow Thursday at 3 pm Geneva time

Dial-in details
+41.58.262.0722 / Participant code: ___________

Kind regards
Pierre

From: GSELL, Pierre  
Sent: 29 January 2020 10:44  
To: Philip.Krause@fda.hhs.gov; Marco.Cavaleri@ema.europa.eu; A.Salvati@aifa.gov.it; stanley.plotkin@vaxconsult.com; b.haagmans@erasusmc.nl; linfa.wang@duke-nus.edu.sg; Claire-Anne.Siegrist@unige.ch; Peter.Smith@lshtm.ac.uk; J.Farrar@wellcome.ac.uk; yguan@hku.hk; Donis@hhs.gov; Murray.Lumpkin@gatesfoundation.org; michael.parker@ethox.ac.uk; William.Dowing@eci.net; Bin.Cao<caobin@163.com>; SPFmg@ralfwagner@pei.de; HENAO RESTREPO, Ana Maria (henaorestrepoe@who.int); PREZIOSI, Marie-pierre (preziosim@who.int); SATHIYAMORRTHY, Vasieeharan (moorthvy@who.int)
Cc: HENAO RESTREPO, Ana Maria (henaorestrepoe@who.int) <henaorestrepoe@who.int>; PREZIOSI, Marie-pierre (preziosim@who.int) <preziosim@who.int>; SATHIYAMORRTHY, Vasieeharan (moorthvy@who.int)

Subject: RE: Invitation to WHO Working Group - Prioritization of nCoV vaccines - Thursday 30 January - 3pm Geneva time

Dear All,

Thanks to all of you who accepted to participate to this Working Group on vaccine prioritization. In order to formally be part of this group and to receive information on vaccines under confidentiality, please fill, sign and return ASAP to me the attached

- Declaration of Interest
- Confidentiality Undertaking

for the purpose of the vaccine prioritization exercise.

Thanks a lot for your support in this important milestone and looking forward to the call tomorrow Thursday at 3pm Geneva time.
Kind regards
Pierre

From: GSELL, Pierre
Sent: 28 January 2020 18:53
To: Philip.Krause@fda.hhs.gov; Marco.Cavaleri@ema.europa.eu; A.Salvati@aifa.gov.it; stanley.plotkin@vaxconsult.com; b.haagmans@erasmusmc.nl; linfa.wang@duke-nus.edu.sg; Claire-Anne.Siegrist@unige.ch; Peter.Smith@lshtm.ac.uk; J.Farrar@wellcome.ac.uk; yguan@hku.hk; ruben.donis@hhs.gov; Murray.Lumpkin@gatesfoundation.org; michael.parker@ethox.ox.ac.uk; William Dowling <william.dowling@cepi.net>; Bin Cao <caobin_ben@163.com>
Cc: HENAO RESTREPO, Ana Maria (henaorestrepa@who.int) <henaorestrepa@who.int>; PREZIOSI, Marie-pierre (preziosim@who.int) <preziosim@who.int>; SATHIYAMOORTHY, Vaseeharan (moorthyv@who.int) <moorthyv@who.int>
Subject: Invitation to WHO Working Group - Prioritization of nCoV vaccines - Thursday 30 January - 3pm Geneva time

Dear All,

In the context of the nCoV outbreak, WHO is very pleased to invite you to participate to a working group on vaccination prioritization. This group will aim to prioritize the candidate vaccines targeting the nCoV for consideration for evaluation under clinical trials, based on the existing available information on the various candidate vaccines, including the candidate vaccines for other coronavirus.

Please mark your calendar and let us know whether you would like to participate. Dial-in details
+41.58.262.0722 / Participant code: (b)(6)

I will circulate additional materials, and DOI, confidentiality undertaking tomorrow.

Kind regards

Pierre

Pierre-Stéphane Gsell
Technical Officer
R&D Blueprint | Health Emergencies Programme | 1136
World Health Organization | Avenue Appia 20 | 1211 Geneva 27 | Switzerland
Desk: +41.22.791.50.74 | Mob: (b)(6) gsellp@who.int
CONFIDENTIALITY UNDERTAKING

Should be sent with the invitation or appointment letter

1. The World Health Organization (WHO), acting through its Department of [PAGE ][PAGE ] World Health Emergencies, has access to certain information relating to Pneumonia nCoV outbreak disease and related medical countermeasures and data, which information WHO considers to be proprietary to itself or to parties collaborating with it (hereinafter referred to as "the Information").

2. The Undersigned, as a member of the WHO R&D Blueprint for Prioritization Group for vaccines against Coronavirus advisory meeting, group or committee (collectively referred to as the "the Advisory Process"), may have access to the Information in the course of his/her participation in the Advisory Process (whether at or in relation to Advisory Process meetings, internet-based collaborative workspaces, telephone conferences or otherwise).

3. WHO is willing to provide the Undersigned the Information, or arrange for the provision of the Information to the Undersigned, for the purpose of performing his/her responsibilities in connection with the activities of the Advisory Process ("the Purpose"), provided that the Undersigned undertakes to treat the Information as confidential and proprietary, and to disclose it only to persons who have a need to know for the Purpose and are bound by like obligations of confidentiality and non-use as are contained in this Undertaking.

4. The Undersigned undertakes to regard the Information as confidential and proprietary to WHO or parties collaborating with WHO and agrees to take all reasonable measures to ensure that the Information is not used, disclosed or copied, in whole or in part, other than as provided in this Undertaking, except that the Undersigned shall not be bound by any such obligations if and to the extent he/she is clearly able to demonstrate that the Information:

   a) was known to him/her prior to any disclosure by or for WHO to the Undersigned; or
   b) was in the public domain at the time of disclosure by or for WHO to the Undersigned; or
   c) becomes part of the public domain through no fault of the Undersigned; or
   d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.

5. The Undersigned also undertakes not to communicate the deliberations and decisions of the Advisory Process to third parties except as agreed by WHO.

6. If requested to do so, the Undersigned agrees to return to WHO any and all copies of the Information.

.../...
Annex C

7. The obligations of the Undersigned shall survive the termination of his/her membership in the Advisory Process.

8. Any dispute relating to the interpretation or application of this Undertaking shall, unless amicably settled, be subject to a conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the UNCITRAL rules of arbitration. The parties shall accept the arbitral award as final.

Name:  
Signature:  
Date:   

DECLARATION OF INTERESTS FOR WHO EXPERTS

WHO's work on global health issues requires the assistance of external experts who may have interests related to their expertise. To ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a potential conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interests (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department). Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Please complete this form and submit it to WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a WHO activity can be confirmed. Please note that not fully completing and disclosing all relevant information on this form may, depending on the circumstances, lead WHO to decide not to appoint you to WHO advisory bodies/functions in the future.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e., you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e., you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be disclosed to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be published in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside WHO if the Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

| Name:       | [PAGE ][ FORMTEXT ] |
| Institution:| [ FORMTEXT ]         |
| Email:      | [ FORMTEXT ]         |

Date and title of meeting or work, including description of subject matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached by the organizer of the activity):
[ FORMTEXT ]

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e., spouse or partner with whom you have a similar close personal relationship) and your children. "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.
EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

1b Consulting, including service as a technical or other advisor

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)

Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work?

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

INVESTMENT INTERESTS

Do you have current investments (valued at more than US $5 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g., short sales)

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)

[ FORMCHECK BOX ] No
[ FORMCHECK BOX ]

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications)

[ FORMCHECK ]
4b Proprietary know-how in a substance, technology or process

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work?

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?

6c Excluding WHO, has any person or entity paid or contributed towards your travel costs in connection with this WHO meeting or work?

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work?

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?

7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work)

Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?
EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. **If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

<table>
<thead>
<tr>
<th>Nos. 1 - 4: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) and basic descriptive details.</th>
<th>Name of company, organization, or institution</th>
<th>Belongs to you, a family member, employer, research unit or other?</th>
<th>Amount of income or value of interest (if not disclosed, is assumed to be significant)</th>
<th>Current interest (or year ceased)</th>
</tr>
</thead>
<tbody>
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<td>[ FORMTEXT ]</td>
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<td>[ FORMTEXT ]</td>
<td>[ FORMTEXT ]</td>
<td>[ FORMTEX T ]</td>
</tr>
</tbody>
</table>
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details [ FORMTEXT ]

CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interests form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Date: ________________  Signature: ____________________________

WHO 850 E CRE (25/09/2014)
I should be able to attend baring any urgent matters on the ground.

Thanks

Linfa (Lin-Fa) WANG, PhD FTSE  
Professor & Director  
Programme in Emerging Infectious Disease  
Duke-NUS Medical School,  
8 College Road, Singapore 169857  
Tel: +65 6516 8397

---

From: GSELL, Pierre <gsellp@who.int>  
Sent: Wednesday, 29 January 2020 1:53 AM  
To: Philip.Krause@fda.hhs.gov; Marco.Cavaleri@ema.europa.eu; A.Salvati@aifa.gov.it; stanley.plotkin@vaxconsult.com; b.haagmans@erasmusmc.nl; Wang Linfa <linfa.wang@duke-nus.edu.sg>; Claire-Anne.Siegrist@unige.ch; Peter Smith <peter.smith@lshtm.ac.uk>; J.Farrar@wellcome.ac.uk; yguan@hku.hk; Donis, Ruben (OS) <os/apr/barda> <ruben.donis@hhs.gov>; Murray.Lumpkin@gatesfoundation.org; michael.parker@ethox.ox.ac.uk; William Dowling <william.dowling@cepi.net>; Bin Cao <caobin_ben@163.com>  
Cc: HENAO RESTREPO, Ana Maria <henaoa@who.int>; PREZIOSI, Marie-pierre <preziomin@who.int>; SATHIYAMOORTHY, Vaseeharan <moorthyv@who.int>  
Subject: Invitation to WHO Working Group - Prioritization of nCoV vaccines - Thursday 30 January - 3pm Geneva time

---

Dear All,

In the context of the nCoV outbreak, WHO is very pleased to invite you to participate to a working group on vaccination prioritization. This group will aim to prioritize the candidate vaccines targeting the nCoV for consideration for evaluation under clinical trials, based on the existing available information on the various candidate vaccines, including the candidate vaccines for other coronaviruses.

Please mark your calendar and let us know whether you would like to participate.

Dial-in details  
+41.58.262.0722 / Participant code: [b(6)]

I will circulate additional materials, and DOI, confidentiality undertaking tomorrow.
Kind regards

Pierre

Pierre-Stephane Gsell
Technical Officer
R&D Blueprint | Health Emergencies Programme | 1156
World Health Organization | Avenue Appia 20 | 1211 Geneva 27 | Switzerland
Desk: +41 22 791 50 74 | Mob: (b)(6) | gsellp@who.int

Important: This email is confidential and may be privileged. If you are not the intended recipient, please delete it and notify us immediately; you should not copy or use it for any purpose, nor disclose its contents to any other person. Thank you.
Dear SAC members,

We have published the meeting minutes from January 31 on the SAC SharePoint site: 
https://

Could we please ask you to give your comments and edits by Friday February 7 COB. I am not sure we captured all that attended, so please flag if you are not on the list and should have been there, or visa versa.

If you have problems with access to the site please contact IT support via this email: it@cepi.net
Marc Salzone will be happy to assist you.

Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI
New vaccines for a safer world

(+47) 901 50 770
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This e-mail and any attachments may contain confidential and/or privileged information. If you are not the intended recipient or have received this e-mail in error, please notify the sender immediately and destroy this e-mail. Any unauthorized copying, disclosure or distribution of the material in this e-mail is strictly prohibited.
Dear All,

I am delighted to today announce that the Government of Ethiopia has committed USD $300,000 funding to CEPI to accelerate our mission to speed vaccine development against emerging epidemic threats - becoming the first African nation to invest in our growing coalition.

The funding was announced by H.E. Dr. Lia Tadesse, State Minister, Ministry of Health, Democratic Federal Republic of Ethiopia, at our official African Union (AU) Summit side event with the Ethiopian Ministry of Health, held today in Addis Ababa.

In 2018, CEPI and Ethiopia signed a memorandum of understanding outlining how we could work together to bridge gaps in epidemic preparedness. Amid the unfolding novel coronavirus outbreak as well as ongoing outbreaks of Lassa fever in Nigeria and Ebola in DRC, this strengthened partnership comes at a critically important time as African nations continue to build upon their tools and facilities to best prepare for and respond to these infectious disease threats.

Today's inspiring event, “Achieving epidemic preparedness & investing in vaccine manufacturing capacity for a healthy Africa” was opened and championed by H.E. Sahle-work Zewde, President of Federal Democratic Republic of Ethiopia and H.E. Amira El Fadil, AU Commissioner for Social Affairs. Focusing on the importance of epidemic preparedness in Africa and the need to enhance vaccine manufacturing capabilities on the continent, the meeting included talks from CEPI Board Member and Director of Africa CDC, John Nkengasong, Professor JI Myumbe (Director General, INRB, DRC), Dr Abebe Genev (Director General of AHRI, Ethiopia) and a video message from WHO Director-General Dr Tedros.

Supporting comments on the importance of vaccination and global collaboration were also made by Chair of the Gavi Board, Dr Ngozi Okonjo-Iweala, and Rwanda’s Minister of Health, Dr Diane Gashumba.

As ever, I would like to thank the CEPI Teams who have made this possible and I hope that, in time, we will see more African countries joining our coalition.

You can find out further details about our announcement on our website. We would also appreciate if you are able to amplify this announcement among your networks.

Best regards,

Richard
A few additional comments on your revised document, some of which covered in the call.

Peter

From: Krause, Philip <Philip.Krause@fda.hhs.gov>
Sent: 07 February 2020 11:56
To: GSELL, Pierre <gSELLp@who.int>; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int; b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH) <connie.schmaljohn@nih.gov>; malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmoudjarrad@eiresearch.org; ilongini@ufl.edu; Murray.Lumpkin@gatesfoundation.org; fggh@virginia.edu; Donis, Ruben (OS) <Ruben.Donis@hhs.gov>; richard.hatchett@cepi.net; COSTA, Alejandro Javier <costaa@who.int>; William Dowling <william.dowling@cepi.net>; HENAO RESTREPO, Ana Maria <henaoestrepoa@who.int>; PREZIOSI, Marie-pierre <preziosim@who.int>; (SPmg) ralf wagner <ralf.wagner@pei.de>; alan.embry@nih.gov; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>;
Cc: madelaine claire [b(6)yahoo.fr]; Alicia Rosello <Alicia.Rosello@lshtm.ac.uk>; Embry, Alan C (NIH) <Embry@lshtm.ac.uk>;
Re: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
Attachments: nCoV vaccine subgroup outline 5Feb2020 pk ps.docx

Phil,

A few additional comments on your revised document, some of which covered in the call.

Peter
Dear Colleagues,

Here is an updated version of the outline that includes comments provided by some members of the group (in red). Talk with you soon.

Thanks!

Phil

From: GSELL, Pierre <gSELL@who.int>
Sent: Friday, July 2, 2020 4:09 AM
To: Krause, Philip <Philip.Krause@fda.hhs.gov>; A_Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int;
b_haagmans@erasmusmc.nl; rbac@email.unc.edu; Schmaljohn, Connie S (NIH) <connie.schmaljohn@nih.gov>
; malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmodjarrad@eidresearch.org; ilongini
<ilongini@ufl.edu>; Peter Smith <peter.smith@lshmt.ac.uk>; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu;
Donis, Ruben (OS) <Ruben.Donis@hhs.gov>; richard.hatchett@cepi.net; COSTA, Alejandro Javier <costaa@who.int>
; William Dowling <william.dowling@cepi.net>; HENAO RESTREPO, Ana Maria <henao@restrpoo@who.int>; PREZIOSI,
Marie-pierre <preziosim@who.int>; (SPmig) ralf wagner <ralf.wagner@pe.de>; alan.embry@nih.gov; Cavalieri Marco
<MARCO.Cavalieri@ema.europa.eu>; Michael.c.kaufmann@pwc.com; COOKE, Emer <cookee@who.int>; Jean-pierre
Amorij <jamorij@unicef.org>; Rene.Gysin@swissmedic.ch; michael.rosu-myles@canada.ca;
guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it;
Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; aportela@aemps.es;
alopez@lshmt.ac.uk; Levis, Robin <Robin.Levis@fda.hhs.gov>
Cc: madelaine.claire@who.int; Alicia Rosello <alicia_rosello@lshmt.ac.uk>; Embry, Alan C (NIH)
<embrya@niaid.nih.gov>; Stemmy, Erik J (NIH) <erik.stemmy@nih.gov>; PLUUT, Elisabeth <pluute@who.int>
; MUBANGIZI, Deusedit <mubangizid@who.int>; RODRIGUEZ HERNANDEZ, Carmen A. <rodriguezhernandez@who.int>
Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call

Dear all

In preparation of the 2nd preparatory call, please find attached the following DRAFT documents that has solely purpose
to inform the deliberations of the group in the perspective of the nCoV forum -

1. NFR from 1st preparatory call
2. NFR from WG on Vaccine Prioritization
3. DRAFT Landscape of candidate vaccines for MERS
4. DRAFT Landscape of candidate vaccines for nCoV
5. DRAFT Landscape of candidate vaccines for SARS
6. DRAFT list of animal models for nCoV
7. DRAFT assessment of cross-reactivity with other coronaviruses
8. DRAFT considerations for coronaviruses vaccine-related disease enhancement
9. DRAFT outline of clinical trial design for Phase 2b/3 vaccine trials
10. DRAFT mapping of virus, reagents, and plans to assess cross-reactivity
11. Confidential analysis from GISAID on nCoV structural characterization

DIAL IN DETAILS – Today at 1pm Geneva time
+41.58.262.0722 / Participant code 1234

Kind regards
Pierre

From: Krause, Philip <Philip.Krause@fda.hhs.gov>
Sent: 06 February 2020 16:11
To: GSELL, Pierre <gsellp@who.int>; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int;
b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH) <connie.schmaljohn@nih.gov>;
malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmodjarrad@eidresearch.org; ilongini
<ilonjini@ufl.edu>; Peter Smith <peter.smith@lshtm.ac.uk>; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu;
Donis, Ruben (OS/ASPR/BARDA) <ruben.donis@hhs.gov>; richard.hatchett@cepi.net; COSTA, Alejandro Javier
<costaa@who.int>; William Dowling <william.dowling@cepi.net>; HENAO RESTREPO, Ana Maria
<henaorestrepoa@who.int>; PREZIOSI, Marie-pierre <preziosim@who.int>; (SPmig) ralf wagner <ralf.wagner@peide.de>;
alan.embry@nih.gov; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>; Michael.c.kaufmann@pwc.com; COOKE, Emer
<cookee@who.int>; Jean-Pierre Amorij <jamorij@unicef.org>; Rene.Gysin@swissmedic.ch; michael.rosu-
myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@ncr-cnrc.gc.ca; kmaustria-lock@fda.gov.ph;
g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepallli ANURADHA@hsa.gov.sg;
aportela@aemps.es; alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl; (SPmig) Robin Levis <robin.levis@fda.hhs.gov>
Cc: madelaine claire********(b)(6)********@yahoo.fr; Alicia Rosello <alia.c.rosello@lshmt.ac.uk>; Embry, Alan C (NIH)
<embrya@niaid.nih.gov>; Stemmy, Erik J (NIH) <erik.stemmy@nih.gov>; PLUUT, Elisabeth <plute@who.int>;
MUBANGIZI, Deusdedit <mubangizid@who.int>; RODRIGUEZ HERNANDEZ, Carmen A. <rodriguezhernandezc@who.int>
Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call

Dear Colleagues,

Thank you for your participation in yesterday’s call to discuss nCoV vaccine R&D. In the attached document, I’ve tried to
categorize key discussion points made yesterday, with some embellishments in places where I thought further
discussion may be useful. I’d like to use this as a general outline for tomorrow morning’s call. In the meantime, if each
of you can take a look at this and identify what you think is missing from the outline and let either Ana Maria and me or
the entire group know via e-mail, we can improve the outline even before tomorrow’s discussion at 1300
CET. Obviously, we’d like to make as much progress as possible is between now and the meeting in Geneva next week,
so your rapid input is greatly appreciated!

Thanks,

Phil

-----Original Appointment-----
From: GSELL, Pierre <gsellp@who.int>
Sent: Tuesday, February 4, 2020 7:00 AM
To: GSELL, Pierre; Krause, Philip; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int;
b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH); malik@hku.hk; linfa.wang@duke-
nus.edu.sg; stanley.plotkin@vaxconsult.com; kmodjarrad@eidresearch.org; ilongini; Peter Smith;
Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu; Donis, Ruben (OS); richard.hatchett@cepi.net; COSTA,
Alejandro Javier; William Dowling; HENAO RESTREPO, Ana Maria; PREZIOSI, Marie-pierre; (SPmig) ralf wagner;
alan.embry@nih.gov; Cavaleri Marco; Michael.c.kaufmann@pwc.com; COOKE, Emer; Jean-pierre Amorij;
Rene.Gysin@swissmedic.ch; michael.rosu-myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@ncr-
cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org;
Poonepallli ANURADHA@hsa.gov.sg; apportela@aemps.es; alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl
Cc: madelaine claire********(b)(6)********@yahoo.fr; Alicia Rosello; Embry, Alan C; Stemmy, Erik; PLUUT, Elisabeth;
MUBANGIZI, Deusdedit; RODRIGUEZ HERNANDEZ, Carmen A.
Subject: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
When: Wednesday, February 5, 2020 1:00 PM-2:00 PM (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where: +41.58.26.20722 / Participant code:____(b)(6)____

Dear All,

We hope your travel is being safely arranged to Geneva for Feb 11-12.
We are very pleased to invite you to participate to the WG on Vaccine R&D, one of the thematic area of the summit.

The aim of this WG is as follow:
1. Overview of state of the art
2. Identification of key knowledge gaps
3. Preliminary list of research priorities

To best prepare the meeting, we would like to convene you to a first teleconference – Tomorrow WEDNESDAY 5 FEBRUARY – 1 pm Geneva time

Dial-in Details
+41.58.26.20722 / Participant code: [b][6]

Kind regards

Pierre on behalf of the Blueprint
WHO NCoV Vaccine Subgroup Goals:

Develop research plan that will facilitate development and evaluation of nCoV vaccines, focusing on elements that are on the “critical path” to obtaining and evaluating a vaccine as rapidly as possible. This should include prioritization by timeline. To do this, we will start by overviewing the state of the art, identify key knowledge gap, and prepare a preliminary list of research priorities.

Provide a mechanism to promote performance of key research tasks, and to share information about performance of these tasks and relevant results.

Operate transparently and openly, with public health as our primary goal. Recommendation to include more investigators/representatives from China/Asia, potentially with translators.

Next meetings: Friday 7 February 13:00 CET, Tuesday and Wednesday 11-12 February in Geneva. Discussion by e-mail in the interim is encouraged.

Information that would be useful to support development of a research plan (to be discussed on Friday’s call):

- Background on MERS/SARS
- WHO TPP for nCoV vaccine (CEPI TPP may be useful to review here, though goals may be different)
- Cross reactivity group conclusions
- Prioritization group conclusions

Tools that would be useful to support research:

- Web-based information sharing tool (WHO will look at ways to accomplish this)
  - Who has reagents?
  - Who is working on key questions?
  - What are results?
  - What are needs?

Cross-cutting critical path research

- Animal models
  - Mouse is obvious first choice. Additional models should be studied to see which models best mimic human infection and may be best suited to studying enhanced disease or identifying potential correlates of protection. Animal models are also useful in evaluation of antivirals.

- Cell culture growth optimization

Commented [PS1]: Add Africa, given Chinese footprint in Africa and weak control programmes

Commented [PS2]: What animal studies required (safety/immunogenicity protection) before proceeding to Phase 1 studies? Are NHP studies required?
Required to optimize neutralizing assays, grow up virus stocks for other experiments including evaluation of cross-reactivity (virus currently reported to be slow-growing at CDC)

Important to know that virus will stay genetically stable through cell culture passage

Also important for antivirals

Natural history of disease

Pathogenesis in humans, cause of death, etc.

Kinetics and durability of virus-specific humoral and cellular immune responses in mild-moderate and severe (survivors and non-survivors) nCoV illness

Other research on the critical path for vaccine evaluation:

Immune response assay development

ELISA

For vaccine response as well as evaluation of background seropositivity

Neutralization

BSL-3

BSL-2 (pseudovirions, including validation of results relative to nCoV neutralization)

Analysis of CD4+ and CD8+ responses to determine which if any are related to protection or enhancement of disease.

If vaccines that induce CMI are preferred due to theoretical reduced risk of enhanced disease, are CMI assays also needed?

Assays to support case definition for clinical trials and epidemiological studies

PCR assays

Other case-definition related assays

Strategy to evaluate potential for enhanced disease

Information to support clinical trials

Epidemiologic data

Attack rates/fatality rates/modeling?

Commented [PS3]: Including target population — initial target may be those most likely to have high morbidity (immunodeficient, elderly with respiratory conditions, etc) or at highest risk of infection (healthcare workers)
Clinical data to support case definition for clinical trial endpoints (fever+viremia vs. severe disease, perhaps other endpoints should be considered if viremia is transient?)

Research on the critical path for vaccine development:

TPP-related considerations (all preferred elements may not be possible to achieve) that could guide investments into additional vaccine types

NOTE: This is a notional TPP and is a placeholder, pending receipt of WHO/CEPI TPPs and more input from prioritization group. The idea is to relate possible TPP elements to different vaccine types, which may in turn suggest different research needs.

A. 1 dose
B. Potential for high level neutralizing Ab
C. previously proven strategy
D. likely to induce cytotoxic CMI response
E. Safety
F. Speed of development,
G. Capability to rapidly make large quantities of vaccine
H. Duration of immunity
I. Vaccine stability (i.e. not prone to mutation)

Vaccine candidate development

<table>
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<th>Vaccination Type</th>
<th>Likely Advantages</th>
<th>Likely Disadvantages</th>
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<td>Inactivated/adjuvanted</td>
<td>B, C, F</td>
<td>E (concern for disease enhancement)</td>
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<tr>
<td>Subunit/adjuvanted</td>
<td>B, C (C depends on protein/expression scheme)</td>
<td></td>
</tr>
<tr>
<td>Live-attenuated</td>
<td>A, B, C, D, E</td>
<td></td>
</tr>
<tr>
<td>Vectored</td>
<td>A, B, C, D, E, G  (A &amp; C depend on vector)</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>B, D, E, F, G</td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td>B, D, E, F</td>
<td></td>
</tr>
</tbody>
</table>

Potency assays for individual vaccines

Stability data

Process development (may be more complex for live-attenuated or vectored vaccines)

Formulation (excipients, adjuvants and preservatives)
Filtration (for sterility)
Storage temperature (stability)
Route of administration
Presentation (monodose vs. multidose; lyo vs liquid)
Process validation
Consistency

Other considerations (not strictly research related, but on the critical path to vaccine development):

- Regulatory harmonization (esp. preclinical studies, clinical trial endpoints):
  will be topic of March 2020 meeting
- Manufacturing/filling capacity (in facilities that have been or could be inspected)
- Other manufacturing considerations (e.g., containment)
- Study design
  - Phase I,II
  - Phase III, IV
- Access to clinical trial sites, etc.
Sorry not to be in a position to free this time slot within 48h...

Best regards,

Claire-Anne

Le 28 janv. 2020 à 18:53, GSELL, Pierre <gsellp@who.int> a écrit :

Dear All,

In the context of the nCoV outbreak, WHO is very pleased to invite you to participate to a working group on vaccination prioritization.
This group will aim to prioritize the candidate vaccines targeting the nCoV for consideration for evaluation under clinical trials, based on the existing available information on the various candidate vaccines, including the candidate vaccines for other coronavirus.

Please mark your calendar and let us know whether you would like to participate.

Dial-in details
+41.58.262.0722 / Participant code: (b)(6)

I will circulate additional materials, and DOI, confidentiality undertaking tomorrow.

Kind regards

Pierre

Pierre-Stéphane Gsell
Technical Officer
R&D Blueprint | Health Emergencies Programme | 1156
World Health Organization | Avenue Appia 20 | 1211 Geneva 27 | Switzerland
Desk: +41.22.791.50.74 | Mob (b)(6) gsellp@who.int
Dear CEPI SAC,

We have just announced the initiation of three programmes to develop vaccines against the novel coronavirus, nCoV-2019. Please see the press release attached – the news has also been shared in Reuters.

The three programmes build on our existing partnerships with Inovio and The University of Queensland. In addition, we are also announcing a new partnership with Moderna, Inc and the U.S. National Institute of Allergy and Infectious Diseases. We are also exploring a fourth partnership, which we hope to announce in coming weeks.

Since my earlier this week, we have seen a significant increase and geographical spread of cases, largely in part due to increased searching and testing for novel coronavirus among those affected with respiratory illness. As of 23 January 2020, there have been 555 cases of 2019-nCoV confirmed across multiple countries: China, Japan, Republic of Korea, Thailand, Taiwan, and US, with seventeen deaths and evidence of human-to-human transmission.

With this in mind, following 2 consultation with the SAC and with the EIC, we have proceeded to sign the partnership agreements through Phase 1. Our partners will use their pioneering rapid response technologies to advance vaccine candidates against nCoV-2019 as quickly as possible – our aspiration is to bring a new pathogen from gene sequence to clinical testing in as little as 16 weeks. While there is no guarantee of success, we hope this work could provide a significant and important step forward in developing a vaccine against this disease.

This has been a huge effort by CEPI staff, the SAC, and with support of the Board and investors, and we are very proud to have been able to move so quickly. I would also like to recognise the collaborative response efforts taken internationally - the speed, determination and transparency of many health authorities, including those in China, WHO and other organisations is testament to the impactful international health response efforts in place today and sets a precedent for the management of future global outbreaks.

We will continue to engage with you in the coming weeks as the situation evolves to help inform us how to proceed.

Best regards,

Richard
CEPI to fund three programmes to develop vaccines against the novel coronavirus, nCoV-2019

OSLO, NORWAY. Jan 23, 2020 – CEPI, the Coalition for Epidemic Preparedness Innovations, today announced the initiation of three programmes to develop vaccines against the novel coronavirus, nCoV-2019.

The programmes will leverage rapid response platforms already supported by CEPI as well as a new partnership. The aim is to advance nCoV-2019 vaccine candidates into clinical testing as quickly as possible.

The nCoV-2019 vaccine development efforts will build on existing partnerships with Inovio (Nasdaq: INO) and The University of Queensland (located in Brisbane, Australia). In addition, CEPI today announces a new partnership with Moderna, Inc. (Nasdaq: MRNA) and the U.S. National Institute of Allergy and Infectious Diseases.

All of these are pioneering technologies designed to speed up the development of vaccines against emerging threats such as nCoV-2019.

CEPI CEO Richard Hatchett said:

“Given the rapid global spread of the nCoV-2019 virus the world needs to act quickly and in unity to tackle this disease. Our intention with this work is to leverage our work on the MERS coronavirus and rapid response platforms to speed up vaccine development.

“There are no guarantees of success, but we hope this work could provide a significant and important step forward in developing a vaccine for this disease. Our aspiration with these technologies is to bring a new pathogen from gene sequence to clinical testing in 16 weeks – which is significantly shorter than where we are now.”

The term “platform technology” broadly refers to systems that use the same basic components as a backbone but can be adapted for use against different pathogens as needed by inserting new genetic or protein sequences.

CEPI has moved with great urgency and in coordination with WHO, who is leading the development of a coordinated international response, to promote the development of new vaccines against the emerging threat of nCoV-2019. The novel coronavirus represents the first new epidemic disease of note to emerge since CEPI’s founding at Davos in 2017, with the express intent that it should be ready to respond to epidemics rapidly and effectively, wherever they emerge.
Inovio | DNA vaccine candidate against Middle East Respiratory Syndrome

CEPI announced a partnering agreement, worth up to US$56 million, with Inovio in April 2018, to advance DNA vaccine candidates against MERS and another of its priority diseases, Lassa fever, through to Phase 2.

Under the agreement, funding will support the development up to the end of Phase 2, providing clinical safety, immunological data, and the establishment of investigational stockpiles that will be ready for clinical efficacy trial testing during outbreaks.

The MERS DNA vaccine candidate is being developed using Inovio’s DNA Medicines platform to deliver optimised synthetic antigenic genes into cells, where they are translated into protein antigens that activate an individual’s immune system to generate robust targeted T cell and antibody responses. Inovio’s immunotherapies function exclusively in vivo, and have generated an antigen-specific immune response against targeted diseases in all clinical trials to date.

Inovio is advancing its MERS vaccine candidate into Phase 2, in the Middle East where most MERS viral outbreaks have occurred, with the support of its collaborators: The Wistar Institute, Laval University, the NIH’s Rocky Mountain Laboratories, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), VGXI/GeneOne Life Science and the International Vaccine Institute.

University of Queensland | The molecular clamp platform

CEPI entered a partnering agreement in January 2019, with University of Queensland, for up to US$10.6 million to develop a “molecular clamp” vaccine platform, a transformative technology that enables targeted and rapid vaccine production against multiple viral pathogens.

The technology works by synthesising viral surface proteins, which attach to host cells during infection, and “clamping” them into shape, making it easier for the immune system to recognise them as the correct antigen. This process requires the sequence of the viral protein which can then be determined from the viral genome. The synthetic antigen can then be purified and rapidly manufactured into a vaccine.

As part of their partnering agreement with CEPI, the University of Queensland will use their molecular-clamp vaccine platform to produce vaccines against known pathogens, including Middle East Respiratory Syndrome coronavirus (MERS-CoV) and will evaluate the safety and immune response of the Influenza and MERS-CoV candidates in a phase 1 clinical trial in humans.

Moderna | mRNA vaccine platform

Under the terms of the agreement with CEPI, Moderna will manufacture an mRNA vaccine against coronavirus, which will be funded by CEPI. Investigational New Drug-enabling studies will be conducted by the Vaccine Research Center (VRC) and a Phase 1 clinical study will be conducted in the
U.S. by the Division of Microbiology and Infectious Diseases (DMID). Both VRC and DMID are divisions of the National Institute of Allergy and Infectious Diseases (NIAID), which is an institute of the NIH.

- ENDS -

About the novel coronavirus

Coronaviruses are a family of viruses that can lead to respiratory illness, including Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Coronaviruses are transmitted between animals and people and can evolve into strains not previously identified in humans. On January 7, 2020, a novel coronavirus (2019-nCoV) was identified as the cause of pneumonia cases in Wuhan City, Hubei Province of China, and additional cases have been found in a growing number of countries.1,2

About vaccine platform technology

The term “vaccine platform technology” broadly refers to a system that uses the same basic components as a backbone, but can be adapted for use against different pathogens by inserting new sequences.

About “molecular clamp” vaccines

Enveloped viruses, like influenza, have proteins on their surface that fuse to host cells during an infection. Although these surface proteins are antigenic — and therefore elicit an immune response — they are inherently unstable. One approach to vaccine design is to synthesise these proteins on their own such that they elicit an immune response, specifically antibodies, that can kill the virus. Unfortunately, they tend to change shape when expressed on their own, a shape that does not reflect the form of the protein on the virus surface. Consequently, the immune response that is induced with these vaccines does not produce antibodies that efficiently lock on to the virus. The University of Queensland has developed a process that can synthesise these surface proteins while “clamping” them into shape, making it easier for the immune system to induce a response that recognises them on the virus surface.

This synthetic antigen can then be purified and rapidly manufactured into a vaccine, within 16 weeks from pathogen identification.

This vaccine platform technology can be used to develop vaccines against a wide range of enveloped viruses (eg, Influenza, Ebola, MERS, Lassa virus, Measles, Herpes Simplex virus, Rabies).

The Molecular Clamp is patented technology developed by Professor Paul Young, Dr Keith Chappell, and Dr Dan Watterson.

The University of Queensland will be developing this vaccine platform in collaboration with The Commonwealth Scientific and Industrial Research Organisation (CSIRO) and a wider consortium including public sector and private sector partners in Australia, USA, and Asia.

About CEPI

CEPI is an innovative partnership between public, private, philanthropic, and civil organisations, launched at Davos in 2017, to develop vaccines to stop future epidemics. CEPI has reached over US$750 million of its $1 billion funding target. CEPI’s priority diseases include Ebola virus, Lassa virus, Middle East Respiratory Syndrome coronavirus, Nipah virus, Rift Valley Fever and Chikungunya virus. CEPI also invests in platform technologies that can be used for rapid vaccine and immunoprophylactic development against unknown pathogens (i.e., Disease X). To date, CEPI has committed to investing over $456 million in vaccine and platform development. Learn more at www.cepi.net. Follow us at @CEPIvaccines.

About Inovio Pharmaceuticals, Inc.

Inovio is taking immunotherapy to the next level in the fight against cancer and infectious diseases. We are the only immunotherapy company that has reported generating CD8+ T cells in vivo in high quantity that are fully functional and whose killing capacity correlates with relevant clinical outcomes with a favorable safety profile. With an expanding portfolio of immune therapies, the company is advancing a growing clinical stage product pipeline, including candidates in Phase 3 and Phase 2. Partners and collaborators include MedImmune, Regeneron, Genentech, The Wistar Institute, University of Pennsylvania, the Parker Institute for Cancer Immunotherapy, DARPA, GeneOne Life Science, Plumbline Life Sciences, ApolloBio Corporation, Drexel University, NIH, HIV Vaccines Trial Network, National Cancer Institute, U.S. Military HIV Research Program, and Laval University. For more information, visit www.inovio.com.

About University of Queensland

UQ rates in the global top 50 as measured by the Permanence Ranking of Scientific Papers for World Universities and was recently rated 7th in Biotechnology world in the Shanghai Global Rankings of 2017. Professor Paul Young, Dr Keith Chappell, and Dr Dan Watterson have extensive expertise in molecular virology, viral pathogenesis and vaccine research.

About Moderna

Moderna is advancing messenger RNA (mRNA) science to create a new class of transformative medicines for patients. mRNA medicines are designed to direct the body’s cells to produce intracellular, membrane or secreted proteins that have a therapeutic or preventive benefit with the potential to address a broad spectrum of diseases. Moderna’s platform builds on continuous advances in basic and applied mRNA science, delivery technology and manufacturing, providing the Company the capability to pursue in parallel a robust pipeline of new development candidates. Moderna is developing therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases and cardiovascular diseases, and autoimmune and inflammatory diseases, independently and with strategic collaborators.

Headquartered in Cambridge, Mass., Moderna currently has strategic alliances for development programs with AstraZeneca Plc. (NASDAQ: AZN) and Merck, Inc. (NASDAQ: MRK), as well as the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense and the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of
Health and Human Services (HHS). Moderna has been named a top biopharmaceutical employer by Science for the past five years. To learn more, visit www.modernatx.com.

**For media enquiries, please contact:**

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Jodie Rogers, Communications Officer, CEPI

Tel: +44(0)79 793 57 459

Email: jodie.rogers@cepi.net
Thanks Michel
Encouraging.
Best
Helen

From: Helen Rees [HRees@wrhi.ac.za]
Sent: 1/22/2020 12:26:34 PM
To: [b][6]@aol.com; 'Stig Tollefsen' [stig.tollefsen@cepi.net]; 'Barrett, Alan' [abarrett@utmb.edu]; 'Alash'le Abimiku' [aabimiku@ihv.umaryland.edu]; 'Allouche, Ali' [Ali.allouche@takeda.com]; christian.brechot@pasteur.fr; cbrechot@usf.edu; happic@run.edu.ng; Schmaljohn, Connie S [nIH] /o=exchangeLabs/ou= Exchange Administrative Group (FYDIOBHF235PDTL)/cn=Recipients/cn=8ba64558b8090495986f4a7257137cc5-HHS-connie.; 'Daniel Brasseur' [b][6]@gmail.com; 'mimi darko' [b][6]@yahoo.co.uk; dongxp238@sina.com; Damon, Inger K (CDc) /o=exchangeLabs/ou= Exchange Administrative Group (FYDIOBHF235PDTL)/cn=Recipients/cn=42b35bd73a34ac66a5698f43f7026e88-HHS-iad7-cd; 'James Robinson' [b][6]@outlook.com; 'Jean Lang' [Jean.Lang@sanopipasteur.com]; Jvhoof1@its.jnj.com; 'John Edmunds' [John.Edmunds@LSHTM.ac.uk]; 'Josie Golding' [j.golding@wellcome.ac.uk]; kneuzil@som.umaryland.edu; 'Jansen, Kathrin' [kathrin.jansen@pfizer.com]; 'Kenji Shibuya' [kenji.shibuya@kcl.ac.uk]; 'Levine, Myron' [mlevine@som.umaryland.edu]; 'Bryant, Paula R [nIH] /o=exchangeLabs/ou= Exchange Administrative Group (FYDIOBHF235PDTL)/cn=Recipients/cn=3eb42f9318014b88c14d39ef311d89-HHS-paula.b]; 'Penny Heaton' [penny.heaton@gatesmri.org]; 'Peter Smith' [Peter.Smith@lshtm.ac.uk]; Krause, Philip
/o=exchangeLabs/ou= Exchange Administrative Group (FYDIOBHF235PDTL)/cn=Recipients/cn=00c6330f0a042f655771c3def792ed-krause; 'Ralf Clemens' [b][6]@outlook.com; 'Stanley Plotkin' [stanley.plotkin@vaxconsult.com]; 'Tom Kariuki' [t.kariuki@assciences.ac.Ke]; 'SatiYAMOORTHY, Vaseeharan' [moorthyv@who.int]; yves.levy@inserm.fr
CC: 'Raimonda Viburiene' [raimonda.viburiene@cepi.net]; 'Richard Hatchett' [richard.hatchett@cepi.net]; 'Melanie Saville' [melanie.saville@cepi.net]; 'Frederik Kristensen' [frederik.kristensen@cepi.net]; 'Joseph Simmonds-Issler' [jsi@cepi.net]; 'Nick Jackson' [nick.jackson@cepi.net]; 'Jakob Cramer' [jakob.cramer@cepi.net]; 'Svein Rune Andersen' [svein.rune.andersen@cepi.net]; 'Debra Yeskey' [debra.yeskey@cepi.net]; Paul Kristiansen [paul.kristiansen@cepi.net]

Subject: Re: SAC meeting minutes January 16, Wuhan situation

From: [b][6]@aol.com [b][6]@aol.com
Date: Wednesday, 22 January 2020 at 17:39
To: 'Stig Tollefsen' <stig.tollefsen@cepi.net>, "Barrett, Alan" <abarrett@utmb.edu>, 'Alash'le Abimiku' <aabimiku@ihv.umaryland.edu>, "Allouche, Ali" <Ali.allouche@takeda.com>, christian.brechot@pasteur.fr <christian.brechot@pasteur.fr>, cbrechot@usf.edu <cbrechot@usf.edu>, happic@run.edu.ng <happic@run.edu.ng>, "Connie, Schmaljohn [nIH]" <Connie.schmaljohn@nih.gov> <Connie.schmaljohn@nih.gov>, 'Daniel Brasseur' [b][6]@gmail.com, 'mimi darko' [b][6]@yahoo.co.uk, dongxp238@sina.com <dongxp238@sina.com>, Helen Rees <HRees@wrhi.ac.za>, "Damon, Inger K. (CDc/OID/NCEZID)" <iad7@cdc.gov>, 'James Robinson' [b][6]@outlook.com, 'Jean Lang' <Jean.Lang@sanopipasteur.com>, 'Jvhoof1@its.jnj.com' <Jvhoof1@its.jnj.com>, John Edmunds <John.Edmunds@LSHTM.ac.uk>, 'Josie Golding' <j.golding@wellcome.ac.uk>, 'kneuzil@som.umaryland.edu' <kneuzil@som.umaryland.edu>, "Jansen, Kathrin" <kathrin.jansen@pfizer.com>, 'Kenji Shibuya' <kenji.shibuya@kcl.ac.uk>, "Levine, Myron" <mlevine@som.umaryland.edu>, "Bryant, Paula (NIH/NIAID) [E]" <paula.bryant@nih.gov>, 'Penny Heaton' <penny.heaton@gatesmri.org>, 'Peter Smith' <Peter.Smith@lshtm.ac.uk>, 'Phil Krause' <philip.krause@fda.hhs.gov>, 'Ralf Clemens' [b][6]@outlook.com, 'Stanley Plotkin' <stanley.plotkin@vaxconsult.com>, 'Tom Kariuki' <t.kariuki@assciences.ac.Ke>, Vaseeharan SatiYAMOORTHY <moorthyv@who.int>, yves.levy@inserm.fr <yves.levy@inserm.fr>
Cc: 'Raimonda Viburiene' <raimonda.viburiene@cepi.net>, 'Richard Hatchett' <richard.hatchett@cepi.net>, 'Melanie Saville' <melanie.saville@cepi.net>, 'Frederik Kristensen' <frederik.kristensen@cepi.net>, 'Joseph Simmonds-Issler' <jsi@cepi.net>, 'Nick Jackson' <nick.jackson@cepi.net>, 'Jakob Cramer'
Thank you for the notes. In case not seen, see link to Moderna: 40 days!  
https://www.cnbc.com/2020/01/22/moderna-is-working-on-a-vaccine-for-chinas-deadly-coronavirus.html

Michel

From: Stig Tollefsen <stig.tollefsen@cepi.net>
Sent: Wednesday, January 22, 2020 3:41 PM
To: Barrett, Alan <abarrett@utmb.edu>; Alash'le Abimiku <aabimiku@ihv.umaryland.edu>; Aloueche, Ali <Ali.aloueche@takeda.com>; christian.brechot@pasteur.fr; cbrechot@usf.edu; happic@run.edu.ng; Connie.schmaljohn@nih.gov; Daniel Brasseur; mimi.darok@yahoo.co.uk; dongxp238@sina.com; hrees@wrhi.ac.za; Damon, Inger K. (CDC/OID/NCEZID) <iad7@cdc.gov>; James Robinson <outlook.com>; Jean Lang <Jean.Lang@sanofipasteur.com>; JVOOF1@its.jnj.com; John Edmunds <John.Edmunds@LSHTM.ac.uk>; Josie Golding <j.golding@wellcome.ac.uk>; kneuzil@som.umaryland.edu; Jansen, Kathrin <kathrin.jansen@pfizer.com>; Kenji Shibuya <kenji.shibuya@kcl.ac.uk>; Michel De Wilde <mdevilde@imperial.ac.uk>; Levine, Myron <mlevine@som.umaryland.edu>; Bryant, Paula (NIH/NIAID) [E] <paula.bryant@nih.gov>; Penny Heaton <penny.heaton@gatesmri.org>; Peter Smith <Peter.smith@lshtm.ac.uk>; Phil Krause <philip.krause@fda.hhs.gov>; Ralf Clemens <outlook.com>; Stanley Plotkin <stanley.plotkin@vaxconsult.com>; Tom Kariuki <t.kariuki@aaasciences.ace.co.ke>; SATHIYAMOORTHY, Vaseeharan <moorthyv@who.int>; yves.levy@inserm.fr
Cc: Raimonda Viburiene <raimonda.viburiene@cepi.net>; Richard Hatchett <richard.hatchett@cepi.net>; Melanie Saville <melanie.saville@cepi.net>; Frederik Kristensen <frederik.kristensen@cepi.net>; Joseph Simmonds-Issler <jsi@cepi.net>; Nick Jackson <nick.jackson@cepi.net>; Jakob Cramer <jakob.cramer@cepi.net>; Svein Rune Andersen <svein.run.andersen@cepi.net>; Debra Yeskey <debra.yeskey@cepi.net>; Paul Kristiansen <paul.kristiansen@cepi.net>

Subject: SAC meeting minutes January 16, Wuhan situation

Dear SAC member,

The meeting minutes from the ad hoc SAC meeting January 16 have been prepared and uploaded to the SAC Sharepoint site: https://cepi.net.

Subsequent to the feedback from SAC we are prioritizing funding rapid response platforms, more information will become available within the next 24 hours.

Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI New vaccines for a safer world

(+47) 901 50 770
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Visiting address: Marcus Thrane gate 2, 0473 Oslo, Norway
This e-mail and any attachments may contain confidential and/or privileged information. If you are not the intended recipient or have received this e-mail in error, please notify the sender immediately and destroy this e-mail. Any unauthorized copying, disclosure or distribution of the material in this e-mail is strictly prohibited.
Dear Colleagues,

Here is an updated version of the outline that includes comments provided by some members of the group (in red). Talk with you soon.

Thanks!

Phil
Dear all,

In preparation of the 2nd preparatory call, please find attached the following DRAFT documents that has solely purpose to inform the deliberations of the group in the perspective of the nCoV forum -

1. NFR from 1st preparatory call
2. NFR from WG on Vaccine Prioritization
3. DRAFT Landscape of candidate vaccines for MERS
4. DRAFT Landscape of candidate vaccines for nCoV
5. DRAFT Landscape of candidate vaccines for SARS
6. DRAFT list of animal models for nCoV
7. DRAFT assessment of cross-reactivity with other coronaviruses
8. DRAFT considerations for coronaviruses vaccine-related disease enhancement
9. DRAFT outline of clinical trial design for Phase 2b/3 vaccine trials
10. DRAFT mapping of virus, reagents, and plans to assess cross-reactivity
11. Confidential analysis from GISAID on nCoV structural characterization

DIAL IN DETAILS – Today at 1pm Geneva time
+41.58.262.0722 / Participant code

Kind regards
Pierre

From: Krause, Philip <Philip.Krause@fda.hhs.gov>
Sent: 06 February 2020 16:11
To: GSELL, Pierre <gsellp@who.int>; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int; b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH) <connie.schmaljohn@nih.gov>; malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmadjarrad@eidresearch.org; ilongini@lornini@ufl.edu; Peter Smith <peter.smith@ishtm.ac.uk>; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu; Donis, Ruben (OS/ASPR/BARDA) <ruben.donis@hhs.gov>; richard.hatchett@cepi.net; Costa, Alejandro Javier <costaa@who.int>; William Dowling <william.dowling@cepi.net>; HENAO RESTREPO, Ana Maria <henaoorestrepopa@who.int>; PREZIOSI, Marie-pierre <preziosim@who.int>; (SPmig) ralf wagner <ralf.wagner@pei.de>; alan.embry@nih.gov; Cavaleri Marco <Marco.Cavaleri@ema.europa.eu>; Michael.c.kaufmann@pwc.com; COOKE, Emer <cookee@who.int>; Jean-pierre Amorij <jamorij@unicef.org>; Rene.Gysin@swissemic.ch; michael.rosu@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli ANURADHA@hsa.gov.sg; aportela@aemps.es; alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl; (SPmig) Robin Levis <robin.levis@fda.hhs.gov>
Cc: madelaine.claire@yahoo.fr; Alicia Rosello <alicia.rosello@ishtm.ac.uk>; Embry, Alan C (NIH) <embry@niaid.nih.gov>; Stemmy, Erik J (NIH) <erik.stemmy@nih.gov>; PLUUT, Elisabeth <pluute@who.int>

Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call

Dear Colleagues,

Thank you for your participation in yesterday’s call to discuss nCoV vaccine R&D. In the attached document, I’ve tried to categorize key discussion points made yesterday, with some embellishments in places where I thought further discussion may be useful. I’d like to use this as a general outline for tomorrow morning’s call. In the meantime, if each of you can take a look at this and identify what you think is missing from the outline and let either Ana Maria and me or the entire group know via e-mail, we can improve the outline even before tomorrow’s discussion at 1300.
CET. Obviously, we’d like to make as much progress as is possible between now and the meeting in Geneva next week, so your rapid input is greatly appreciated!

Thanks,

Phil

-----Original Appointment-----
From: GSELL, Pierre <gsellp@who.int>
Sent: Tuesday, February 4, 2020 7:00 AM
To: GSELL, Pierre; Krause, Philip; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int; b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH); malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmodjarrad@eideareresearch.org; ilongini; Peter Smith; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu; Donis, Ruben (OS); richard.hatchett@cepi.net; COSTA, Alejandro Javier; William Dowling; HENAO RESTREPO, Ana Maria; PREZIOSI, Marie-pierre; (SPmig) ralf wagner; alan.embry@nih.gov; Cavaleri Marco; Michael.c.kaufmann@pwc.com; COOKE, Emer; Jean-pierre Amorij; Rene.Gysin@swissmedic.ch; michael.rosu-myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli ANURADHA@hsa.gov.sg; aporleta@aemps.es; alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl
Cc: madelaine claire; Alicia Rosello; Embry, Alan C (NIH); Stemmy, Erik J (NIH); PLUUT, Elisabeth; MUBANGIZI, Deusdedit; RODRIGUEZ HERNANDEZ, Carmen A.
Subject: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
When: Wednesday, February 5, 2020 1:00 PM-2:00 PM (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where: +41.58.26.20722 / Participant code: \[b(6)\]

Dear All,

We hope your travel is being safely arranged to Geneva for Feb 11-12.

We are very pleased to invite you to participate to the WG on Vaccine R&D, one of the thematic area of the summit. The aim of this WG is as follow:
1. Overview of state of the art
2. Identification of key knowledge gaps
3. Preliminary list of research priorities

To best prepare the meeting, we would like to convene you to a first teleconference – Tomorrow WEDNESDAY 5 FEBRUARY – 1 pm Geneva time

Dial- in Details
+41.58.26.20722 / Participant code: \[b(6)\]

Kind regards

Pierre on behalf of the Blueprint
WHO NCoV Vaccine Subgroup Goals:

Develop research plan that will facilitate development and evaluation of nCoV vaccines, focusing on elements that are on the “critical path” to obtaining and evaluating a vaccine as rapidly as possible. This should include prioritization by timeline. To do this, we will start by overviewsing the state of the art, identify key knowledge gap, and prepare a preliminary list of research priorities.

Provide a mechanism to promote performance of key research tasks, and to share information about performance of these tasks and relevant results.

Operate transparently and openly, with public health as our primary goal. Recommendation to include more investigators/repsentatives from China/Asia, potentially with translators

Next meetings: Friday 7 February 13:00 CET, Tuesday and Wednesday 11-12 February in Geneva. Discussion by e-mail in the interim is encouraged.

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Cross-cutting critical path research

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Required to optimize neutralizing assays, grow up virus stocks for other experiments including evaluation of cross-reactivity (virus currently reported to be slow-growing at CDC)

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For vaccine response as well as evaluation of background seropositivity

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BSL-3

BSL-2 (pseudovirions, including validation of results relative to nCoV neutralization)

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Other case-definition related assays

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Clinical data to support case definition for clinical trial endpoints (fever+viremia vs. severe disease, perhaps other endpoints should be considered if viremia is transient?)

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Vaccine candidate development

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Potency assays for individual vaccines

Stability data

Process development (may be more complex for live-attenuated or vectored vaccines)

Formulation (excipients, adjuvants and preservatives)
Filtration (for sterility)
Storage temperature (stability)
Route of administration
Presentation (monodose vs. multidose; lyo vs liquid)

Process validation
Consistency

Other considerations (not strictly research related, but on the critical path to vaccine development):

Regulatory harmonization (esp. preclinical studies, clinical trial endpoints):
will be topic of March 2020 meeting

Manufacturing/filling capacity (in facilities that have been or could be inspected)

Other manufacturing considerations (e.g., containment)

Study design
Phase I, II
Phase III, IV

Access to clinical trial sites, etc.
Thanks for your participation in Friday’s call. Here is an updated version of the draft research outline, on which I attempted to capture comments that were made on Friday. I’d appreciate your review of the document to help correct any errors and to provide a basis for further discussion tomorrow in Geneva. Look forward to seeing you soon.

Best regards,

Phil

-----Original Appointment-----

From: GSELL, Pierre <gsellp@who.int>
Sent: Wednesday, February 5, 2020 3:56 AM
To: GSELL, Pierre; Krause, Philip; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int;
b.ahaemans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH); malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmoddjarrad@eiresearch.org; ilongini [ilongini@ufl.edu]; Peter Smith [peter.smith@ishtm.ac.uk]; Levis, Robin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ba6458b8090499598f4a7257137cc5-HHS-connie.]; malik@hku.hk; linfa.wang@duke-nus.edu.sg; stanley.plotkin@vaxconsult.com; kmoddjarrad@eiresearch.org; ilongini [ilongini@ufl.edu]; Peter Smith [peter.smith@ishtm.ac.uk]; Levis, Robin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d09dadd7be5da4d983b8436c0ef01b5-levis]; Murray.Lumpkin@gatesfoundation.org; fgh@virginia.edu; Donis, Ruben (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dea126c25cab404db922973cd7cbb459-HHS-Ruben.D]; richard.hatchett@cepi.net; COSTA, Alejandro Javier [costaa@who.int]; William Dowling [william.dowling@cepi.net]; HENAO RESTREPO, Ana Maria [henaorestrepoa@who.int]; madelaine claire [---------b(6)---------]@yahoo.fr; Alicia Rosello [alicia.rosello@ishtm.ac.uk]; PREZIOSI, Marie-pierre [preziosim@who.int]; (SPmir) ralf wagner [ralf.wagner@pei.de]; alan.embry@nih.gov; Cavaleri Marco [Marco.Cavaleri@ema.europa.eu]; Embry, Alan C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=77b7c944cd334abe9c6ee0ff4cb53320-HHS-embrya-]; Stemmy, Erik J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3401b66d3c8241666e0dcd82288d829-HHS-erik.st]

Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 2nd preparatory call
Attachments: nCoV vaccine subgroup outline 9Feb2020.docx
WHO NCoV Vaccine Subgroup Goals:

Develop research plan that will facilitate development and evaluation of nCoV vaccines, focusing on elements that are on the “critical path” to obtaining and evaluating a vaccine as rapidly as possible. This should include prioritization by timeline. To do this, we will start by overviewing the state of the art, identify key knowledge gap, and prepare a preliminary list of research priorities.

Provide a mechanism to promote performance of key research tasks, and to share information about performance of these tasks and relevant results.

Operate transparently and openly, with public health as our primary goal. Recommendation to include more investigators/representatives from China/Asia, potentially with translators

Next meetings: Tuesday and Wednesday 11-12 February in Geneva. Discussion by e-mail in the interim is encouraged.

Information that would be useful to support development of a research plan (to be discussed on Friday’s call):

- WHO TPP for nCoV vaccine  (CEPI TPP may be useful to review here, though goals may be different)

- Most recent reports of other working groups are available online (https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/)

Tools that would be useful to support research:

- Web-based information sharing tool (WHO is looking at ways to accomplish this)
  - Who has reagents?
  - Who is working on key questions?
  - What are results?
  - What are needs?

Current summary of available reagents (more detail is available in summary of most recent Cross-reactivity workgroup call)

- Virus (in Australia, UK, Canada, France, Germany, US, others)
- Purified spike protein (VRC, in limited supply)
- Plasmid used to express spike protein (VRC)
- Serum and B cells (in very limited quantities, request through US government)
- Monoclonals (production underway)
Some proteins and monoclonals reported available from fee-for-service providers in China

**Cross-cutting critical path research**

**Animal models**

Mouse is obvious first choice. Additional models should be studied to see which models best mimic human infection and may be best suited to studying enhanced disease or identifying potential correlates of protection. Animal models are also useful in evaluation of antivirals.

CEPI is supporting work on ferret model in Australia.

Discussion of animal models needed for 1st-in-human studies. Prioritization and other needs may be different from regulatory needs. Animal models may help to address enhancement issues, but other strategies may also be employed (e.g., informed consent, initial vaccination of volunteers at low risk for nCoV exposure).

**Cell culture growth optimization**

Required to optimize neutralizing assays, grow up virus stocks for other experiments including evaluation of cross-reactivity. Virus reported to grow well in Vero cells.

Important to know that virus will stay genetically stable through cell culture passage. Sequencing results pending from several labs.

Large stocks will be useful, including standardized stocks for challenge experiments.

Also important for antivirals

**Natural history of disease**

Pathogenesis in humans, cause of death, etc.

Kinetics and durability of virus-specific humoral and cellular immune responses in mild-moderate and severe (survivors and non-survivors) of nCoV illness

Extent of subclinical infection

Shedding sites (early results suggest significant shedding)

**Immunological cross-reactivity with other coronaviruses**

Antigens

Monoclonals vs. SARS, MERS

Antibodies vs. nCoV

Other
Other research on the critical path for vaccine evaluation:

Immune response assay development

ELISA

For vaccine response as well as evaluation of background seropositivity

Standards may be important

Neutralization

BSL-3

BSL-2 (pseudovirions)

Will need comparison/validation of results relative to nCoV neutralization (note that pseudovirion neutralization for MERS was more sensitive than PRNT, though with correlation)

Different strategies include lentivirus, VSV, different nCoV components

Large stocks for distribution will be useful

Analysis of CD4+, CD8+, and cytokine responses to determine which if any are related to protection or enhancement of disease.

Assays to support case definition for clinical trials and epidemiological studies

PCR assays

Other case-definition related assays

Strategy to evaluate potential for enhanced disease

Importance of cellular tropism (monocytes/macrophages)

Information to support clinical trials

Epidemiologic data

Attack rates/fatality rates/modeling?

Clinical data to support case definition for clinical trial endpoints (fever+viremia vs. severe disease, perhaps other endpoints should be considered if viremia is transient?)

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Process validation
Consistency

Other considerations (not strictly research related, but on the critical path to vaccine development):

Regulatory harmonization (esp. preclinical studies, clinical trial endpoints):
  will be topic of March 2020 meeting in Brussels, sponsored by ICMRA
Manufacturing/filling capacity (in facilities that have been or could be inspected)
Other manufacturing considerations (e.g., containment)

Study design
  Phase I, II
  Phase III, IV
  Should vaccine be tested in those with greatest risk from disease (e.g., elderly, immunocompromised) vs. those in whom clinical trials could most expeditiously evaluate efficacy? Immunogenicity in these special target groups will nonetheless be important to evaluate.
  Importance of clinical endpoint efficacy studies (that could also address enhancement question in humans)

Access to clinical trial sites, etc.

Intellectual property
  WHO has MTA tools (link to be shared)

Note parallel efforts (e.g., NIAID DMID/BARDA group to assign sub-groups to address some of these issues analogous to FANG for Ebola; NIBS working on challenge stocks, dose, route, etc.)
Dear Colleagues,

Thank you for your participation in yesterday's call to discuss nCoV vaccine R&D. In the attached document, I've tried to categorize key discussion points made yesterday, with some embellishments in places where I thought further discussion may be useful. I'd like to use this as a general outline for tomorrow morning's call. In the meantime, if each of you can take a look at this and identify what you think is missing from the outline and let either Ana Maria and me or the entire group know via e-mail, we can improve the outline even before tomorrow's discussion at 1300 CET.

Obviously, we'd like to make as much progress as possible between now and the meeting in Geneva next week, so your rapid input is greatly appreciated!

Thanks,

Phil

----- Original Appointment -----

From: GSELL, Pierre <gsellp@who.int>

Sent: Tuesday, February 4, 2020 7:00 AM

To: GSELL, Pierre; Krause, Philip; A.Salvati@aifa.gov.it; barney.graham@nih.gov; jokim@ivi.int; b.haagmans@erasmusmc.nl; rbaric@email.unc.edu; Schmaljohn, Connie S (NIH); michael.rosu-myles@canada.ca; guillaume.poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; kmaustria-lock@fda.gov.ph; g.pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; aportela@aemps.es; alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl; Levis, Robin; Embry, Alan C (NIH); fgh@virginia.edu; Richard.Hatchett@cepi.net; COSTA, Alejandro Javier; William Dowling; HENAO RESTREPO, Ana Maria; PREZIOSI, Marie-pierre; (SPmig) ralf wagner; alan.embry@nih.gov; batista@javerina.org; Cavaleri Marco; Michael.c.kaufmann@pwc.com; COOKE, Emer; Jean-pierre Amorij; [jamorij@unicef.org]; Rene.Gysin@swissmedic.ch; Michael.Rosu-Myles@canada.ca; Guillaume.Poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; Kmaustria-lock@fda.gov.ph; G.Pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; Aportela@aemps.es; Alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl; Levi, Robin; Embry, Alan C (NIH); /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF235PDLT)/cn=Recipients/cn=dea1262c25ab404db922973cd7cb459-HHS-Ruben.D; richard.hatchett@cepi.net; COSTA, Alejandro Javier [costaa@who.int]; William Dowling [william.dowling@cepi.net]; HENAO RESTREPO, Ana Maria [henaorestrepopa@who.int]; PREZIOSI, Marie-pierre [preziosim@who.int]; (SPmig) ralf wagner [ralf.wagner@peid.de]; alan.embry@nih.gov; Cavaleri Marco [Marco.Cavaleri@ema.europa.eu]; Michael.c.kaufmann@pwc.com; COOKE, Emer [cookee@who.int]; Jean-pierre Amorij [jamorij@unicef.org]; Rene.Gysin@swissmedic.ch; Michael.Rosu-myles@canada.ca; Guillaume.Poliquin@canada.ca; Lakshmi.Krishnan@nrc-cnrc.gc.ca; Kmaustria-lock@fda.gov.ph; G.Pistritto@aifa.gov.it; Mike.Udell@mhra.gov.uk; Nicola.Rose@nibsc.org; Poonepalli_ANURADHA@hsa.gov.sg; Aportela@aemps.es; Alopezn@aemps.es; Lukasz.Montewka@urpl.gov.pl; Levi, Robin; Embry, Alan C (NIH); /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF235PDLT)/cn=Recipients/cn=d09d047be5d4a44d983b843630ecf01b5-levis]

Subject: RE: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call

Attachments: nCoV vaccine subgroup outline 5Feb2020.docx
CC: madelaine claire; Alicia Rosello; Embry, Alan C (NIH); Stemmy, Erik J (NIH); PLUUT, Elisabeth; MUBANGIZI, Deusdedit; RODRIGUEZ HERNANDEZ, Carmen A.

Subject: WHO nCoV R&D Summit 11-12 February - Vaccine R&D Working Group - 1st preparatory call
When: Wednesday, February 5, 2020 1:00 PM-2:00 PM (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna.
Where: (b)(6) / Participant code: (b)(6)

Dear All,

We hope your travel is being safely arranged to Geneva for Feb 11-12.

We are very pleased to invite you to participate to the WG on Vaccine R&D, one of the thematic area of the summit. The aim of this WG is as follow:
1. Overview of state of the art
2. Identification of key knowledge gaps
3. Preliminary list of research priorities

To best prepare the meeting, we would like to convene you to a first teleconference – Tomorrow WEDNESDAY 5 FEBRUARY – 1 pm Geneva time

Dial-in Details (b)(6) / Participant code: (b)(6)

Kind regards

Pierre on behalf of the Blueprint
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Required to optimize neutralizing assays, grow up virus stocks for other experiments including evaluation of cross-reactivity (virus currently reported to be slow-growing at CDC)

Important to know that virus will stay genetically stable through cell culture passage

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**Other research on the critical path for vaccine evaluation:**

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  - ELISA
  - Neutralization
    - BSL-3
    - BSL-2 (pseudovirions, including validation of results relative to nCoV neutralization)

If vaccines that induce CMI are preferred due to theoretical reduced risk of enhanced disease, are CMI assays also needed?

- Assays to support case definition for clinical trials and epidemiological studies
  - PCR assays

- Strategy to evaluate potential for enhanced disease

- Information to support clinical trials
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Regulatory harmonization (esp. preclinical studies, clinical trial endpoints):

will be topic of March 2020 meeting

Manufacturing/filling capacity (in facilities that have been or could be inspected)

Access to clinical trial sites, etc.
Dear all:

Today’s Videocon will be very busy. I am expecting that we will come to consensus on many issues but we will also have to grapple with a few remaining problematic ones. Enormous progress has been made this week by the Subgroup on Clinical Trial Issues and the Subgroup on Challenge Virus Strain Issues in resolving a number of obstinate issues. Virtually all technical issues have now been addressed and solutions proposed. Attached you will find:

- A draft Consent Form prepared by Anna Durbin and members of both Teams of the Subgroup on Clinical Trials Issues
- An updated summary from Kanta Subbarao on criteria for selection of challenge virus strains
- Responses from the Challenge Virus Selection Team to a series of questions on virus selection.
- An update (v2) On Points to Consider in identification of candidate GMP Batch CMOs (updates by Shobana Balasingam, Debbie King & Kanta Subbarao)
- Proposed Batch criteria to be sent to the prospective CMOs and remaining issues.

<table>
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<tr>
<th>Agenda for the May 19, 2020 videocom</th>
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<tbody>
<tr>
<td>Introduction</td>
<td>Mike Levine</td>
<td>4 minutes</td>
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<tr>
<td>Update from Subgroup on Clinical Trials Issues</td>
<td>Anna Durbin</td>
<td>20 minutes</td>
</tr>
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<td>Discussion</td>
<td>Subgroup members and the full Advisory Group</td>
<td>20 minutes</td>
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<tr>
<td>Update on SARS-CoV-2 strain selection issues</td>
<td>Kanta Subbarao</td>
<td>11 minutes</td>
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<tr>
<td>Discussion</td>
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</tr>
<tr>
<td>Update on identifying CMOs to make GMP Batches of viruses: issues addressed and issues remaining</td>
<td>Kanta Subbarao, Debbie King and Shobana Balasingam</td>
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<td>Update on the Advisory Group Report</td>
<td>Mike Levine</td>
<td>3 minutes</td>
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<tr>
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<td></td>
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<td>Ana Maria Henao-Restrepo &amp; Phil Krause</td>
<td>4 minutes</td>
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Many thanks and warm regards to all.

Mike
Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
Associate Dean for Global Health, Vaccinology & Infectious Diseases
Founder & Former Director, Center for Vaccine Development (1974)
University of Maryland School of Medicine
685 W. Baltimore Street
Baltimore, Maryland 21201, USA
Tel: +1 (410) 706-7588; Fax: +1 (410) 706-6207
Email: mlevine@som.umaryland.edu
ADULT INFORMED CONSENT

Principal Investigator:
Study Title: Evaluation of SARS-CoV-2 virus strains for use in a closely-monitored COVID-19 human challenge model

Ethics Committee No.: 
Sponsor: 
Principal Investigator Version Date:

Key Information about the Study
We are asking you to volunteer for a research study to investigate the virus, SARS-CoV-2, that causes COVID-19 illness. We want to give you the COVID-19 virus to see if you develop mild symptoms and signs of COVID-19, something called a COVID-19 human challenge model. We hope we can use a COVID-19 human challenge model to better understand COVID-19 and whether an initial episode of mild COVID-19 illness stimulates immunity (protection) against a subsequent challenge, and to test new vaccines to prevent COVID-19.

- You do not have to join the study; it is your choice and there is no penalty for not joining. Ask as many questions as you need to help you make your decision. If you decide to join the study, you may change your mind and drop out later. Please review the details outlined in the rest of this consent document before deciding.
- You may be eligible for this study because you are a healthy adult 18-25 years old who does not have any underlying medical problems.
- If you join, you will have one or more screening visits (2-3 hours) to see if you are eligible up to XX days before getting the COVID-19 virus. If you are healthy and your labs are normal, you will be invited to enroll in the study – meaning you will be admitted to an isolation unit and given the COVID-19 virus in your nose.
- You will stay in an inpatient research isolation unit for approximately 2.5-3 weeks if you do not become infected with the virus and for up to 5-6 weeks (or longer) if you do become infected. Because you might be contagious with COVID-19 virus, you cannot leave the unit during the inpatient period until your tests for virus are negative on three consecutive days.
- You will also have 8 (30-60 minutes) outpatient visits. Some of the visits may include a brief medical history and physical, review of sexual history and pregnancy prevention, bloodwork, and collection of saliva (drool), a swab from your nose, urine and other bodily fluids.
- Most people who have symptoms of COVID-19 have fever, chills, headache, cough, sore throat, body aches, diarrhea, and loss of smell or taste.
- Approximately 10% of people who have COVID-19 get hospitalized. They have shortness of breath, infection in their lungs, and can have blood clotting problems that lead to stroke. Some people need to be put on a breathing machine. Some people develop shock. Approximately X% of hospitalized patients 20-29 years of age die from COVID-19.
- If you join the study, you will not personally benefit from this research. We hope that the information we gather from this study can be used to help learn more about COVID-19 and how to prevent it.
- This study will last approximately 12 months (360 days), which will include the follow-up visits to collect blood and to follow your health for months after your discharge form the isolation unit.
- There will be no costs to you for being in this study. If you get sick with acute COVID-19 illness in this study, you will be treated at no cost to you.
• Study doctors will be available at all times while you are in the study to check on you and treat you for any medical care resulting from you taking part in this research study. You will be compensated for your time and travel.
• For taking part in this research, you may be compensated up to a total of $XXXX. A detailed breakdown is provided below.

Why is this research being done?
This research study is being done to develop a human challenge model for COVID-19. We want to find a dose of the COVID-19 virus that gives some symptoms of mild illness but doesn’t make people very sick. A COVID-19 human challenge model can be used in the future to test vaccines and drugs against COVID-19. The use of the COVID-19 virus in this research study is investigational. The word “investigational” means that the COVID-19 virus not approved for this use by the national regulatory agency (Food and Drug Administration [FDA] in USA; European Medicines Agency [EMA] in many European countries; Medicines and Healthcare products Regulatory Agency [MHRA] in the UK; Therapeutic Goods Administration [TGA] in Australia); The national regulatory agency is allowing the use of the COVID-19 virus in this study.

During the study, we will frequently check you for side effects and illness. We will check your nose, blood, saliva, and urine for COVID-19 virus. We will also study how your immune system responds to COVID-19. To do this, we will measure disease fighting proteins (antibodies) in your blood and collect different blood cells. We will also collect cells & fluid from your nose and mouth with a swab. We hope that this study will also help us learn more about signs and symptoms of COVID-19 infection and how to treat it.

Background Information:
Information about COVID-19
COVID-19 is an illness caused by the SARS-CoV-2 virus. In December 2019, China reported that people were becoming sick from a new infection. This infection was later found to be caused by the SARS-CoV-2 virus and the clinical illness was named COVID-19. Since then, COVID-19 has spread around the world causing a pandemic. During the pandemic more than 4,750,000 people are thought to have gotten COVID-19 and more than 300,000 people have died (Johns Hopkins Coronavirus Resource Center, [ HYPERLINK "https://coronavirus.jhu.edu/map.html" ], accessed May 18, 2020). The COVID-19 virus (SARS-CoV-2) causes flu-like symptoms including; fever, headache, cough, sore throat, and body aches. About 10% of people who get COVID-19 get severe disease. They have trouble breathing. Severe cases of COVID-19 developed pneumonia and had to be put on a breathing machine (a ventilator). COVID-19 also causes blood clots, stroke (loss of ability to move parts of your body), and shock. Most people who develop severe illness from COVID-19 are older and have some health problems like diabetes, heart disease, and obesity but even young healthy adults have gotten severe COVID-19 and have died. In young children, COVID-19 can cause the immune system to become over-active causing lung, liver, kidney, and skin problems. Some children have died.

Who can join this study?
Healthy male and non-pregnant females 18-25 years old are eligible to screen for the study. Before entering the study, you will have blood and urine tests to see if you are healthy. The overall visit is called the "screening visit" and may occur over one or more visits.

To find out about your health, you will have:
• A complete medical history
• A physical examination

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• Several laboratory tests, including:
  o A complete blood count (CBC)
  o A blood clotting test (PT/PTT)
  o Blood chemistries (including tests of your kidneys, liver, and muscle)
  o A test for diabetes
  o Pregnancy test(s) and pregnancy prevention counseling.
  o A urinalysis
  o A urine screen for opiates
  o HIV test (a test for the virus that causes AIDS)
  o Hepatitis B test (a test for a virus that hurts the liver)
  o Hepatitis C test (a test for another virus that hurts the liver)
  o There may be additional blood tests if the doctor judges they are needed

You will be told of any abnormal results that may require you to follow up with your personal doctor. Based on the results of these screening tests, you may be invited to join the study. There may be reasons why you cannot take part in this study.

If your tests show that you have HIV, the study doctor may have to notify the local health department. A separate HIV testing education form explains how positive results are reported to the local health department. Counseling will also be made available to you to discuss your positive HIV test and to receive information on how to get treatment for HIV if you do not have a regular doctor.

If your tests show that you have hepatitis B or hepatitis C virus, the study doctor may have to notify the health department. If so, the health department will be notified in writing of the following information: laboratory test date, type of test, result of test, your name, age, sex, and address. We will also provide information to you to follow up with a doctor if you do not have a regular doctor.

We encourage questions. If you have any questions or concerns about this, please talk to the research staff.

Because we do not know how COVID-19 affects an unborn baby, you cannot be in the study if you are pregnant. If you become pregnant during the study, tell the staff right away. We may ask you to continue to come in for regular study visits and/or ask you to agree to let us keep checking on you until the end of your pregnancy. If you do not have your own doctor to care for you during your pregnancy, we will refer you to an obstetrician (OB) to care for you. We will ask you to sign a medical information release form so that we can learn about your pregnancy and, if applicable, your baby's health at birth. If the study ends prior to your delivery, we may ask you to return for one or more visits until you deliver and/or call you on the phone.

What will happen if you join this study?
If you are invited to enroll in this study, you will be asked to participate in all of the following study visits. Below is a detailed description of what will occur during the inpatient stay and follow up visits. If you have any questions, please discuss them with research staff. A total of up to XX subjects may be enrolled in this study.

**Study Day -14:** You will have nasal swab test to see if you are silently infected with the COVID-19 virus.

**Study Day -7:** You will have nasal swab test to see if you are silently infected with the COVID-19 virus.
Study Day -2:
You will come to the inpatient isolation unit on Day -2 (two days before you get the COVID-19 virus) and be admitted. You will have nasal swab test to see if you are silently infected with the COVID-19 virus. The isolation unit is a smoke-free hospital-like setting where you will be confined to a hospital room. It is important that you know:

- Visitors are not allowed.
- You will be asked to stay on the isolation unit 24 hours per day so you will not be able to come and go from your room or from the unit.

Once you are admitted to the inpatient unit, you will need to stay in the unit for 3 – 4 weeks or longer. You will not be allowed to leave the isolation unit until you are no longer positive for COVID-19 virus in your nose.

It is important that you stay in the unit until we tell you it is OK to leave (be discharged). We want to be sure that if you get symptoms of COVID-19 infection, we can monitor you and give you treatment if necessary. We also want to be sure that you cannot spread COVID-19 to other people. You need to be available and willing to stay in the unit for at least 3-4 weeks. You should make plans for childcare needs or emergencies that may occur during the study. If you do not think you can stay in the inpatient unit you should not join the study.

Challenge Day (Study Day 0):
On study day 0, you will have your blood drawn, discuss your medical history, receive a physical examination, have blood taken, saliva collected, urine collected, and a swab taken from your nose.

You will then get the dose of COVID-19 virus (SARS-CoV-2) in your nose. The COVID-19 virus will be given by drops in both sides of your nose (both nostrils). After receiving the nose drops, you will be monitored for at least 30 minutes to check if you feel sick or have any side effects.

You will stay in the inpatient isolation unit until for approximately 3 weeks if you do not become infected or for 5 – 6 weeks if you do develop infection. In natural COVID-19 infection the virus takes from as short as only 2 days to as long as 12 days to start showing up in your nose in 99% of cases, with most cases taking a period of 5 days. Once infected, you may shed virus from your nose or mouth for 3-4 weeks through talking, shouting and singing even though you are no longer sniffling, sneezing or coughing. Therefore, you cannot be released until you have had negative tests for shedding virus for three consecutive days.

Each day you are in the isolation unit, you will have a history and physical exam, and vital signs taken (pulse, breathing rate, blood pressure and temperature) at least three times daily. You will wear a device on your finger that tells us how much oxygen is in your blood. Each day a swab will be placed in your nose to test for the COVID-19 virus. On specified days, you will also be required to give blood, urine, and saliva. These samples will be used to check your health and to see if you

Follow-up Visits:
Here is a schedule of what you will be asked to do each day if you agree to be part of this study. In addition to the table below, other blood tests can be done any time during the study if the doctor thinks it’s needed for your health and safety. The procedures we will do are listed in the table below (Table 1).
### Procedures during the study

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Inpatient Isolation Unit Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Day</strong></td>
<td>-14</td>
</tr>
<tr>
<td>COVID-19 virus given</td>
<td>X</td>
</tr>
<tr>
<td>Admitted to isolation unit</td>
<td>X</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
</tr>
<tr>
<td>Symptom review</td>
<td>X(^1)</td>
</tr>
<tr>
<td>Physical exam</td>
<td>X(^2)</td>
</tr>
<tr>
<td>Vital signs</td>
<td>X(^3)</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X</td>
</tr>
<tr>
<td>Blood Draw</td>
<td>X(^4)</td>
</tr>
<tr>
<td>Urine sample</td>
<td>X</td>
</tr>
<tr>
<td>N-P Swab</td>
<td>X</td>
</tr>
<tr>
<td>Saliva sample</td>
<td>X</td>
</tr>
<tr>
<td>Discharge from inpatient unit</td>
<td>X(^5)</td>
</tr>
<tr>
<td>Review Pregnancy Prevention</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Symptom review will be performed each day the volunteer is confined to the isolation unit.
2. Physical examination will be performed each day the volunteer is confined to the isolation unit.
3. Vital signs will be twice daily and more frequently as indicated every day the volunteer is on the isolation unit.
4. A blood draw is needed for the pregnancy test on Study Day -2. The blood draws represented here are for clinical laboratory studies and research studies. It is anticipated that blood draws will be required on most of these days but will be finalized in the protocol.
5. Discharge may occur sooner (or later) depending when the N-P becomes negative for COVID-19 virus by PCR.
6. Represents the longest potential stay in the inpatient isolation unit.
Follow-up Visits after discharge:
You will have monthly follow-up visits for the first 5 months after discharge and then a follow-up visit at month 9 and month 12 (1 year after being given the COVID-19 virus). Each follow-up visit will take approximately 30-60 minutes. At each visit we will perform some or all of the following:

- Ask you questions about how you are feeling and if you have been sick
- Review your temperature card
- Pregnancy test and pregnancy prevention counseling
- Draw your blood
- Collect an NP swab
- Give you a physical examination
- Check your vitals (blood pressure, pulse, temperature, respiration rate)

Prior to discharge, you will receive education regarding the proper use of a thermometer, the signs and symptoms of potential side effects, and how and when to contact study staff. We will give you a thermometer. You will be told how to take your temperature and how often to write it down for record-keeping purposes.

We will test up to 3 different doses of the COVID-19 viruses. We will start testing a low dose of the virus and then test higher doses if needed. You will know which dose group (cohort) you are in. **You will only get one dose of the COVID-19 virus.** Each dose will be studied in up to 20 – 25 volunteers. A total of up to 75 people will be enrolled in this trial. Each dose cohort will be divided into approximately 4 different groups of volunteers (Table 2). As shown below in Table 1, the first group will consist of only 1 – 3 volunteers. If the COVID-19 virus doesn’t cause symptoms or causes only mild symptoms in the first few volunteers, the next group of volunteers will be increased to 3 – 5 and will be given the same dose as per the table below. The group sizes will be increased until the first dose of COVID-19 virus has been given up to a total of 20 -25 volunteers. Depending on the signs and symptoms induced by this dose of COVID-19 virus, a higher dose may be studied. It would be studied in the same manner as shown for the low dose in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Subjects</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-3</td>
<td>Lowest dose COVID-19 virus</td>
</tr>
<tr>
<td>2</td>
<td>3-5</td>
<td>Lowest dose COVID-19 virus</td>
</tr>
<tr>
<td>3</td>
<td>5-10</td>
<td>Lowest dose COVID-19 virus</td>
</tr>
<tr>
<td>4</td>
<td>10-15</td>
<td>Lowest dose COVID-19 virus</td>
</tr>
</tbody>
</table>

Blood Sample Collection: You will have blood drawn while you are in the isolation unit and at most study visit(s). Each time we will take less than 5 tablespoons of blood. The total amount of blood to be taken from you during the 12-month study is a little more than 1 ½ pints.

The blood we draw at your visits will be tested to:

- Check on your health after receiving the COVID-19 virus
- Look for COVID-19 virus in your blood
- See if your body has made antibodies (germ fighters) against COVID-19
- Test markers on your white blood cells and genes and look for proteins in your blood that may be important for your body to fight COVID-19 infection
In addition:

- A study doctor can be reached 24 hours a day during the study.
- If you become ill during the study, additional tests (for example blood tests, nasal swab, or x-rays) may be done. You will not be charged for these tests. Any risks associated with these tests will be explained to you before they are performed. You may refuse to have these tests done if you do not want them.
- We will contact you to remind you of study visits and to check on you if you miss a study visit. We may contact you by one or more of the following means:
  - Telephone call
  - Text message
  - Electronic media (Twitter, Facebook, etc.)
  - Email message
  - Card mailed by Postal Service
  - Ask one of the people you provided as a contact to remind you to come to the clinic
  - We will contact you to remind you about the study and discuss pregnancy prevention approximately every 30 days

What are my responsibilities if I take part in this research?
If you take part in this research, you will be responsible to:

- Tell the staff if you become sick or feel bad. We may ask you to come to the clinic after discharge so that we can check on you.
- Because COVID-19 is spread by droplets in the air, you will not be able to leave the unit until you are medically discharged. See “Risks of Transmission” below for more details.
- Contact the staff or study doctor before taking medication or receiving any vaccines. This includes medicines that you buy without a prescription like herbal or over-the-counter medicines, such as Advil; and medicines that affect the immune system, such as prednisone.
- Not getting any live vaccines 60 days before you come on the isolation unit, not getting any killed (inactivated) vaccines 30 days before you come on the unit and waiting to get either a live or killed vaccine until after you are discharged. This may put you at more risk for illness such as the flu. Depending on the time of year, we may offer you a flu vaccine prior to admission on the inpatient unit [within acceptable time constraints].
- We will ask you to tell us if you do get a licensed vaccine anytime during the study.
- Not donate any blood products.
- Tell the staff if you receive any blood products.
- Women who are of childbearing potential must use a reliable form of birth control (hormonal birth control, surgical sterilization or intrauterine device). Exception: women who only have sex with women and women who are postmenopausal (no period for at least 1 year).
- If you become pregnant during the study, tell the staff right away.

Will clinical care test results be shared with you?
We will share all results related to your care with you while in you are on the isolation unit. These will include your blood count results, tests of liver and kidney function, blood clotting tests, any ultrasound of the lungs, or chest x-ray results. We will also share the results of any other tests that are done as part of the care of your COVID-19 infection.
Will research test results be shared with you?
The research tests we perform are not like routine medical tests and may not relate directly to your medical care, so we may not put future test results in your medical record.

New Findings
The study doctor or staff will share with you any new findings that may develop while you are participating in this study that might change your decision to be in this study. You may be asked to sign a revised consent form if this occurs.

How long will you be in the study?
As stated above, your participation in this study will last for approximately 12 months from when you are given the COVID-19 infection. Screening visits occur within 60 days before you get the shot.

In the event that you become sick during the study and it has not resolved by the end of the study, you may be followed somewhat longer, typically until the issue is resolved or stabilized.

It is very important for you to come to all of your study visits. If you are unable to return to the center for study visits, you may be asked to have blood drawn at a local clinical lab so that we can follow you for safety. It is very important that you understand the requirements of the study before you decide to sign this consent form and join the study.

What happens to data and biospecimens that are collected in the study?
Biospecimens may include any of the following: blood, tissue, saliva, urine, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person. The biospecimens we collect during this study will be tested as outlined above in the section “What will happen if you join this study?”

What will happen to my unused samples?
We will store any unused blood, urine, and N-P swab samples once this study is finished. Your samples will be used only for research. We may use these samples to learn more about COVID-19 and other diseases. The blood samples may be used for tests to detect:

- Immune responses to the test virus (immunology)
- How long COVID-19 can be found in the body
- How COVID-19 makes people sick
- How COVID-19 and your immune response to COVID-19 affects other viral infections
- Genetic differences in responses to COVID-19 or other viral infections (samples will be used anonymously)

Your samples will not be sold. Your samples will not be used to make commercial products. If researchers use them to create a new product or idea, including those that may have commercial value, you will not benefit financially from these efforts. We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you private to the extent permitted by law. In some cases, institutional review board (IRB) will review new research proposals that would like to use your samples. The IRB is a group of people who perform independent review of research.

Your data and/or biospecimens may be shared:

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- directly with research collaborators, other researchers, sponsors, government agencies, publishers of papers and other research partners
- through government or other databases/repositories

Data/biospecimen sharing could change over time and may continue after the study ends. Generally, if we share your data/biospecimens without identifiers (such as your name, address, date of birth) new uses of the data/biospecimens do not need further review and approval by an IRB.

Reports about research with your samples will be kept with the study records only. There will be no direct benefit to you. From studying your samples, we may learn more about how to prevent, treat, or cure ZIKV diseases or other diseases. Results from research using your samples may be presented in publications and meetings but your name will not be used.

**Genetic Information Nondiscrimination Act (GINA)**
This study involves genetic testing on samples that you provide. There are risks associated with a loss of confidentiality of your health information and genetic testing results. Information about genetic test results may affect your employment, insurance, or family relationships. The sponsor cannot be certain that your genetic test results could never be linked to you.

The Genetic Information Nondiscrimination Act (GINA) is a federal law that helps reduce the risk of discrimination by health insurers or employers based on your genetic information. GINA does not protect you from discrimination if you apply for other types of insurance (such as life, disability or long-term care). GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Genetic information is unique to you and your family. Even without your name or other identifiers, it may be possible to identify you or other members of your family with your genetic information.

The doctors doing this study follow procedures so that people who work with your DNA information for research cannot discover it belongs to you, unless you have given consent. However, new techniques may be developed that in the future make it easier to link your genetic data to you, so we cannot promise that your genetic information will never be linked to you.

**You must agree to the use of your samples for future research if you want to join the study. If you do not want your unused samples used for future research, you should not join this study.**

If you agree to the future use of specimens, you have the right to change your mind at any time after you have joined the study. If you do change your mind, call or write the study doctor or study nurse and let them know. Then your samples will no longer be made available for research. Your samples will be destroyed.

**What are the risks or discomforts of the study?**
In this study, you will be intentionally exposed to the virus that causes COVID-19. This virus is currently causing a world-wide pandemic of severe respiratory disease. Humans have only experienced infections with this virus over the last 4 to 6 months, and the complete spectrum of disease caused by COVID-19 virus is not fully known. Although most severe cases of COVID-19 disease are usually seen in the elderly (over 65 years of age) and those with pre-existing conditions, severe COVID-19 disease can occur in young, healthy adults. The factors that might increase the risk of such
events in young persons are unknown and may not have been detected in the screening process that you underwent before entering the study. Therefore, at present it is not possible to predict accurately and completely the risks to you from participating in this study. The potential risks of participation, based on available information as of this date, are described below.

**Potential risks due to infection with COVID-19**

Common risks from the COVID-19 infection: One or more of these symptoms are seen in almost all identified cases:

- You may have a flu-like symptoms. These include fever, headache, sore throat, runny nose, cough, and body aches.
- You could lose your sense of smell and/or sense of taste.
- You could have diarrhea

Less common and more serious risks from COVID-19 infection are listed below. It is not possible to predict at this time what your risks of developing these complications are. However, based on current knowledge they appear to occur in fewer than 1 in 10 cases, and mostly, but not only, in older adults.

- You may develop shortness of breath.
- You may develop pneumonia. The pneumonia may be severe and you may need to receive supplemental oxygen by mask or by placing small tubes near your nose.
- You may become so short of breath that you cannot breathe on your own. In this case, you will need to be placed on a ventilator (a mechanical breathing machine). About one-half of patients who reach this state of severity will die.
- You may develop blood clots. These could cause swelling in your legs, or they could lead to a stroke. A stroke is a clinical event that occurs when a blood vessel that brings oxygen and nutrients to your brain becomes blocked by a clot, or the blood vessel ruptures. A stroke may be minor, or it may be more serious, leading to paralysis of one side of your body, inability to speak, or other serious nervous system problems. These outcomes from a stroke could be long lasting or even permanent. If you have a stroke you could be permanently disabled or you could never recover your full strength, or, in a few instances, you may die.
- Although the risk is small, you could develop low blood pressure or shock. If this happens you will be given medication and other support to maintain your blood pressure. Treatments for shock in COVID-19 are not always successful, and death is in such circumstances regrettably common.
- You could develop kidney disease (your kidneys do not work as well). This could be permanent. Permanent kidney failure may require use of an artificial kidney system (dialysis) or may require that you receive a renal transplant.
- You could develop liver disease (your liver will not work as well). This could be permanent. Severe liver disease can be fatal or could require a liver transplant.
- You may develop a newly described complication in which the body’s immune system turns against your body’s tissues, destroying blood vessels, the skin, and other organs. This syndrome is seen primarily in younger patients and can be fatal.
- You could develop painful swelling of your toes (“COVID toes”). This usually lasts 3 – 4 weeks.
The FDA, EMA, MHRA and TGA have not approved any drugs to treat COVID-19. Should you become ill with COVID-19, you will be given the current recommended treatments to help you get better. These may include giving you oxygen, putting you on a breathing machine, giving you medications to help your blood pressure, or other treatments that are not yet known. The best available treatment, whatever its cost, will be made available for you.

**Risks of Transmission**

- COVID-19 can be spread by an infected person’s coughing, singing, speaking, or by her/his touching things (writing utensils, packages, door handles, elevator [lift] buttons, etc.). A susceptible contact person who is near a COVID-19-infected individual who has coughed, sneezed, spoken or sang or who touches objects previously touched by the infected individual can, in turn, become infected. The susceptible person becomes infected by breathing air contaminated by the infected person. The susceptible person can also be infected by rubbing their eyes, picking their nose or putting fingers into their mouth after touching objects contaminated by the infected person. The virus that causes COVID-19 is very contagious. By agreeing to participate in this study, you are agreeing to stay in the unit/hospital for 3 – 5 weeks or longer after you are admitted. You will be tested for the presence of the COVID-19 virus on a daily basis while in the research facility.

- While you are in the study unit/hospital, you must remain in your room, unless accompanied by study staff for study procedures, and you are not allowed to have visitors. Friends and relatives may leave things for you at the study unit but are not allowed to enter. You are not allowed to send materials, such as mail or packages, while you are in the research isolation unit.

- You will not be allowed to leave the research isolation unit until you have been shown to be no longer contagious. Early studies of challenge with COVID-19 virus are expected to be carried out under a legal QUARANTINE. Quarantine will extend in duration from the day you receive the challenge virus until you no longer have evidence of infection, as evidenced by three days of negative tests for the virus. You may “leave the study” at any time, which is one of your rights as a volunteer. However, even if you decline to participate further in the study, you are legally bound to remain on the research isolation unit until the end of the Quarantine. Depending on local health ordinances you will be committing a crime by trying to leave the Quarantined unit and each attempt to do so will be considered a separate offence. The reason for this severe restriction is to protect other individuals in your home and in the community with whom you may have contact from acquiring COVID-19 from you. Whereas you have volunteered to enter this study and to be exposed to the highly contagious virus that causes COVID-19, others have not. To repeat, once you have been challenged with the COVID-19 virus and the research isolation unit is in Quarantine, you will have to remain until you are no longer capable of spread COVID-19, to others outside, that is until you and the others have been shown no longer to harbor the virus on repeated testing.

**Risks from blood drawing**

- Taking blood may cause minor, momentary pain, bruising where the needle enters the body, a lump called a hematoma, or (very rarely) infection at the place where blood is taken. To ease the discomfort, a cream may be spread on the skin over the vein where your blood will be collected to diminish the feeling of the prick of the needle, if both you and the health professional drawing your blood agree to its use.
• In the occasional adult the act of drawing blood can cause you to feel lightheaded or result in fainting. Such a drop in blood pressure is never dangerous but to minimize the chance of this happening and the discomfort that ensues, we can draw your blood specimens while you are lying down.
• Some individuals bleed a bit from the site of blood draw. Putting on a small bandage and applying pressure for some minutes prevents this.

**Discomfort of N-P swab sample collection.** We will take a sample from your nose with a swab called a nasopharyngeal or N-P swab. The swab will be placed in your nose and will be moved back until the tip of the swab is in the back of the throat. This can cause discomfort and may cause a gagging sensation.

**Local risks of getting the COVID-19 virus placed in your nostrils**
• You may experience a runny or stuffy nose immediately after drops containing the virus that causes COVID-19 are put into your nostrils.

**Other risks**
• We will ask you to wait to get a routine licensed vaccines like the flu shot or nasal spray flu vaccine from before 30 days prior (killed vaccine) or 60 days prior (live vaccine) to the COVID-19 challenge. This may put you at more risk for illness such as the flu.
• You may become anxious, lonely or depressed by being confined to the isolation unit for 3 – 4 weeks without being able to see family or friends.
• There may be psychological or social risks that result from taking part in the study, such as concern about being tested for HIV. Disclosure of a positive test may result in discrimination by friends, family, employers, insurance companies and others.
• Risks occasionally associated with the use of topical anesthetic cream include temporary skin discoloration, skin irritation, rash, hives, and rarely, dizziness or drowsiness.
  - If you become pregnant while you are in the study, you must tell your study doctor. You must also inform your obstetrician, midwife, or seek the care of an obstetrician or midwife, if you do not have one.

**There may be other side effects and risks that we don’t know about yet.**
If we learn about any new side effects or risks while you are in the study, we will tell you and you can decide if you want to continue in the study.

**Interviews or questionnaires**
You may get tired or bored when we are asking you questions about your medical history, sexual history or pregnancy prevention information. Some questions may make you feel embarrassed or uncomfortable. Let us know if you feel distressed.
You do not have to answer any question you do not want to answer.

**Personal Privacy**
Research staff will work to protect your personal privacy throughout the study. Sensitive questions regarding your medical history, sexual history and pregnancy prevention will be asked in a private area. All forms where personal information is recorded will be kept securely stored at the study site in a locked area. Please discuss any concerns you have about protecting your personal privacy with research staff.
**Identifiable private information**

There is a risk that information about you may become known to people outside this study. We will protect your information to reduce the chance of this happening. We assign you a study ID number upon screening to minimize use of identifying information on forms, documents and specimens.

All study-related information will be stored securely at the study site in a locked area with limited access. All laboratory specimens, reports, study data collection, and administrative forms will be identified by coded number to maintain your confidentiality. All local databases will be secured with password-protected access systems.

**How will the confidentiality of your data be protected?**

The Sponsor of this study has given us a **Certificate of Confidentiality** for this study. This Certificate does not mean that the local, state of federal government approves or disapproves of this study. This Certificate adds special protection for research information that identifies you. It allows us, in some circumstances, to refuse to give out study information about you without your consent when it is sought in a legal action. Still, we may disclose identifying information about you if, for example, you need medical help. We may also give out information about you if the government audits us. The research team will also give information to local or state authorities:

- if they suspect abuse or neglect of a child or a dependent adult;
- if certain infectious/communicable diseases are present; and
- if the team learns that you plan to harm someone. In this case, the team also may warn the person who is at risk
- if you need medical help

A description of this clinical trial will be available on https://ClinicalTrials.gov/, as required by federal laws. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

Information from this study will be given to the Sponsor. The Sponsor is the organization responsible for financing and overseeing this study. The Sponsors of this study are XXXX. "Sponsor" includes any persons, institutions, companies or foundations that are contracted by the sponsor to have access to the research information during and after the study. Information about side effects of the challenge virus will also be given to the national regulatory agency (in the USA this is the Food and Drug Administration [FDA]; in many European countries this is the European Medicines Agency [EMA]; in UK this is the Medicines and Healthcare products Regulatory Agency [MHRA]). It may be given to governmental agencies in other countries where the challenge viruses may be considered for approval.

Medical records which identify you, including photographs, and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by the sponsor, and may be looked at and/or copied for research or regulatory purposes by:

- The regulatory agency providing oversight) (e.g., US FDA, EMA for many European countries, MHRA for UK, Australian TGA, National Medical Products Administration [NMPA] for China, etc.)
- Governmental agencies to whom certain diseases must be reported
- Governmental agencies in other countries
- The Hospital or institution where the research isolation unit is located
- University or academic institutions affiliated with the research isolation unit

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at scientific and public health meetings or in publications. Your identity will not be disclosed in those presentations.

Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

What are the potential benefits to being in the study?
There are no known direct benefits to you for participating in this study. We hope that the information we gather from this study will lead to a COVID-19 vaccine that could help many people around the world. There is a chance you could develop antibodies against COVID-19. We don’t know if you will develop antibodies or if those antibodies would protect you against another COVID-19 infection.

What are your options if you do not want to be in the study?
This research is not designed to diagnose or treat any disease. Your alternative is to decline to participate in the study.

If you do not join, your care at XXXX hospital or clinic will not be affected.

If you do not join, your employment/education at will not be affected.

Will it cost you anything to be in this study?
There will be no costs to you for being in this study. Ask your study doctor (provider) to discuss the costs of treating possible side effects. Otherwise, you might have unexpected expenses from being in this study.

Will you be compensated if you join this study?
For taking part in this research, you may be compensated up to a total of $XXXX (€XXX, etc.). Your compensation will be broken down as follows:
- You will receive a voucher for parking or public transportation tokens, as needed, for the days that you screen or have study visits.
- You will be compensated $XX (€XX, etc.) for your screening visit only if you are enrolled in the study. compensate
- You will be compensated $XX (€XX, etc.) for each inpatient day (Study Days -2 to 28, or longer)
• If you are an alternate, you will be admitted on Study Day -2 and stay on the inpatient unit overnight. If you are not given the COVID19 challenge, you will be compensated $XXX (€XXX, etc.) for your time and discharged on Study Day 0. If you receive the COVID-19 challenge virus you will be enrolled in the study.
• You will be compensated $XX (€XX, etc.) for each of the 9 out-patient clinic visits.
• If you complete all study visits on time and adhere to all inpatient policies, you will be given a $XXX (€XXX, etc.) bonus. You may only receive a portion of the bonus if not all study visits are completed on time or for failure to follow inpatient policies.
• If you choose to withdraw (dropout) before the study is completed, you will only receive payment for the number of visits that you have completed.

Compensation will be distributed by check or Visa card according to the following schedule:
• Insert schedule when known

You may be required to provide your social security number or national identity number to get compensation for taking part in this study. Tax laws of some countries require that you report your research payments when you file your taxes. If your total payments from XXXXX institution exceed $XXX or €XXX per year, XXXXX institution will report these payments to the government tax office and you will receive a form from us.

Can you leave the study early?
• Your participation in this study is voluntary.
• You can agree to be in the study now and change your mind later.
• If you wish to stop, please tell us right away.
• You may leave the study at any time, but you cannot physically leave the unit until the period of legal Quarantine is discontinued. Please see the section on Risk of Transmission above.
• If you “leave the study” early you will not have to have additional study procedures but you will have to stay on the research isolation unit while the Quarantine is still active.
• Leaving this study early will not stop you from getting regular medical care. If you are ill with COVID-19 and leave the study early but are still on the research isolation unit, we will still take care of you and give you the medical treatment you need.
• Leaving this study early will not affect your employment/education.

If you leave the study early, the investigators and the Sponsors of the study may use or share your health information that it has already collected if the information is needed for this study or any follow-up activities.

Your decision not take part or to withdraw from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to leave the study, the samples that have been collected will be used as described in this consent form. If you do not wish us to use these samples after you leave the study, you may request that we destroy them and they will be destroyed. You should ask the study doctor listed below any questions you may have about this research study. You may ask questions in the future if you do not understand something that is being done.
We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

**Why might we take you out of the study early?**
You may be taken out of the study (withdrawn) at any time by the study doctor or the sponsor without your consent if:
- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You have a side effect that requires stopping the research.
- You become pregnant.
- The study is cancelled.
- The study staff or the study sponsor decides to discontinue your participation for any reason.
- You do not follow instructions from the staff or do not keep appointments.
- The Data and Safety Monitoring Board (a scientific review board that monitors clinical research studies) concludes that the study should be stopped.
- The regulatory agency providing oversight of the study, the institution in which the research isolation unit is located, or the Sponsors decide that the study should be stopped.
- If new information becomes available regarding the safety of the challenge virus.
- You do not consent to continue in the study after being told of changes in the research that may affect you.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, the investigators and the Sponsor may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

**Will the study require any of your other health care providers to share your health information with the researchers of this study?**
As a part of this study, the researchers may ask to see your health care records from your other health care providers.

**What information is being collected, used, or shared?**
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment). Prior to contacting your health care provider to release your health information, we will discuss with you what records we will be requesting and why.

**Who will see, use or share the information?**
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other health professionals at the hospital in which the research isolation unit is located, for example, if needed for your clinical care or study oversight. To improve coordination of your research and clinical care, some information about
the study you join will be included in your electronic medical record. By signing this form, you give permission to the research team to share your information with others outside of the institution where the research isolation unit is located. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

**Do you have to sign this Authorization?**
You do if you wish to participate in the study. If you do not sign, you may not join the study.

**How long will your information be used or shared?**
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

**What if you change your mind?**
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

**What treatment costs will be paid if you are injured in this study?**

**For potential US research isolation unit study sites:**
A study doctor will be available at all times while you are in the study to check on you and treat you for any short-term medical care resulting from you taking part in this research study. You are a young adult and therefore at a lower risk to get severe COVID-19 illness. If you, despite of this small chance you do become seriously ill, the services at the hospitals affiliated with the research isolation unit will be available to you at no cost to you. Medical care will be given while you are on the isolation unit. If you require movement to an intensive care unit, this will be provided including, provision of a ventilator, if necessary, to help you to breathe. You will also be provided with any available drug against the infection, at whatever its cost. Should you require long-term care for illness suffered as part of this study, long-term medical care or financial compensation for research-related injuries will be offered by the institutions affiliated with the research isolation unit, the Sponsor, or the state or federal government. The study will also provide a financial settlement to your beneficiaries should you die from COVID-19 infection as a result of being in the study and your life insurance company does not cover provide coverage.

By signing this form, you will not give up any rights you have to seek compensation for injury.

**For potential European or U.K. sites:**
Vincente, Halvor, Peter, Robert – Can you please address the above for European sites?

**What other things should you know about this research study?**
If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study doctor and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

**What is the Ethical Committee and how does it protect you?**

This study has been reviewed by an Ethical Committee (EC), a group of people including scientists and community people, that reviews human research studies. The EC can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the EC at [insert phone number] or [insert email address].

[insert all contact information, name, address, etc]

**What should you do if you have questions about the study, or are injured or ill as a result of being in this study?**

Contact the principal investigator, [Name], at the phone numbers or address listed below.

[List name, address, affiliation, phone number and email address]

If the principal investigator is unavailable, you can call your study coordinator at the contact number provided to you. If you wish, you may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or study coordinator or wish to talk to someone else, call the EC office at [insert phone number].

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call the [insert name of PI] at [insert phone number].

**What does your signature on this consent form mean?**

Your signature on this form means that you have reviewed the information in this form, you have had a chance to ask questions, and you agree to join the study. You will not give up any legal rights by signing this consent form.

**WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM**
Signature of Participant  
(Date/Time)  

(Print Name)

Signature of Person Obtaining Consent  
(Date/Time)  

(Print Name)

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT.
Points to consider in selecting a SARS-CoV-2 challenge virus strain

**Background:**

There are 2 main lineages of SARS-CoV-2 (A and B) that can then be subdivided into a number of component lineages. The bulk of the infections currently world-wide are derived from the B.1 lineage which is associated with the large Italian/European outbreak and now, most cases across the US are lineage B.1 after multiple introductions from Europe.

Coronaviruses acquire genetic variation by mutation and recombination and mutations can emerge as a consequence of passage in cell culture.

There are two options for selection of a challenge virus strain:

1. A biological isolate should be obtained from a healthy subject who does not have known risk factors (e.g., age <50 years, no hx of diabetes, hypertension, CVD, renal or hepatic disease). It will have to be isolated in a qualified cell line and manufactured under cGMP conditions.
2. Use a reverse-genetics derived virus that is rescued in qualified cells. The advantage of this approach is that a genetic tag can be introduced into the challenge virus and it can be tracked. There are a few labs who have this technology but the virus will be a genetically modified organism, that may be problematic for use in some countries.

**Assumptions:**

- The challenge virus pool will have to be generated under cGMP conditions in a qualified cell line (likely Vero cells)
- More than one virus should be selected in case growth or yield differs
- The virus will be passaged about 5-10 times in the manufacturing process

**Criteria in selecting a virus:**

- Should represent as close to a consensus sequence for the selected clade
- Select one or two viruses from each of the dominant clades
- It is not important to select among the viruses that have been used in animal models. It would be better to confirm virulence in animal models after the selected virus has been isolated, plaque purified and sequenced.

**What will be needed:**

- Original clinical material from which the virus was isolated/sequenced so that the virus can be re-isolated in qualified cells.
- Virus isolate will have to be plaque purified X3 or purified by limiting dilution.
- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.

**Advice from experts:**

The B.1 lineage has a mutation in spike (D614G) which is generally thought to be a significant mutation molecularly but there is debate as to its importance in terms of its effect on pathogenesis and transmissibility. **Viruses at the base of the B.1 lineage can be selected with the D614G mutation but few other mutations.**
If you were to do two variants, then possibly one of the original A viruses would make sense (it doesn’t have the D614G mutation). It is possibly diminishing in frequency but there are still cases in Europe and the USA (plus many other parts of the world).

A number of groups have seen a significant deletion in the spike protein associated with culturing in Vero cells. This removes the furin cleavage site. One expert suggested avoiding viruses with the deletion of the furin cleavage site but another expert suggested choosing a purified plaque of S1/S2 deletion mutant that is stable on multiple passages in Vero cells as the challenge virus because it would be safer for the unvaccinated control volunteer.

Not addressed

- How to bring it out of BSL3?
- How long it will take to manufacture and release a challenge virus pool?
Responses to Mike Levine’s questions:

1. As I understand from your report, your Subgroup with input from other consultants are proposing that original clinical specimen material be sent to the CMO as the source of the virus for culture, along with relevant clinical information. Is that correct?
   A. *The virus will need to be isolated in qualified Vero cells. If the CMO is able to isolate virus from original clinical material, they can do this. If not, the virus can be isolated in a lab and sent to the CMO but the qualified Vero cells will have to be provided to the lab.*

2. You suggest that the virus should be from an infected healthy subject. I am presuming that this could include a person with overt but non-severe clinical COVID-19 illness but one who does not have known risk factors (e.g., age <50 years, no hx of diabetes, hypertension, CVD, renal or hepatic disease) rather than from a clinically asymptomatic infection.
   A. *A I am not aware that there is a genetic difference between viruses isolated from severe, non-severe or clinically asymptomatic infection. The important factor is the isolation from a previously healthy subject who does not have known risk factors (e.g., age <50 years, no hx of diabetes, hypertension, CVD, renal or hepatic disease).*

3. If the original clinical source material is frozen away in a freezer of a laboratory somewhere, could this perhaps also be a virus that was propagated in Vero cells and might have had a challenge performed in non-human primates? If those data are available, we would know the virus is still virulent (at least in NHPs) after passage and we would know the challenge dose used in the NHP experiment. I have read that NHP challenges are often intratracheal as well as intranasal and the dose used is ~10E6 TCID50. The NHP experimenters were aiming for pneumonitis. We want to avoid that.
   A. *A I don’t see this as a critical issue. Most laboratories that set up animal models do so with the first virus isolates that they receive and amplify. They have not selected isolates based on the principles we outlined. It would be better to test the viruses after they are plaque purified and sequenced by the CMO, to test their virulence in hamsters and non-human primates.*

4. If we receive clinical material from a donor lab source in one country, and have to send it to another country, we can arrange that. It will not be a problem.
   A. *OK*

5. Depending on where the CMO is geographically located, it may be complicated if both the primary virus source information and the primary clinical information are in a language neither readable nor understandable to the CMO. We will then need a certified translation document for the translation. If the origin of the virus is the highest priority, we should be able to arrange translation of documents.
   A. *OK*

6. Clade B1 virus primary clinical material sources might be obtainable from a European country or from somewhere in the USA. Is that correct? If so, can you reach out to colleagues to identify two specific A1 viruses and two specific B1 viruses that we can request? Who might be sources for such viruses?
   A. *This is a little complicated because many sequences were generated from viruses that were identified with molecular tests and few laboratories have virus isolates to go along with them. In many instances, the clinical material may not be available. It may be somewhat easier to track in countries like Australia because a handful of labs are uploading the sequences to GISAID.*
I will ask my colleagues for a list of 5 or 6 clade A.1 and B.1 viruses that are close to the base of the tree and see if we can track them.

7. Clade A1 viruses could be obtained from the State of Washington, USA or from China. Is that correct?
   A. May not be limited to Washington state. I will ask.

8. Each of the two clade A1 virus candidates and each of the two selected clade B1 viruses would be sent to the CMO where they would be isolated in a qualified Vero cell line. Each of these four viruses then would have to be purified by plaque purification x3 or purified by limiting dilution. For each virus next generation sequencing of the virus at the start of the purification and at the end would have to be done and the virus sequences then compared.
   A. Correct

9. Where the discussion gets a bit fuzzy for me is on the next two points. You mention that “a number of groups have seen a significant deletion in the spike protein associated with culturing in Vero cells and that this deletion removes the furin cleavage site that sets SARS-CoV-2 apart from SARS-CoV and is thought to be the most likely reason for its greater transmissibility. That would be one you certainly want to avoid.” Can we discuss these important points? If the aims of a human challenge model (assuming that a therapy becomes available to stop the progression of the illness from reaching serious disease) are to examine the effect of immunity (be it derived from initial challenge before re-challenge 6 weeks later, or from a vaccine) on prevention of both clinical illness and on shedding, shouldn’t the challenge be with the most representative SARS-CoV-2 viruses? Or are you considering this from the perspective of safety for nursing staff and other staff in contact with the challenged volunteers?
   A. I was relaying what the experts we consulted said. One said we should avoid viruses that acquire a deletion of the furin cleavage site on passage but the other said it would be better to choose a virus with a deletion in the furin cleavage site as long as it was stable, because it would be safer for the unvaccinated volunteers.

   Our subgroup feels that we should try to select a virus that maintains the furin cleavage site because it is present in the original isolate. However, emergence of furin cleavage site deletions may be inevitable in cultured virus and as long as the virus replicates to high titer, we can proceed with a virus that is otherwise stable.

10. You also state that “A heterogeneous mixture of S1/S2 junction deletion mutants are inevitable if the SARS-CoV-2 is expanded in Vero 5 times. From our experience on the first Hong Kong strain, 3 passages in Vero E6 results in 30 to 40% of the virus plaques having various types of S1/S2 deletion mutations around the 685/686 cleavage site and also some mutations upstream at around 660. These mutants are generally less virulent in the hamster model. I would choose one purified plaque of S1/S2 deletion mutant which is stable on multiple passages in Vero cells as the challenge virus. This virus strain should be highly stable and standardized. Most importantly, this virus should be safer for the unvaccinated control volunteer.”
   A. See above

11. Based on the above, may I ask you and your Team identify the starting clade A1 and B1 viruses from reliable sources and to craft a rationale for selection of the final clones to undergo larger scale culture in Vero cells to be able to make the challenge batches.
   A. The document we sent (and will update) provides the principles to follow and the rationale for selection of strains. We could potentially provide a list of 5 strains from A.1 and B.1 that would meet the genetic criteria.
But we do not have the ability to track down which lab uploaded the sequence, whether they have the original clinical material and can share it, ascertain the clinical history of the patients from whom the viruses were recovered, ascertain that we have permission to use the viruses. This is beyond the scope of an advisory committee and will have to be done by the WHO or other public health authorities. WHO consult some clinical labs or biobanks for sharing samples and sequence information.

12. Finally, you will have selected from four clinical isolate viruses (two from clade A1 and two from clade B1) to be cultured in Vero cells and sequenced and made ready to be passaged approximately 5 times in Vero cells to make a batch of each with sufficient virus to fill and finish the final formulations and presentations. This will be accomplished (I presume) by aliquoting three different dose levels of each virus into vials. Thus, some vials of each challenge virus will contain dose level 1, other vials will contain dose level 2, while the remaining vials will contain virus dose level 3. The vials (or needle-less syringes) with liquid virus suspension will then be frozen. Are there cryopreservatives that have to be added (e.g., glycerol) before finalizing a formulation prior to aliquoting?

A. This is a matter that the regulatory agencies or manufacturers will have to address. A stability testing program will have to be designed to ensure that the material is stable for 2 years.

13. Do we make a total of four separate GMP batches in case one or more selected batches do not either infect or cause mild clinical illness? Or do we down select beforehand and make only two or three GMP batches? The aliquoting to fill and finish the final drug product will have to be done for each batch.

A. It is possible that the yield of the viruses will vary. I would suggest carrying four viruses through plaque purification, NGS and if needed, test virulence in hamsters (or NHPs). Then select one virus from each clade to manufacture as the final drug product.

14. We have to inform the CMO what the three dose levels of virus are going to be. The only information that I have is that ~2x10E6 TCID50 of a couple of SARS-CoV-2 viruses administered intrathoracically have caused pulmonary infection in NHPs. The CMO will need to know how much virus per ml to prepare at each dose level. Whom can we consult with to help with that key decision? Do we approach folks who do challenges in NHPs? Or approach clinical virologists, or both?

A. I would not base the dose levels on NHP studies. At LID, NIAID we always used 10^4-6 TCID50 of virus with 1 ml given intratracheally and 1 ml intranasally for respiratory virus studies in non human primates. These doses used in NHPs are not linked to median human infectious doses.

The dose levels in humans should start with a low dose and go up to find the HID50.
Points to consider in identifying manufacturers for a GMP batch of SARS-CoV-2 challenge virus

Background:

Manufacture of a SARS-CoV-2 challenge virus pool will require a BSL3 manufacturing facility. The type of formulation and the dosing in the vials should be selected to minimize handling.

Assumptions:

- The challenge virus pool will have to be generated under cGMP conditions in a BSL3 facility
- More than one virus may have to be tested by the manufacturer in case growth or yield differs
- The virus will likely be passaged about 5-10 times in the manufacturing process. Perhaps the titer and volume should be predefined.
- Should we consider a reverse genetically derived virus with a genetic bar code to identify the virus.

What will be needed:

- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.
- The ability to formulate liquid versus lyophilised material and different virus concentrations.
- Information on how long it will take to manufacture and release a challenge virus pool.

Questions to ask potential manufacturers:

- Indemnification by the manufacturer or carried by the sponsor?
- Price
- How long will it take?

Not addressed

- How to bring it out of BSL3?
- How to transport it?
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Manufacturer 1: Ology Bioservices in Bethesda, USA</th>
<th>Manufacturer 2: Bharat Biotech</th>
<th>Manufacturer 3: Biomark Colorado State</th>
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<tr>
<td>BSL3 and GMP</td>
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<td>Previous experience of production of GMP challenge inoculum</td>
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<tr>
<td>Cost</td>
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<tr>
<td>Timeline</td>
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<td>3-4 months (information provided)</td>
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<td>Validated GMP cell line exists</td>
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<td>Release testing</td>
<td>Needs to be defined up front – typically sterility, potency and adventitious agent testing</td>
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<tr>
<td>Validated assays available</td>
<td>No. Will need to be transferred or set up (included in timeline)</td>
<td>No. Will need to be transferred or set up (included in timeline)</td>
<td></td>
</tr>
<tr>
<td>All assays in house?</td>
<td>TBC</td>
<td>No – some assays including NGS will need to be outsourced</td>
<td></td>
</tr>
<tr>
<td>Capacity</td>
<td>Need to check slot availability</td>
<td>Some capacity in July onwards</td>
<td></td>
</tr>
<tr>
<td>Challenge strain</td>
<td>NIH could make some available – they have the Italy strain and others</td>
<td>Needs to be provided</td>
<td></td>
</tr>
<tr>
<td>Final Batch size/no of vials</td>
<td>Dependent on titre obtained and volume/vial to be advised</td>
<td>Dependent on titre obtained and volume/vial to be advised</td>
<td></td>
</tr>
<tr>
<td>Preformed syringes</td>
<td>May be difficult to do as won’t know what titre is needed for inoculation – depended on dose escalation study</td>
<td>Not known as yet</td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>No storage available</td>
<td>Available</td>
<td></td>
</tr>
<tr>
<td>Indemnity</td>
<td>Need a clause in the agreement</td>
<td>Need a clause in the agreement/ additional insurance may be needed</td>
<td></td>
</tr>
</tbody>
</table>

*call with Biomark will be scheduled this week
### SARS-CoV-2 Challenge Agent Manufacturing Considerations

<table>
<thead>
<tr>
<th>Stage</th>
<th>Issue</th>
<th>Comments/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source material of virus plus accompanying clinical description</td>
<td>A1 (virus 1)</td>
<td>Provenance could be from West Coast, USA</td>
</tr>
<tr>
<td></td>
<td>A1 (virus 2)</td>
<td>Provenance could be from West Coast, USA</td>
</tr>
<tr>
<td></td>
<td>B1 (virus 1)</td>
<td>Provenance could be from East Coast, USA</td>
</tr>
<tr>
<td></td>
<td>B1 (Virus 2)</td>
<td>Provenance could be from Europe</td>
</tr>
<tr>
<td>Clinical description documentation for each virus selected</td>
<td>Each virus selected must be accompanied by clinical information about the patient</td>
<td>If the clinical information describing the patient and her/his clinical course is in a language other than English, the translation must be accompanied by a Certificate of Translation documenting the accuracy of the translation</td>
</tr>
<tr>
<td>Transfer to manufacturer</td>
<td>BSL3 agent, clinical material.</td>
<td>Import and export permits will be required. Shipping as Dangerous Goods. Inform reg authorities (e.g., HSE, UK; CDC, USA; ?? EU countries)</td>
</tr>
<tr>
<td>Total Volume</td>
<td>The Subgroup on Clinical Trials Issues and other sources need to estimate the number of challenge studies that may be anticipated, which will allow the number of challenge doses needed to be manufactured. Note that this must be estimate without knowing the effective human ID_{50} infective dose and the human clinical ID_{50}. This will have to a consensus guess.</td>
<td></td>
</tr>
<tr>
<td>Titre (TCID_{50}/ml)</td>
<td>TCID_{50}/ml to be ascertained by manufacturer</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Proposed Dose level 1 will be 10^{2} TCID_{50}/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proposed Dose level 2 will be 10^{3} TCID_{50}/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proposed Dose level 3 will be 10^{4} TCID_{50}/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid or minimise handling of challenge agent. Dilution would require BSL3 laboratory at site. Other handling would also appear to require BSL3.</td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>Frozen liquid or lyophilised. Lyophilised would add cost and would require a reconstitution step at the clinical site, which may pose a risk The same formulation would serve for both human and animal (NHP) use.</td>
<td></td>
</tr>
<tr>
<td>Fill volume</td>
<td>The target dose levels would be per ml, since 0.5 ml would be instilled per nare of each volunteer. If vials contain frozen inoculum, after thawing, 1.0 ml would be drawn and 0.5 ml instilled per nare of each volunteer. Vials could be filled with 2.2 ml (for challenging two volunteers), with 3.3 ml for challenging three volunteers, or with 5.5 ml (with enough to challenge five volunteers). The advantages and disadvantages of each of these fill volumes will be discuss and a decision made. If syringes are pre-filled to be used, the fill volume will have to be 1.1 ml single-dose fills. This would require a lot of storage volume.</td>
<td></td>
</tr>
<tr>
<td>Fill presentation</td>
<td>Defrosted vial material will need to be transferred to syringes or pipettes for the act of intranasal challenge (0.5 ml per nare per volunteer). Pre-filled syringes would be single-dose.</td>
<td></td>
</tr>
<tr>
<td>Transfer from manufacturer to research facilities</td>
<td>BSL3 agent</td>
<td>Import and export permits will be required. Shipping as Dangerous Goods. Inform reg authorities HSE (UK), CDC (USA) Other (country specific)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Use in humans</td>
<td>USA – FDA permission. IND number needed for import. UK – Europe -</td>
<td></td>
</tr>
<tr>
<td>Use in animals</td>
<td>USA – Dept of Agriculture</td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>Secure BSL3 facility needed</td>
<td>Need a stability plan to follow TCID&lt;sub&gt;50&lt;/sub&gt;/ml of each formulation (dose level) of each virus batch over time</td>
</tr>
<tr>
<td>Storage at multiple locations may be needed/desirable (separate freezers within each site that receives virus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewardship</td>
<td>Some agency needs to provide close oversight for every vial or syringe sent to storage sites and to clinical sites and for the repository.</td>
<td></td>
</tr>
</tbody>
</table>
From: Levine, Myron [Mlevine@som.umd.edu]
Sent: 5/4/2020 5:16:01 PM
To: [Email redacted]; mimi darko[b][b]@yahoo.co.uk; 'rosanna.lagos@adsl.tie.cl' [rosanna.lagos@adsl.tie.cl]; adurb1n1@jhu.edu; Stanley Plotkin [stanley.plotkin@vaxconsult.com]; Treanor, John [OS]; /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIOH23SPDLT)/cn=Recipients/cn=043d9cf65ad94fa49d37b1522637a0af-HHS-John.Tr); John_Treanor@URMC.Rochester.edu; Peter Kremsner [peter.kremsner@uni-tuebingen.de] [peter.kremsner@uni-tuebingen.de]; robert.sauerwein@radboudumc.nl; vicente.estrada@salud.madrid.org[b][b]; Punnee Pitsuttitium [punnee.pit@mahidol.ac.th]; vrati@rcb.res.in; 石正莉 [zlshi@wh.iov.cn]; Subbarao, Kanta [kanta.subbarao@influenzacentre.org ]; zeb.jamrozik@monash.edu; d.king@wellcome.ac.uk; 'Halvor Sommerfelt' [Halvor.Sommerfelt@uib.no]; sabdulla@ihi.or.tz
CC: HENAO RESTREPO, Ana Maria [henaorestrepoa@who.int]; Krause, Philip [o=ExchangeLabs/ou=Exchange Administrative Group (FYDIOH23SPDLT)/cn=Recipients/cn=00c6330fea0042fdb5571c3fdef792ed-krause]; Charlie Weller [C.Weller@wellcome.ac.uk]; D.King@wellcome.ac.uk; Anastazia Oldier Aguilar (Anastazia.OlderAguilar@gatesfoundation.org) [Anastazia.OlderAguilar@gatesfoundation.org]; Mafungu, Neddy (mafungu@who.int) [mafungu@who.int]; Laurie, Ximena (lauriex@who.int) [lauriex@who.int]
Subject: PROPOSED AGENDA ITEMS FOR THE 2nd VIDEOCON of the WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines

Dear all:

The purpose of this note is to suggest some key AGENDA items for Discussion tomorrow during our weekly Advisory Group videoconference. We only have one hour and we have four Subgroups and lots of loose ends. Accordingly, I propose that tomorrow we focus mainly on the remits of the Subgroup on Clinical Trial Issues and of the Subgroup on Challenge Virus Strain Issues. For the former an update on issues that the Details of Study Design Team have been discussing would be of particular interest and importance. Some of the ultimate recommendations of that Team will have bearing on virus strain selection (e.g., fully virulent low passage versus, moderate passage, versus genetically attenuated). Team members will have an opportunity to make individual comments. Time willing, we may also be able to fit in a short synopsis of early work of the Infection Control Team. On the next videoconference we will have input in greater depth from that Team.

Next on the Agenda we will have a progress report from the Subgroup on Challenge Virus Strain Issues, in particular on information to be shared by the Challenge Virus Strain Selection Team.

Depending on remaining time we can have brief updates from the other two Subgroups including the Subgroup on Measurement of Immune Responses Pre- and Post-Challenge and the Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. The next teleconference will focus more closely on the work of these two Subgroups.

I propose 5 minutes on more general updates about COVID-19 disease and SARS-CoV-2 relevant to establishing a maximally safe challenge model. It seems that every week there is some important new clinical development. Particularly, a brief update from WHO or a well-wired Advisory Group member on any promising therapeutic breakthroughs will be welcome.

In the remaining time before bringing the meeting to a close, I would request our WHO Secretariat, Ana Maria Henao Restrepo and Phil Krause, to provide updates, guidance and to advise us on expected timelines for the deliverables.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
Associate Dean for Global Health, Vaccinology & Infectious Diseases
Founder & Former Director, Center for Vaccine Development (1974)
University of Maryland School of Medicine
685 W. Baltimore Street
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Tel: +1 (410) 706-7588; Fax: +1 (410) 706-6207
Email: mlevine@som.umaryland.edu
From: Levine, Myron [Mlevine@som.umaryland.edu]  
Sent: 5/4/2020 5:14:24 PM  
To: "[redacted]"@gmail.com; mimi darko[redacted]@yahoo.co.uk; 'rosanna.lagos@adsl.tie.cl' [rosanna.lagos@adsl.tie.cl]; adurbin1@jhu.edu; Stanley Plotkin [stanley.plotkin@vaxconsult.com]; Treanor, John (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOF23SPDLT)/cn=Recipients/cn=043d9cf65ad94fa49d37b1522637a0af-HHS-John.Tr]; John_Treanor@URMC.Rochester.edu; Peter Kremsner [peter.kremsner@uni-tuebingen.de] [peter.kremsner@uni-tuebingen.de]; robert.sauerwein@radboudumc.nl; vicente.estrada@salud.madrid.org; [redacted]@yahoo.com; Punnee Pitsuttithum [punnee.pit@mahidol.ac.th]; vrati@rcb.res.in; 石正丽 [zlshi@wh.iouv.cn]; Subbarao, Kanta [kanta.subbarao@influenzacentre.org]; zeb.jamrozik@monash.edu; d.king@wellcome.ac.uk; 'Halvor Sommerfelt' [Halvor.Sommerfelt@uib.no]; sabdulla@ihi.or.tz  
CC: HENAO RESTREPO, Ana Maria [henaorestrepoa@who.int]; Krause, Philip [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOF23SPDLT)/cn=Recipients/cn=00c6330fea0042fbb557c13fdef792ed-krause]; Charlie Weller [C.Weller@wellcome.ac.uk]; D.King@wellcome.ac.uk; Anastazia Older Aguilar [Anastazia.OlderAguilar@gatesfoundation.org] [Anastazia.OlderAguilar@gatesfoundation.org]; Mafungu, Neddy [mafun@who.int] [mafungu@who.int]; Laurie, Ximena [lauriex@who.int] [lauriex@who.int]  
Subject: Re-structuring of the Subgroups of the WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines

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Many thanks and warm regards to all.

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Founder & Former Director, Center for Vaccine Development (1974)
University of Maryland School of Medicine
685 W. Baltimore Street
Baltimore, Maryland 21201, USA
Tel: +1 (410) 706-7588; Fax: +1 (410) 706-6207
Email: mlevine@som.umaryland.edu
Subject: Re: Scientific Advisory Committee Meeting

I am sorry that I missed Anna-Marie's presentation on the Solidarity project as I had to join another call. Is it possible to share her presentation please. Thanks

With best wishes,
Alash'le Abimiku
Dear All,

This is an invite to the VTC SAC meeting.

The agenda will follow in a separate email.

Best,

Eric.

Here’s how to join the meeting

From web browser & other ways to join:
https://(b)(6)

From Microsoft Skype4B:
(b)(6)

From a video system (SIP/H.323):
(b)(6)

From telephone:
(b)(6) (for other countries check web browser link)
Use conference Code (b)(6)
Dear Neddy:

May I ask you to please send out the link for next week's Videocon and to make it for 90 minutes. I have copied the WHO Secretariat and the Subgroups Leads

Many thanks,

Mike

Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
Associate Dean for Global Health, Vaccinology & Infectious Diseases
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Baltimore, Maryland 21201, USA
Tel: +1 (410) 706-7588; Fax: +1 (410) 706-6207
Email: mlevine@som.umd.edu
Excellent!

Many thanks,

Ana Maria

Sent from my iPhone

On 3 May 2020, at 12:14, 石正丽 <zlshi@wh.iov.cn> wrote:

Dear Mike,

Thank you for your email. I'll be happy to be the "lead" for the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. I'll try my best to complete the work with the collaboration of other members.

Best regards,

Zhengli,

-----原始邮件-----

发件人:"Levine, Myron" <mlevine@som.umd.edu>
发送时间:2020-05-03 09:17:37 (星期日)
收件人: "石正丽" <zlshi@wh.iov.cn>
抄送: "HENAO RESTREPO, Ana Maria" <henaorestrepoa@who.int>, "philip.krause@fda.hhs.gov" <philip.krause@fda.hhs.gov>
主题: Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge

Dear Zeng-Shi:

I trust that you are well. Kanta Subbarao has informed me how helpful you have been already on the Sub-Group for Selection of a Challenge Virus Strain. Many thanks.

I now need to ask you a question about the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. A few individuals in the Advisory Group, as expected, were not happy with their assignment to a Sub-Group and requested to be moved to a different Sub-Group. We had informed everyone that they could make such requests. One Advisory Group member who made such a request is Robert Sauerwein, who requested to be moved from the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge to the Sub-Group on Measurement of Immune Responses Pre- and Post-Challenge. I have done that, in response to his request. Meanwhile, Sudhanshu Vrati
has requested to be moved from the Sub-Group on Measurement of Immune Responses Pre- and Post-Challenge to the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. I have done that as well.

The purpose of this email is to ask you if you are willing and are able to care out the time to be the “Lead” for the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. To serve this role, you will need to coordinate with the other members of that Sub-Group (Kanta and Sudhanshu) to finalize your recommendations of the virological and molecular methods to be used. You and your Sub-Group will then need to write up the Methods and Conclusions to be sent to me to collate into the overall report to be submitted to the Secretariat. One of the big issues will be for you and the team to propose what to do with volunteers who remain RT-PCR-positive but their cultures are negative for recovery of SARS-CoV-2. Are those volunteers shedding RNA fragments only, and these individuals are not infectious? Or should they be considered infectious?

If for any reason you cannot commit to serve as the Lead on the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge, please let me know as quickly as possible.

I look forward to working with you.

Warm regards,

Mike

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发件人:"Levine, Myron" <mlevine@som.umd.edu>
发送时间:2020-05-03 09:17:37 (星期日)
收件人: "石正丽" <zlshi@wh.iov.cn>
抄送: "HENAO RESTREPO, Ana Maria" <henaorestrepa@who.int>, "philip.krause@fda.hhs.gov" <philip.krause@fda.hhs.gov>
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I look forward to working with you.

Warm regards,

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685 W. Baltimore Street
Baltimore, Maryland 21201, USA
Tel: +1 (410) 706-7588; Fax: +1 (410) 706-6207
Email: mlevine@som.umaryland.edu
From: Levine, Myron [mlevine@umaryland.edu]
Sent: 5/4/2020 8:23:08 PM
To: rosanna.lagos@adsl.tie.cl; adurbin1@hhu.edu; Stanley Plotkin [stanley.plotkin@vaxconsult.com]; Treanor, John (OS) [t@exchange.labs/ou=exchange.adm.49321 @yahoo.com]; [rosanna.lagos@adsl.tie.cl]; [b][6][b]
John_Treanor@URMC.Rochester.edu; Peter Kremsner [peter.kremsner@uni-tuebingen.de] [peter.kremsner@uni-
tuebingen.de]; robert.sauerwein@radboudumc.nl; vicente.estrada@salud.madrid.org; [b][6][b]@yahoo.com;
Punnee Pitsuttithum [punnee.pit@mahidol.ac.th]; vrati@rcb.res.in; 石正丽 [zlshi@wh.iov.cn]; Subbarao, Kanta
[kanta.subbarao@influenzacentre.org]; zeb.jamrozik@monash.edu; d.king@wellcome.ac.uk; 'Halvor Sommerfelt'
[halvor.sommerfelt@uib.no]; sabdulla@ihi.or.tz
CC: HENAO RESTREPO, Ana Maria [henaoestrepoa@who.int]; Krause, Philip [krause@exchange.labs/ou=exchange
Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=043d9cf6c49fda49d37b1522637a0af-HHS-John.Tr];
Charlie Weller [c.weller@wellcome.ac.uk]; [b][b][b]@gatesfoundation.org] [Anastazia.OlderAguilar@gatesfoundation.org]; Mafungu, Nedly
[mafungan@who.int] [mafungan@who.int]; Laurie, Ximena [lauriex@who.int] [lauriex@who.int]
Subject: FW: 2nd teleconference - WHO WG on HCS
Attachments: Call in numbers_webex.pdf

Dear all:

A few of you in the USA did not receive this invitation and asked me to forward Nedly’s email from WHO. Just in case, I
am forwarding it to the entire Advisory Group, whatever your geographic site.

All the best,

Mike

From: MAFUNGA, Nedly <mafungan@who.int>
Sent: Saturday, May 2, 2020 12:30 PM
Subject: 2nd teleconference - WHO WG on HCS
Importance: High

Good evening all,

The 2nd teleconference for the WG on Human Challenge Studies will take place on Tuesday, 5 May 2020 at 13h00
Geneva time.

Please see connection details below:

Meeting link - https://who.webex.com/who/j.php?MTID=mc2385fc22d6f45412dea9efb4b9f221 or

Join by number
- https://signin.webex.com/collabs/#/meetings/joinbymeetroom?TrackID=&hbxref=&goid=attend-meeting

Meeting number/access code (6) password (6)

On audio tab please click on “call using computer” and mute yourself to avoid background noise disruption
unless you are speaking.

Dial in numbers
Kind regards,

Ms Neddy MAFUNGA
Assistant (R&D Blueprint)

Office of the Executive Director
WHO Health Emergencies Preparedness & Response
World Health Organization
20 Avenue Appia
1211 Geneva 27
Tel direct: +41 22 791 2421
Fax direct: +41 22 791 4865
E-mail: mafungan@who.int

Website https://www.who.int/blueprint/en/
This e-mail, together with any attachments, is intended for the named recipients only and is confidential. It may also be privileged or otherwise protected by legal rules. If you have received it in error, please notify the sender immediately by return and delete it and any attachments from your system. You must not copy or disclose its contents to anyone.
The World Health Organization has taken every effort to ensure that outgoing messages are free of computer viruses. However, given the nature of the threat posed by computer viruses and the Internet, the recipient is advised to scan this e-mail and any attached files for viruses upon receipt.
<table>
<thead>
<tr>
<th>Calling from</th>
<th>Call-in Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Toll</td>
<td>+1-415-655-0003</td>
</tr>
<tr>
<td>AUSTRALIA Toll</td>
<td>61283175551</td>
</tr>
<tr>
<td>AUSTRIA Toll</td>
<td>+43-720-815306</td>
</tr>
<tr>
<td>Argentina Toll</td>
<td>+54-11-5984-2766</td>
</tr>
<tr>
<td>Australia Toll (Adelaide)</td>
<td>+61-8-7079-0395</td>
</tr>
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Dear Prof. Levine,

Noted with thanks,

Best Regards,

Punnee

Professor Dr. Punnee Pitisuttithum

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Head, Vaccine Trial Centre,
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From: Levine, Myron <Mlevine@som.umaryland.edu>
Sent: Monday, May 4, 2020 9:13:37 AM
To: ___________ (b)(6) ___________ @gmail.com; mimi darko; rosanna.lagos@ads1.tle.ci; adurbin1@jhu.edu; stanley.plotkin@vaxconsult.com; treanor, john (os/aspr/barada) (ctr); john, treanor@urm.rochester.edu; peter kremser (peter.kremsner@uni-tuebingen.de); robert.sauerwein@radboudumc.nl; vicente.estrada@salud.madrid.org; ___________ (b)(6) ___________ @yahoo.com; vrat@rcb.res.in; 石正丽; subbarao, kanta; zeb.jamrozik@monash.edu; d.king@wellcome.ac.uk; ‘halvor sommerfelt’; halvor.sommerfelt@uib.no; sabdulla@ihi.or.tz
Cc: HENAO RESTREPO, Ana Maria; philip.krause@fda.hhs.gov; charlie weller; d.king@wellcome.ac.uk; Anastazia Older Aguilar (Anastazia.OlderAguilar@gatesfoundation.org)
Subject: Re: Re-structuring of the Subgroups of the WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines

Dear all:

This email is to bring to your attention a bit of re-structuring of the Advisory Group based on requests of some members to be moved to a different theme as their primary assignment as well as a desire to simplify the administrative structure in a way that harmonizes well with WHO guidelines and constraints. Simplification is important because we have a short timeline to complete our deliverable.
In the re-structuring we have, I believe, acceded to the specific requests of several members who asked for a re-assignment.

We have reduced the number of Subgroups to four. We accomplished this by merging two Subgroups with closely related areas of focus and interdependency to create one Subgroup but now having two Teams. This was done in two instances. In the two Subgroups that now each have two Teams, the Subgroup Lead is also the Lead of each of the two Teams. I discussed this revised structure in depth today with the WHO Secretariat (Ana Maria Henao Restrepo and Philip Krause) and we are in agreement on the advantages of this leaner structure. Several of you are on more than one Subgroup (pursuant to your request or because we particularly need your expertise there). The Observers remain unchanged.

This email is intended to provide you with a preliminary familiarization with the revised organogram (shown below). We will spend a few minutes at the Tuesday teleconference briefly elaborating on a few aspects of the changes.

Several of the Subgroups have already made substantial, impressive progress in the work scopes.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.  
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Associate Dean for Global Health, Vaccinology & Infectious Diseases  
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**Subgroup on Clinical Trial Issues** – Anna Durbin (Lead)  
**Details of Study Design Team** - Anna Durbin (Lead), John J Treanor, Halvor Sommerfelt, Punnee Pitsutthium, Zem Jamrozik, Robert Sauerwein  
**Infection Control Team** (nosocomial transmission prevention, containment levels, PPE, staffing) - Anna Durbin (Lead), Yasin Arabi, Peter Kremsner, John Treanor, Vicente Estrada, Salim Abdullah.

**Subgroup on Challenge Virus Strain Issues** – Kanta Subbarao (Lead)  
**Challenge Virus Strain Selection Team** – Kanta Subbarao (Lead), Zeng Li Shi, Sudhanshu Vrati  
**Potential Manufacturers of a GMP Batch of Challenge Virus Team** – Kanta Subbarao (Lead), Delese Mimi Darko, Deborah King, Stanley Plotkin, John Treanor

**Subgroup on Measurement of Immune Responses Pre- and Post-Challenge** – Stanley Plotkin (Lead), Kanta Subbarao, Robert Sauerwein, Rosanna Lagos (immune enhancement on second exposure is a safety question).

**Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge (RT-PCR, culture, timing)** – Zeng Li Shi (Lead), Kanta Subbarao, Sudhanshu Vrati
Dear Zeng-Shi:

I trust that you are well. Kanta Subbarao has informed me how helpful you have been already on the Sub-Group for Selection of a Challenge Virus Strain. Many thanks.

I now need to ask you a question about the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. A few individuals in the Advisory Group, as expected, were not happy with their assignment to a Sub-Group and requested to be moved to a different Sub-Group. We had informed everyone that they could make such requests. One Advisory Group member who made such a request is Robert Sauerwein, who requested to be moved from the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge to the Sub-Group on Measurement of Immune Responses Pre- and Post-Challenge. I have done that, in response to his request. Meanwhile, Sudhanshu Vrati has requested to be moved from the Sub-Group on Measurement of Immune Responses Pre- and Post-Challenge to the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. I have done that as well.

The purpose of this email is to ask you if you are willing and are able to care out the time to be the “Lead” for the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. To serve this role, you will need to coordinate with the other members of that Sub-Group (Kanta and Sudhanshu) to finalize your recommendations of the virological and molecular methods to be used. You and your Sub-Group will then need to write up the Methods and Conclusions to be sent to me to collate into the overall report to be submitted to the Secretariat. One of the big issues will be for you and the team to propose what to do with volunteers who remain RT-PCR-positive but their cultures are negative for recovery of SARS-CoV-2. Are those volunteers shedding RNA fragments only, and these individuals are not infectious? Or should they be considered infectious?

If for any reason you cannot commit to serve as the Lead on the Sub-Group on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge, please let me know as quickly as possible.

I look forward to working with you.

Warm regards,

Mike

Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
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Founder & Former Director, Center for Vaccine Development (1974)
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Email: mlevine@som.umaryland.edu
All,

Please find a summary of the clinical working group discussion meeting from this morning. The majority of the discussion centered around what the endpoint of a challenge model would look like. It will be important that a challenge model has reproducible endpoints that occur with relatively high frequency. What the endpoints are may affect the usefulness of the model for down-selection of candidate vaccines and accelerated approval. Please take a look - I look forward to more discussion tomorrow.

All the best,
Anna

Anna Durbin, M.D.
Professor, International Health

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On May 4, 2020, at 5:14 PM, Levine, Myron <Mlevine@som.umd.edu> wrote:

Dear all:
The purpose of this note is to suggest some key AGENDA items for Discussion tomorrow during our weekly Advisory Group videoconference. We only have one hour and we have four Subgroups and lots of loose ends. Accordingly, I propose that tomorrow we focus mainly on the remits of the Subgroup on Clinical Trial Issues and of the Subgroup on Challenge Virus Strain Issues. For the former an update on issues that the Details of Study Design Team have been discussing would be of particular interest and importance. Some of the ultimate recommendations of that Team will have bearing on virus strain selection (e.g., fully virulent low passage versus, moderate passage, versus genetically attenuated). Team members will have an opportunity to make individual comments. Time willing, we may also be able to fit in a short synopsis of early work of the Infection Control Team. On the next videoconference we will have input in greater depth from that Team.

Next on the Agenda we will have a progress report from the Subgroup on Challenge Virus Strain Issues, in particular on information to be shared by the Challenge Virus Strain Selection Team.

Depending on remaining time we can have brief updates from the other two Subgroups including the Subgroup on Measurement of Immune Responses Pre- and Post-Challenge and the Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. The next teleconference will focus more closely on the work of these two Subgroups.

I propose 5 minutes on more general updates about COVID-19 disease and SARS-CoV-2 relevant to establishing a maximally safe challenge model. It seems that every week there is some important new clinical development. Particularly, a brief update from WHO or a well-wired Advisory Group member on any promising therapeutic breakthroughs will be welcome.

In the remaining time before bringing the meeting to a close, I would request our WHO Secretariat, Ana Maria Henao Restrepo and Phil Krause, to provide updates, guidance and to advise us on expected timelines for the deliverables.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.  
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Clinical Protocol working Group – Summary of first working group discussions

Below is a summary of individual and our group discussions around various elements to be considered in developing a challenge model for SARS-CoV-2. Most of the discussion centered around what would be appropriate endpoints of a challenge model (infection model vs illness model). Highlights around that discussion are presented in more detail below. Where general agreement was reached is indicated. Items 1.1.4 – 1.1.8 were not discussed but comments were solicited from a draft document that was circulated.

1.1 ELEMENTS OF PROTOCOL

1.1.1 Volunteer selection
- Normal healthy volunteers (exclusion of co-morbidities)
- Mental health screening due to burden of long stay in isolation unit)
- **Age range: a consensus was reached that volunteers 18 – 25 should be enrolled.** This was done by polling the group. Members felt that enrolling subjects older than 25 could increase the risk to the volunteer
- Gender balance: Some members felt it would be prudent to begin enrolling a greater number of women for safety reasons. Others did not feel strongly on this point. Does WHO have epidemiological data on incidence of disease by age and gender or incidence of infection by age and gender?

1.1.2 Size of initial groups
There was some consensus that the initial challenge should involve smaller groups (≤ 5) to assess safety of the challenge dose. If the safety and clinical endpoints profiles are acceptable, then dose expansion can occur to confirm the profiles and better assess the incidence of symptoms/endpoints. If the symptom profile or virologic profile do not occur in a sufficient number of subjects, then dose escalation could occur. During initial challenge and/or up-titration, preliminary safety endpoints can be assessed when viral loads and /or symptoms begin to regress (rather than waiting for complete resolution).

1.1.3 Endpoints to be achieved with SARS-CoV-2 challenge model.
The majority of our discussion was around endpoints of a challenge model. This generated great discussion and consensus was not achieved. The following is a summary of our discussion. This first consideration we came to was can we develop different challenge models for different purposes.? Two such models were discussed. The first was an infection model. The second was an illness model. Some discussion points and pros/cons that were discussed are presented below. The model should produce the defined endpoint in a relatively high proportion of challenged naïve subjects (≥ 70%) to minimize the number of volunteers needed in the study.

1.1.3.1 Infection model:
- The endpoint is recovery of challenge virus from the nasopharynx or oropharynx
- Virus would be quantified, preferably by both PCR and culture.
- This model would presumably be safer and may require fewer volunteers if clinical endpoints cannot be achieved in a sufficient number of young healthy volunteers without inducing more severe disease in others.
• This model may not be able to differentiate between vaccines for down-selection if the vaccine does not affect replication of the upper respiratory tract. It may not be sufficient from a regulatory perspective for accelerated approval of a vaccine.

1.1.3.2 Illness Model
• The endpoint would be a constellation of clinical signs or symptoms that constitute a “case definition”. The model for this would be influenza challenge studies and the endpoint would be a type of “influenza-like” illness.
• The clinical endpoint case definition could evolve as data are collected from the first challenge studies. What symptoms do subjects develop? How long do symptoms last? What proportion of subjects develop symptoms that could define a illness endpoint.
• Quantification of virus would be included in the endpoints.
• Careful up-titration of viral dose should aim to show degree to which spectrum of disease is predictable at even low doses of inoculum. Wide variations in disease severity should prompt a pause in up-titration and assessment of reasons for unexpected severity.
• Pros of this model is that it may better assess which vaccines should move forward and which should not. It may be more acceptable to regulatory authorities for an accelerated approval pathway.
• Cons: there may not be a dose-ranging effect with up-titration and we may not be able to define a dose that induces an acceptable clinical case definition.

It is important to note that in development of the challenge model, we may prefer one model over the other but, that we may not be able achieve the ideal model. The development of the model should be iterative with reassessment of what type of model can be achieved as dose ranging and dose expansion occur.

1.1.4 Aims of different cohorts included in a challenge model experiment
• Naïve participants: (i) develop model of infection against which to test vaccines +/- other interventions, (ii) risk of transmission (especially during asymptomatic infection)
• Previously exposed participants: risk of re-infection, CoP and
  o Risk of re-infection should be disaggregated into risk of asymptomatic SARS-CoV-2 reinfection and symptomatic SARS-CoV-2 infection.

1.1.5 Method of administration
There was general consensus to use droplet administration and not nasal spray or aerosol. This was to reduce the likelihood that the challenge virus would be deposited in the lower respiratory tract.

1.1.6 Discharge criteria
• Consensus that we must reduce the risk to third parties to as near zero as possible. To this, we anticipate requiring inpatient stays of 3 – 4 weeks.
• Can a correlate between PCR titer and infectious (replicating) virus be established from current clinical cases. If so, discharge could occur sooner. Or if,
the studies have the capability of performing virus culture, may be able to
discharge when replicating virus is no longer detected. This would require BSL-3.

1.1.7 Laboratory studies
- Should include planned sample collection for study of disease pathogenesis,
  immunological response, CoP
- Must be done under guidelines for blood collection limits in ill patients

1.1.8 Treatment protocols
- Remdesivir is now considered standard of care for SARS-CoV-2 infection in the
  US. Must include criteria in the protocol for initiation of remdesivir (or other
  drug(s) that may show efficacy against SARS-CoV-2, and revise treatment criteria
  as new data emerge. This does not mean all subjects would receive treatment –
  it would be based on treatment guidelines that would be in place at the time of
  the challenge.
Dear Maria,

I'm happy to participate in the subgroup.

One question, we only provide suggestions or we need also to do some tests in our labs.

Best regards,
Zhengli,

----原始邮件-----
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收件人:"John Treanor@URMC.Rochester.edu" <John_Treanor@URMC.Rochester.edu>, "GSELL, Pierre" <gsellp@who.int>, "kanta.subbarao" <kanta.subbarao@influenzacentre.org>, "Dsmall@som.umaryland.edu", "MAFUNGA, Neddy" <mafungan@who.int>, "robert.sauerwein@radboudumc.nl" <robert.sauerwein@radboudumc.nl>, "Halvor.Sommerfelt@uib.no" <Halvor.Sommerfelt@uib.no>, "(SPmig) Mimi Darko" <b(6)@yahoo.co.uk>, "b(6)@gmail.com" <b(6)@gmail.com>, "S.Balasingam@wellcome.ac.uk" <S.Balasingam@wellcome.ac.uk>, "C.Weller@wellcome.ac.uk" <C.Weller@wellcome.ac.uk>, "Vrati@rcb.res.in" <Vrati@rcb.res.in>, "D.King@wellcome.ac.uk" <D.King@wellcome.ac.uk>, "Mlevine@som.umaryland.edu" <Mlevine@som.umaryland.edu>, "zlshi@wh.iov.cn" <zlshi@wh.iov.cn>, "philip.krause@fda.hhs.gov" <philip.krause@fda.hhs.gov>, "punnee.pit@mahidol.ac.th" <punnee.pit@mahidol.ac.th>, "peter.kremsner@uni-tuebingen.de" <peter.kremsner@uni-tuebingen.de>, "(SPmig) Rosanna Lagos" <rosanna.lagos@adsl.tie.cl>, "b(6)@gmail.com" <b(6)@gmail.com>, "zeb.jamrozik@monash.edu" <zeb.jamrozik@monash.edu>, "vicente.estrada@salud.madrid.org" <vicente.estrada@salud.madrid.org>, "Stanley Plotkin <stanley.plotkin@vaxconsult.com>, "adurbin1@jhu.edu" <adurbin1@jhu.edu>, "LITTNER, Katherine" <littlerk@who.int>, "RIVEROS BALTA, Alina Ximena" <laurielx@who.int>
抄送:
主题: Proposed subgroups WHO Advisory Group on Human Challenge Studies
Dear Stig,

Many thanks for sharing this information and for the opportunity to present the work that WHO is leading regarding SARS CoV2 - Immunology and animal models.

As this is a team effort, I have taken the liberty to copy my colleagues Cesar Velasco, Simon Funnell, Ximena Laurie and Pierre Gsell, who contribute and coordinate this area of work together with Bill.

Please find attached the slides from the presentation by Dr. Sigrid Schuster from the WHO.SWISS. The presentation includes diagrams and data tables.
Perhaps you can consider inviting them at least for this session of the meeting?

With thanks and kind regards,

Ana Maria

From: Stig Tollefsen <stig.tollefsen@cepi.net>
Sent: Tuesday, May 5, 2020 11:12 AM
To: External Partner - Barrett Alan <abarrett@utmb.edu>; Alash’s Abimiku <aabimiku@ihv.umaryland.edu>; Allouche, Ali <Ali.allouche@takeda.com>; christian.brecho <christian.brecho@pasteur.fr>; cbrecho <cbrecho@usf.edu>; happic <happic@run.edu.ng>; Schmaljohn, Connie (NIH/NAID) [E] <connie.smichaljohn@nih.gov>; Daniel Brassere [b(6)] b6@gmail.com; [SPmig] Mimi Darko <b(6) b6@yahoo.co.uk>; dongxp238 <dongxp238@sina.com>; External Partner - REES Helen <hrees@wrhi.ac.za>; Damon, Inger K. (CDC/DDID/NEZID/DHCP) <iad7@cdc.gov>; James Robinson <b(6) b j@outlook.com>; Jean Lang <Jean.Lang@sanoiphastus.com>; JHHOF1 <jvhoof1@its.jnj.com>; John Edmunds <john.edmunds@lshtm.ac.uk>; Josie Golding <j.golding@wellcome.ac.uk>; kneuzil <kneuzil@som.umaryland.edu>; Jansen, Kathrin <kathrin.jansen@pfizer.com>; Shibuya, Kenji <kenji.shibuya@kcl.ac.uk>; Michel De Wilde <b(6) b6@aol.com>; Levine, Myron <Mmeye@som.umaryland.edu>; Bryant, Paula (NIH/NAID) [E] <paula.bryant@nih.gov>; Penny Heaton <penny.heaton@gatesmri.org>; Peter Smith <peter.smith@lshtm.ac.uk>; philip.krause@fda.hhs.gov
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Subject: [EXT] CEPI SAC meeting May 13.

Dear CEPI SAC members, Ana Maria and others,

We hope that you are well.

This email is just to inform about the agenda for the SAC meeting scheduled for Wednesday 13th May 2020 from 1400 CET to 1700 CET. The meeting that was scheduled for the 12th of May is now cancelled. Cancellation should come in a separate calendar cancellation note.

Underneath is the proposed agenda for the meeting. The pre-reads will be uploaded to the SAC SharePoint site within the course of the week. A notification will be sent when the docs are ready.
<table>
<thead>
<tr>
<th>May 13</th>
<th>Agenda Item</th>
<th>Agenda Item: COVID-19</th>
<th>Presenter</th>
</tr>
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<tbody>
<tr>
<td>14:00 - 14:10</td>
<td></td>
<td>Welcome and brief introduction of today’s item</td>
<td>Helen, Richard</td>
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<tr>
<td>14:10 - 14:20</td>
<td>#1</td>
<td>The ACT Accelerator</td>
<td>Richard</td>
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</tbody>
</table>
| 14:20 - 14:50 | #2 | Advances in scientific knowledge SARS CoV2- Immunology and animal models;  
- Q: From the knowledge how does this impact which candidates likely to be the most successful? | Bill |
| 14:50 – 15:50 | #3 | Review of current portfolio  
- Q: What are the gaps in the portfolio? | Nick |
| 15:50 – 16:30 | #4 | Review of Landscape  
- Q: What are the most promising candidates we should consider in the RfP? | Nick et al. |
| 16:30 - 16:40 | #5 | Solidarity 3 protocol | Ana Maria |
| 16:40 – 17:00 |  | Final remarks | Helen, Melanie, Richard |

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<tr>
<th>Parking lot</th>
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<tbody>
<tr>
<td>August TC</td>
<td>Non Covid portfolio</td>
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<tr>
<td>August TC</td>
<td>CEPI 2.0</td>
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</table>

We’d also like to inform you that the planned F2F meeting in August will now also be a TC meeting.

If you have problems with accessing the SharePoint site or other IT related issues with the CEPI content please contact it@cepi.net.

Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI New vaccines for a safer world

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This e-mail and any attachments may contain confidential and/or privileged information. If you are not the intended recipient or have received this e-mail in error, please notify the sender immediately and destroy this e-mail. Any unauthorized copying, disclosure or distribution of the material in this e-mail is strictly prohibited.
Dear all:

I am sending these two items on behalf of Anna Durbin and the Subgroup on Clinical Trial Issues. One is the draft agenda that she prepared before yesterday’s meeting of that Subgroup and the other is her post-meeting summary.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
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Clinical protocol working group

1 PROTOCOL SYNOPSIS FOR DEVELOPMENT OF COVID-19 HUMAN CHALLENGE MODEL

1.1 ELEMENTS OF PROTOCOL

1.1.1 Volunteer selection.
Early epidemiologic data show that males, even young males, appear to be more susceptible to disease than women.
- Should first enrollment include more women than men for safety reasons?
- Should we try to acquire more data regarding the incidence of disease in males compared to females, including younger populations?

What is the age range of volunteers who should be enrolled? The concern is that the risk of disease on a population level increases with older age, particularly those > 60 years of age. However, a significant burden of disease occurs in those 35 – 60.
- 18 – 25?
- 18 – 30?
- 21 – 25 or 30

1.1.2 Size of initial groups – what is the appropriate size?
For safety reasons, should smaller groups be enrolled (≤ 5 volunteers) to assess safety of challenge dose. If safety and clinical endpoints profiles are acceptable, can then expand to include a greater number of subjects.

1.1.3 Naïve vs naïve + previously exposed in initial cohorts. Including some subjects who have documented previous infection with SARS-CoV-2 can provide important data on risk of re-infection, CoP. Additional experiments could also include placebo controls to assess transmission of virus.

1.1.4 Clinical Endpoints: What are the appropriate pre-defined clinical endpoints of a suitable challenge model? Appropriate case definition for clinical endpoints of SARS-CoV-2 challenge model should include a reproducible clinical endpoint that can be achieved in a high proportion of susceptible volunteers should be the goal.
- Should include the detection of SARS-CoV-2 virus in upper respiratory tract
- Consider inclusion of laboratory markers of SARS-CoV-2 infection such as lymphopenia, elevated inflammatory markers (CRP, d-dimer, IL-6).
- Include U/S of lungs regularly (prior to symptom development)? U/S machine can be kept on unit without requiring subject transport to imaging suite. Should CT or MRI be required, the subject would require transport.
- We don’t know enough about the spectrum of illness to know if the severity of illness is dose dependent. Will the spectrum of disease be broad at even low doses of inoculum? If so, this it will be difficult to develop a model with an acceptable safety profile.

1.1.5 Dose levels: What dose to start with?
- Can we extrapolate from animal models?
• Can we extrapolate from influenza challenge models in which subjects have some pre-existing immunity to influenza?
• Will likely need to identify dose levels to be tested so that the product can be vialled in single dose vials. Otherwise, product will have to be prepared on site and this presents risks to those preparing the product, particularly if the product needs to be prepared under BSL-3.
• Would likely start with low dose, evaluate clinical response, and decide to dose expand or dose escalate
• Method of administration: droplet vs nasal spray. The smaller the size of the particle administered, the greater the likelihood it can be deposited in the lower respiratory tract possibly resulting in more severe illness.

1.1.6 **Discharge criteria:** How to determine when to discharge subject from inpatient unit
• Can we rely on PCR? Subjects may be PCR -positive for several weeks. Can subjects be kept in patient for 3 – 4 weeks, under aerosol precautions?
• Can a correlate between PCR titer and infectious virus be established from current clinical cases. If so, discharge could occur sooner.

1.1.7 **Laboratory studies:** Should include planned sample collection for study of disease pathogenesis, immunological response, CoP
• Must be done under guidelines for blood collection limits in ill patients.

1.1.8 **Treatment protocols:** Remdesivir is now considered standard of care for SARS-CoV-2 infection. Must include criteria for initiation of remdesivir (or other drug(s) that may show efficacy against SARS-CoV-2

1.2 **Unit Requirements for the Conduct of SARS-CoV-2 Challenge Models**

1.2.1 **Infection control requirements**
• Aerosol precautions. Clinical cases are kept under aerosol precautions. Rooms are under negative pressure with all staff in full PPE (PAPRs (or N-95 with face mask), gowns, gloves. Should have designated areas for donning and doffing PPE.
• Protocols will be needed for subjects who decide they do not want to remain in the study. Can the units be deemed “under quarantine” such that subject could withdraw from study but would remain on unit? How to ensure they would not expose others?

1.2.2 **Medical Expertise / Support care**
• SARS-CoV-2 challenge study should be conducted in facility that has available critical care facilities and staff. Subjects who develop signs of moderate to severe illness may require extensive monitoring and possible supplemental oxygen or ventilatory &/or cardiovascular support. In addition, the site should have the capability to evaluate other complications of SARS-CoV-2 infection such as vascular complications. These should be available on site or at an adjacent site to which the subject could be transferred quickly.
Clinical Protocol working Group – Summary of first working group discussions

Below is a summary of individual and our group discussions around various elements to be considered in developing a challenge model for SARS-CoV-2. Most of the discussion centered around what would be appropriate endpoints of a challenge model (infection model vs illness model). Highlights around that discussion are presented in more detail below. Where general agreement was reached is indicated. Items 1.1.4 – 1.1.8 were not discussed but comments were solicited from a draft document that was circulated.

1.1 ELEMENTS OF PROTOCOL

1.1.1 Volunteer selection
- Normal healthy volunteers (exclusion of co-morbidities)
- Mental health screening due to burden of long stay in isolation unit
- Age range: a consensus was reached that volunteers 18 – 25 should be enrolled. This was done by polling the group. Members felt that enrolling subjects older than 25 could increase the risk to the volunteer
- Gender balance: Some members felt it would be prudent to begin enrolling a greater number of women for safety reasons. Others did not feel strongly on this point. Does WHO have epidemiological data on incidence of disease by age and gender or incidence of infection by age and gender?

1.1.2 Size of initial groups
There was some consensus that the initial challenge should involve smaller groups (≤ 5) to assess safety of the challenge dose. The very first participants should be challenged one by one, as a preliminary demonstration of safety. Subsequently, in small groups, if the safety and clinical endpoints profiles are acceptable, then dose expansion can occur to confirm the profiles and better assess the incidence of symptoms/endpoints. If the symptom profile or virologic profile do not occur in a sufficient number of subjects, then dose escalation could occur. During initial challenge and/or up-titration, preliminary safety endpoints can be assessed when viral loads and/or symptoms begin to regress (rather than waiting for complete resolution).

1.1.3 Endpoints to be achieved with SARS-CoV-2 challenge model.
The majority of our discussion was around endpoints of a challenge model. This generated great discussion and consensus was not achieved. The following is a summary of our discussion. This first consideration we came to was can we develop different challenge models for different purposes? Two such models were discussed. The first was an infection model. The second was an illness model. Some discussion points and pros/cons that were discussed are presented below. The model should produce the defined endpoint in a relatively high proportion of challenged naïve subjects (≥ 70%) to minimize the number of volunteers needed in the study.

1.1.3.1 Infection model:
- The endpoint is recovery of challenge virus from the nasopharynx or oropharynx
- Virus would be quantified, preferably by both PCR and culture.
- This model would presumably be safer and may require fewer volunteers if clinical endpoints cannot be achieved in a sufficient number of young healthy volunteers without inducing more severe disease in others.
This model may not be able to different between vaccines for down-selection if the vaccine does not affect replication of the upper respiratory tract. It may not be sufficient from a regulatory perspective for accelerated approval of a vaccine.

- An infection model may, however, be useful for (i) selecting among multiple vaccines for larger field trials (if some vaccines suppress viral replication significantly more than others) aimed at reducing transmission/herd immunity, (ii) investigating correlates of protection (e.g., by comparing challenge of naive vs. recovered) even if this protection is to infection rather than disease, (iii) investigating viral dose-severity relationships (presumably at lower doses), (iv) clarifying transmission risks posed by asymptotically infected individuals.

1.1.3.2 Illness Model

- The endpoint would be a constellation of clinical signs or symptoms that constitute a "case definition". The model for this would be influenza challenge studies and the endpoint would be a type of "influenza-like" illness.
- The clinical endpoint case definition could evolve as data are collected from the first challenge studies. What symptoms do subjects develop? How long do symptoms last? What proportion of subjects develop symptoms that could define a illness endpoint.
- Quantification of virus would be included in the endpoints.
- Careful up-titration of viral dose should aim to show degree to which spectrum of disease is predictable at even low doses of inoculum. Wide variations in disease severity should prompt a pause in up-titration and assessment of reasons for unexpected severity.
- Pros of this model is that it may better assess which vaccines should move forward and which should not. It may be more acceptable to regulatory authorities for an accelerated approval pathway.
- Cons: there may not be a dose-ranging effect with up-titration and we may not be able to define a dose that induces an acceptable clinical case definition.

It is important to note that in development of the challenge model, we may prefer one model over the other but, that we may not be able achieve the ideal model. The development of the model should be iterative with reassessment of what type of model can be achieved as dose ranging and dose expansion occur.

1.1.4 Aims of different cohorts included in a challenge model experiment

- Naive participants: (i) develop model of infection against which to test vaccines +/- other interventions, (ii) risk of transmission (especially during asymptomatic infection)
- Previously exposed participants: risk of re-infection, CoP and
  - Risk of re-infection should be disaggregated into risk of asymptomatic SARS-CoV-2 reinfection and symptomatic SARS-CoV-2 infection.

1.1.5 Method of administration

There was general consensus to use droplet administration and not nasal spray or aerosol. This was to reduce the likelihood that the challenge virus would be deposited in the lower respiratory tract.
1.1.6 Discharge criteria

- Consensus that we must reduce the risk to third parties to as near zero as possible. To this, we anticipate requiring inpatient stays of 3 – 4 weeks.
- Can a correlate between PCR titer and infectious (replicating) virus be established from current clinical cases. If so, discharge could occur sooner. Or if, the studies have the capability of performing virus culture, may be able to discharge when replicating virus is no longer detected. This would require BSL-3.

1.1.7 Laboratory studies

- Should include planned sample collection for study of disease pathogenesis, immunological response, CoP
- Must be done under guidelines for blood collection limits in ill patients

1.1.8 Treatment protocols

- Remdesivir is now considered standard of care for SARS-CoV-2 infection in the US. Must include criteria in the protocol for initiation of remdesivir (or other drug(s) that may show efficacy against SARS-CoV-2, and revise treatment criteria as new data emerge. This does not mean all subjects would receive treatment – it would be based on treatment guidelines that would be in place at the time of the challenge.
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Subject: CEPI SAC meeting May 13.

Dear CEPI SAC members, Ana Maria and others,

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<td>16:30 - 16:40</td>
<td>#5 Solidarity 3 protocol</td>
<td>Ana Maria</td>
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<tr>
<td>16:40 – 17:00</td>
<td>Final remarks</td>
<td>Helen, Melanie, Richard</td>
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<td>Non Covid portfolio</td>
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<td>August TC</td>
<td>CEPI 2.0</td>
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</table>

We’d also like to inform you that the planned F2F meeting in August will now also be a TC meeting.
If you have problems with accessing the SharePoint site or other IT related issues with the CEPI content please contact it@cepi.net.

Best wishes
Stig

STIG TOLLEFSEN
Head of Strategic Science

CEPI New vaccines for a safer world

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Dear colleagues - please find attached two documents from the Subgroup on Challenge Virus Strain Issues for today's discussion.

Best wishes,
Kanta

[cid:image001.png;image002.jpg;Points to consider in selecting a challenge virus.docx;Points to consider in identifying manufacturers of a challenge virus.docx]
Dear all:

The purpose of this note is to suggest some key AGENDA items for Discussion tomorrow during our weekly Advisory Group videoconference. We only have one hour and we have four Subgroups and lots of loose ends. Accordingly, I propose that tomorrow we focus mainly on the remits of the Subgroup on Clinical Trial Issues and of the Subgroup on Challenge Virus Strain Issues. For the former an update on issues that the Details of Study Design Team have been discussing would be of particular interest and importance. Some of the ultimate recommendations of that Team will have bearing on virus strain selection (e.g., fully virulent low passage versus, moderate passage, versus genetically attenuated). Team members will have an opportunity to make individual comments. Time willing, we may also be able to fit in a short synopsis of early work of the Infection Control Team. On the next videoconference we will have input in greater depth from that Team.

Next on the Agenda we will have a progress report from the Subgroup on Challenge Virus Strain Issues, in particular on information to be shared by the Challenge Virus Strain Selection Team.

Depending on remaining time we can have brief updates from the other two Subgroups including the Subgroup on Measurement of Immune Responses Pre- and Post-Challenge and the Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge. The next teleconference will focus more closely on the work of these two Subgroups.

I propose 5 minutes on more general updates about COVID-19 disease and SARS-CoV-2 relevant to establishing a maximally safe challenge model. It seems that every week there is some important new clinical development. Particularly, a brief update from WHO or a well-wired Advisory Group member on any promising therapeutic breakthroughs will be welcome.

In the remaining time before bringing the meeting to a close, I would request our WHO Secretariat, Ana Maria Henao Restrepo and Phil Krause, to provide updates, guidance and to advise us on expected timelines for the deliverables.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.
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WARNING: This message originated from outside the Northern/Melbourne/Western Health e-mail network. The sender cannot be validated. Caution is advised. Contact IT Services for more information.
Points to consider in selecting a SARS-CoV-2 challenge virus strain

Background:
A challenge virus should be isolated from a healthy subject with a complete medical history. It will have to be isolated in a qualified cell line and manufactured under cGMP conditions. Coronaviruses acquire genetic variation by mutation and recombination and mutations can emerge as a consequence of passage in cell culture.

Assumptions:
- The challenge virus pool will have to be generated under cGMP conditions in a qualified cell line (likely Vero cells)
- More than one virus should be selected in case growth or yield differs
- The virus will be passaged about 5-10 times in the manufacturing process

Information we need for selecting a virus:
- What is the extent of difference in the spike/RBD in the different clades that are dominant in different parts of the world?
- What mutations/deletions are attributed to cell culture passage?

Criteria in selecting a virus:
- Should represent as close to a consensus sequence for the selected clade
- Select one or two viruses from each of the dominant clades

What will be needed:
- Original clinical material from which the virus was isolated/sequenced so that the virus can be re-isolated in qualified cells.
- Virus isolate will have to be plaque purified X3 or purified by limiting dilution.
- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.

Not addressed
- How to bring it out of BSL3?
- How long it will take to manufacture and release a challenge virus pool?

Advice received to date:
There are 2 main lineages of SARS-CoV-2 (A and B) that can then be subdivided into a number of component lineages. The bulk of the infections currently world-wide are derived from the B.1 lineage which is associated with the large Italian/European outbreak and now, most cases across the US are lineage B.1 after multiple introductions from Europe. The B.1 lineage has a mutation in spike (D614G) which is generally thought to be a significant mutation molecularly but there is debate as to its importance in terms of its effect on pathogenesis and transmissibility. Viruses at the base of the B.1 lineage can be selected with the D614G mutation but few other mutations.

If you were to do two variants, then possibly one of the original A viruses would make sense (it doesn’t have the D614G mutation). It is possibly diminishing in frequency but there are still cases in Europe and the USA (plus many other parts of the world).
A number of groups have seen a significant deletion in the spike protein associated with culturing in Vero cells. This removes the furin cleavage site (the feature of SARS-CoV-2 that sets it apart from SARS-CoV and is thought to be the most likely reason for its greater transmissibility). That would be one you certainly want to avoid.

A heterogeneous mixture of S1/S2 junction deletion mutants are inevitable if the SARS-CoV-2 is expanded in Vero 5 times. From our experience on the first Hong Kong strain, 3 passages in Vero E6 results in 30 to 40% of the virus plaques having various types of S1/S2 deletion mutations around the 685/686 cleavage site and also some mutations upstream at around 660. These mutants are generally less virulent in the hamster model. I would choose one purified plaque of S1/S2 deletion mutant which is stable on multiple passages in Vero cells as the challenge virus. This virus strain should be highly stable and standardized. Most importantly, this virus should be safer for the unvaccinated control volunteer.
Points to consider in identifying manufacturers for a GMP batch of SARS-CoV-2 challenge virus

**Background:**

Manufacture of a SARS-CoV-2 challenge virus pool will require a BSL3 manufacturing facility. The type of formulation and the dosing in the vials should be selected to minimize handling.

**Assumptions:**

- The challenge virus pool will have to be generated under cGMP conditions in a BSL3 facility
- More than one virus may have to be tested by the manufacturer in case growth or yield differs
- The virus will likely be passaged about 5-10 times in the manufacturing process. Perhaps the titer and volume should be predefined.
- Should we consider a reverse genetically derived virus with a genetic bar code to identify the virus.

**What will be needed:**

- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.
- The ability to formulate liquid versus lyophilised material and different virus concentrations.
- Information on how long it will take to manufacture and release a challenge virus pool.

**Not addressed**

- How to bring it out of BSL3?

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<th>Name of manufacturer</th>
<th>BSL3 available</th>
<th>Lyophilization/multiple dosing levels/time to manufacture</th>
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<tr>
<td>Ology Bioservices in Bethesda, USA (<a href="mailto:info@ologybio.com">HYPERLINK mailto:info@ologybio.com</a>)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>BioReliance in Scotland, UK</td>
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<tr>
<td>Meridian Life Sciences, USA</td>
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</tbody>
</table>
Dear Anna Maria,

I feel to make the best contribution in the "clinical team" and the "immunology" team. Stand-by for "Viral detection" being not my expertise.

Many thanks

Robert

Van: HENAO RESTREPO, Ana Maria <henaorestrepa@who.int>
Verzonden: vrijdag 1 mei 2020 8:56
Aan: John_Treanor@URMC.Rochester.edu; GSELL, Pierre <gsellp@who.int>; kanta.subbarao <kanta.subbarao@influenzacentre.org>; Dsmall@som.umaryland.edu; MAFUNGA, Neddy <mafungan@who.int>; Sauerwein, Robert <Robert.Sauerwein@radboudumc.nl>; Halvor.Sommerfelt@uib.no; (SPmig) Mimi Darko <mimidarko@yahoo.co.uk>; Halvor.Sommerfelt@uib.no; S.Balasingam@wellcome.ac.uk; C.Weller@wellcome.ac.uk; Vrati@rcb.res.in; D.King@wellcome.ac.uk; Mlevine@som.umaryland.edu; zkshi@wh.iov.cn; peter.krause@fda.fhs.gov; punnee.pit@mahidol.ac.th; peter.kremsner@uni-tuebingen.de; (SPmig) Rosanna Lagos <rosanna.lagos@adsl.tie.cl>; zeb.jamrozik@monash.edu; vicente.estada@salud.madrid.org; Stanley Plotkin <stanley.plotkin@vaxconsult.com>; adurbin1@jhu.edu; LITTLER, Katherine <littlerk@who.int>; RIVEROS BALTA, Alina Ximena <lauriex@who.int>

Onderwerp: Proposed subgroups WHO Advisory Group on Human Challenge Studies

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Thank you Anna-Maria for arranging this group. I think I will be happy to help on clinical trial design, but I do not consider myself an expert on facility biosafety containment.

Yaseen

Twitter @Yaseenarabi

Yaseen Arabi, MD, FCCP, FCCM, ATSF
Chairman, Intensive Care Department
Medical Director, Respiratory Services
Professor, College of Medicine
King Saud Bin Abdulaziz University for Health Sciences
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(b)(6)@yahoo.com

On Friday, May 1, 2020, 12:25:50 PM GMT+3, Peter Kremsner <peter.kremsner@uni-tuebingen.de> wrote:

Dear Ana-Maria, thanks for bringing us together. I feel myself best placed under 'Clinical trial parameters, design'. Greetings Peter

Zitat von "HENAO RESTREPO, Ana Maria" <henaorestrepoa@who.int>:
>

FDA-CBER-2020-5341-0004268
Hi Mike (and others),

Here are some suggested edits and comments on the most recent shared version of the document. I look forward to our next discussion.

Phil

---

From: Levine, Myron <Mlevine@som.umd.edu>
Sent: Wednesday, May 27, 2020 12:22 AM
To: mimi darkos@yahoo.com; rosanna.lagos@adsl.tie.cl; adurbin1@jhu.edu; Stanley Plotkin <stanley.plotkin@vaxconsult.com>; Treanor, John (OS) <John.Treanor@hhs.gov>; John_Treanor@URMC.Rochester.edu; Peter Kremersn (peter.kremsner@uni-tuebingen.de) <peter.kremsner@uni-tuebingen.de>; robert.sauerwein@radboudumc.nl; vicente.estrada@salud.madrid.org; punnee.pit@mahidol.ac.th; vrati@rcb.res.in; zlb@wh.iov.cn; Subbarao, Kanta <kanta.subbarao@influenzacentre.org>; zeb.jamrozik@monash.edu; d.king@wellcome.ac.uk; 'Halvor Sommerfelt' <Halvor.Sommerfelt@uib.no>; sabdulla@ihi.or.tz
Cc: HENAOSTREPO, Ana Maria <henaorestepoa@who.int>; Krause, Philip <Philip.Krause@fda.hhs.gov>; Charlie Weller <C.Weller@wellcome.ac.uk>; D.King@wellcome.ac.uk; Anastazia.OlderAguilar@gatesfoundation.org <Anastazia.OlderAguilar@gatesfoundation.org>; Mafunga, Neddy (mafungan@who.int) <mafungan@who.int>; Laurie, Ximena (lauriex@who.int) <lauriex@who.int>

Subject: NEW ITEMS AND AGENDA FOR THE 5th VIDEOCON of the WHO Advisory Group on Human Challenge Studies for COVID-19 Vaccines

Dear all,

Attached is an updated rough draft (version 4) of the report that ~90% complete report that has a numbering system for different sections and topics and sub-topics. This also has a few edits to the regulatory section about the GMP batch.

Read for content!!

I am also attaching on behalf of Anna Durbin the latest Informed Consent Form and a draft of a typical exam to ascertain volunteer comprehension.
THE AGENDA FOR THE CALL IS TO TRY TO GET FEEDBACK FROM YOU ON THE REPORT. I will have both version 3 and version 4 in front of me so when someone makes a comment, we will know what section the Advisory Group member is referring to with the comment.

Many thanks and warm regards to all.

Mike

Myron M. Levine, M.D., D.T.P.H.
Simon & Bessie Grollman Distinguished Professor
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FINAL REPORT

World Health Organization Advisory Group Tasked to Consider the Feasibility, Potential Value and Limitations of Establishing a Closely Monitored Challenge Model of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers

1. PREAMBLE

The COVID-19 Public Health Emergency of International Concern (PHEIC) that is presently traversing the planet as a global pandemic, has already taken an enormous toll of cases and fatalities in high-income countries in North America, Europe and East Asia, despite their sophisticated healthcare infrastructures, intensive care units and pulmonary intensive care capability. And COVID-19 is now invading sub-Saharan Africa, where many regions have few, if any, intensive care beds and pulmonary care support available. Medical and public health authorities worldwide agree on the critical importance of developing vaccines and monoclonal antibody preparations to prevent COVID-19 disease for all the world’s populations. There is a similar consensus to identify drugs and immunotherapies to curtail the progression to severe pulmonary disease and to lower case fatality rates. Therapies that may be effective include the antiviral drug remdesivir and plasma and immune globulin preparations containing neutralizing antibody from recovered COVID-19 patients.

Dozens of SARS-CoV-2 vaccine candidates are in preclinical development and several have already entered clinical trials. [ADDIN REFMR.REF]

Commented [KP1]: I strongly recommend preparing a (no more than) 1-2 page executive summary that covers the major findings of the consultation.

Commented [KP2]: There are other promising therapies as well, also under Intensive Investigation. In a WHO document, it may be better not to call out specific candidates, since it may be considered as an endorsement.

Commented [KP3]: More than two hundred

Commented [KP4]: There have been early promising results from other candidates also, and it may be impossible to fairly cite them all. In this case, Moderna hasn’t published any data, so it isn’t even clear to the scientific community that the summarized results are “highly encouraging” (read, for instance, William Haseltine’s editorial). I would stay away from calling out specific products, also to avoid creating the appearance of endorsement.

Commented [KP5]: These are regulatory details that may be unnecessary here.
2. WHO'S ACTIVITIES TO ACCELERATE COVID-19 VACCINE DEVELOPMENT AND CLINICAL TESTING
2.1. A multi-center, multi-vaccine randomized, placebo-controlled trial

The World Health Organization is playing a key role in assisting the development of tools to accelerate assessments of the efficacy of candidate vaccines to prevent COVID-19 disease. One tool is an overarching umbrella protocol for this includes a large multi-site, multi-vaccine, international placebo-controlled field trial to assess vaccine efficacy in high-risk adults that is designed to achieve rapid and scientifically rigorous evaluation of multiple vaccines – such as healthcare workers. [HYPERLINK "https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Fpublications-detail%2Ffan-international-randomised-trial-of-candidate-vaccines-against-covid-19&data=02%7C01%7C0%7C6f7f791926e04e03a97308d7eb8be46b%7C7c17009a620de461a88940312a395ca6%7C0%7C63732685970087094&sdata=GogK%2BWLFXhi9nWgwP2RqdhGROGS4cua%2F3KZ%7FfX4%3D&reserved=0"]

Under the common protocol in this trial, recruitment will ensue under the supervision of investigators at many experienced clinical trial sites in low- and middle-income countries, as well as in high-income countries in both the Northern and Southern hemispheres. In this way, momentum in generating data will be maintained, even if SARS-CoV-2 is found to exhibit influenza-like seasonality, with peak months of transmission being reversed between the Northern and Southern hemispheres.

2.2. Assessing a possible role for experimental challenge studies

Recognizing the helpful role that experimental challenge studies in healthy adult volunteers have played (and are still playing) in the development of other vaccines, ADDIN REFMGR.CITE ADDIN EN.CITE.DATA ADDIN EN.CITE.DATA ] some behavioral engineers, epidemiologists, biostatisticians and vaccinologists have advocated a role for such studies with virulent SARS-CoV-2. ADDIN REFMGR.CITE ADDIN EN.CITE.DATA ] However, SARS-CoV-2 is special. The severity of COVID-19 disease evidenced by its high case fatality in certain sub-populations (elderly, diabetics, hosts with pre-existing pulmonary and cardiac disease), occasional occurrences of severe disease requiring ventilator support in younger adults (without knowing the risk factors responsible), the increasing recognition of severe thromboembolic events in young adults, the high transmissibility of SARS-CoV-2 from person-to-person, and the virus’ ability to remain viable on some fomites for hours, ADDIN REFMGR.CITE ADDIN EN.CITE.DATA ] have all led some to explore the potential utility of these studies. The introduction mostly describes concerns about the disease, 2.2.1 focuses mostly on time for clinical trials without really covering the time for the challenge studies (but comes across as concluding that there is no benefit in accelerating timelines), 2.2.2 covers non-vaccine evaluation benefits of the studies, and 2.2.3 focuses on rescue therapy. But nowhere is there a clear exposition of the benefits of the studies in the context of evaluation of specific vaccines. I thought that the consultation was based on the idea that some of these aspects simply aren’t known, and thus we should openly figure out how these studies could be expedited and performed so that no stone is left unturned in the search for a COVID-19 vaccine.
Medicine for Ebola, the time required to go from virtually no clinical experience (August 2014) to convincing evidence of
efficacy (June 2015) was a period of 10 months.

The time from Phase 1 and 2 trial results that established the dose level and evidence of immunogenicity
(December 2014) until initiation of the field trial in Guinea (March 2015) was three months. This includes site
set-up.

The time period until the randomized controlled field trial provided clear evidence of efficacy was four
months (March through June 2015). Efficacy was revealed in the course of a pre-determined interim
assessment of safety and efficacy by an independent Data Safety Monitoring Board (DSMB). The DSMB
concluded that a randomized control group was no longer indicated.

It is important to appreciate that the field trial of efficacy of rVSVΔG-ZEBOV-GP was performed in Guinea, a
low-income country without a research infrastructure, clinical investigators or field staff experienced in the
tenets of Good Clinical Practice (GCP).[ADDIN REFMRG.CITE ADDIN EN.CITE.DATA ] In contrast, COVID-19
vaccines can be assessed in high-income countries with experienced clinical and laboratory research
staffs, as well as in LMIC.
In addition to the “Ebola ça Suffit” trial’s legacy of experienced clinical investigators in West Africa, there now exist multiple sites throughout sub-Saharan Africa with experienced clinical trial teams that could participate in a multi-center field efficacy trial to assess the efficacy of COVID-19 vaccines to generate data relevant to conditions in that geographic region of the world.

2.2.2. Contributions that a COVID-19 challenge model could make to eventual control of the disease even if the model would not accelerate the time required to achieve an EUA or licensure for a candidate vaccine.

Even if an experimental challenge model of SARS-CoV-2 does not shorten the time to obtain evidence of efficacy of a specific COVID-19 vaccine and to receive regulatory approval for wide-scale “compassionate use”, such a model could still yield important scientific insights that are not easily obtained through randomized, placebo-controlled field trials. These include controlled studies of whether a prior experimental clinical COVID-19 infection confers significant protection against clinical illness and shedding of virus upon the “veterans” upon re-challenge ~2 months later versus a naive control group. By extending the challenge time, this could help to document the period of protection. One could also assess whether IgG anti-spikes antibodies correlate with re-challenge protection. These observations would be of considerable values to public health strategists and epidemiologists who are now attempting to ascertain whether mild SARS-CoV-2 infections elicit immunity and the relation of the immunity to the type of antibodies being measured by most serological tests that are being used in serosociological studies. Furthermore, a volunteer challenge model would allow the kinetics of the viral infection and of the immune response, including the early innate response to be characterized.

2.2.3. “Rescue therapy” for volunteers who would participate in a COVID-19 challenge model.

The pace of generating evidence to confirm or refute the efficacy of certain anti-COVID-19 therapies (e.g., remdesivir, plasma and Ig from recovered COVID-19 patients, etc.) from well-conducted, randomized, controlled clinical trials is extremely rapid and was monitored by the Advisory Group during the weeks of its deliberations. [ADDIN REFMGR.CITE
<Refman><Cite><Author>Kupferschmidt</Author><Author>Year>2020</Year><RecNum>18925</RecNum><IDText>Race to find COVID-19 treatments accelerates</IDText><MDL Ref_Type="Journal">Ref_Type=Journal</Ref_Type><Ref_ID>18925</Ref_ID><Title_PRIMARY>Race to find COVID-19 treatments accelerates</Title_PRIMARY><Authors_PRIMARY><Author>Kupferschmidt,K.</Author><Author>Cohen,J.</Author><Authors_PRIMARY>Date_PRIMARY>2020/3/27</Date_PRIMARY><Abstract_Advance>Adenosine Monophosphate</Abstract_Advance><Keywords>adverse effects</Keywords><Keywords>alanine</Keywords><Keywords>analogs & derivatives</Keywords><Keywords>antiviral agents</Keywords><Keywords>Betacoronavirus</Keywords><Keywords>Biomedical Research</Keywords><Keywords>chloroquine</Keywords><Keywords>Clinical Trials as Topic</Keywords><Keywords>Coronavirus infections</Keywords><Keywords>drug combinations</Keywords><Keywords>drug therapy</Keywords><Keywords>epidemiology</Keywords><Keywords>humans</Keywords><Keywords>Hydroxychloroquine</Keywords><Keywords>Lopinavir</Keywords><Keywords>mortality</Keywords><Keywords>organization & administration</Keywords><Keywords>Pandemics</Keywords><Keywords>Pneumonia, Viral</Keywords><Keywords>Ritonavir</Keywords><Keywords>therapeutic use</Keywords><Keywords>world health organization</Keywords><Reprint_Not_In>File</Reprint_Not_In><Start_Page>1412</Start_Page><End_Page>1413</End_Page><Periodical>Science.</Periodical><Volume>367</Volume><Issue>6485</Issue><ISSN>ZZ_JournalStdAbbrev</ISSN><MDL ID="ZZ_WorkformID1"/></MDL></Ref>
On April 29, 2020, preliminary results were announced that the anti-viral drug remdesivir in a randomized, placebo-controlled, double blinded, multi-center international trial supported by the U.S. National Institutes of Health demonstrated that remdesivir-treated hospitalized patients with confirmed COVID-19 disease had their hospitalization duration shortened to 11 days compared to 15 days in placebo recipients. The difference in this primary aim was statistically significant. In the midst of a COVID-19 epidemic that is overwhelming the health care system such that there is a shortage of ICU beds and ventilators, what appears to be a modest efficacy of shortening length of hospitalization by four days can free up many ICU beds and increase the capacity of a teetering health care system to weather the storm through the peak of the epidemic. Thus, on May 1, 2020, the FDA issued an EUA for use of remdesivir in hospitalized cases of COVID-19 disease.

Relevant to providing information to advise the establishment of an experimental challenge model of SARS-CoV-2 infection in healthy adult volunteers, it is expected that by June 2020 data will become available to confirm or refute the efficacy of several new therapies in interrupting the progression of COVID-19 infection from mild or moderate illness to severe and fatal disease. Should one of these interventions or several in combination prove to be highly efficacious in stopping the progression from mild/moderate illness to severe COVID-19 disease, this would increase the feasibility of undertaking volunteer challenge models with wild type virus in young adults in a low-risk, narrow age group (e.g., 18-25 years of age). It would then bring a COVID-19 model closer, by comparison, to several other viral disease models. Nevertheless, a COVID-19 model will still have to grapple with the high transmissibility of the virulent agent and its Biosafety Level-3 status for some steps in the clinical procedures that would be constraining. This would be particularly true during the step of instilling the infective inoculum into the upper respiratory tract of volunteers.

3. WHY NOW FOR AN ADVISORY GROUP CONSIDER THE FEASIBILITY, POTENTIAL VALUE AND LIMITATIONS OF ESTABLISHING A CLOSELY MONITORED CHALLENGE MODEL OF EXPERIMENTAL COVID-19 INFECTION AND ILLNESS IN HEALTHY YOUNG ADULT VOLUNTEERS?

The World Health Organization considered April 2020 to be a propitious time to convene a multi-disciplinary group of experts from across the world to discuss from different perspectives the concept of volunteer challenge studies with SARS-CoV-2. The Advisory Group assembled included experts with experience in:

- The design and performance of human volunteer challenge models;
- SARS-CoV-2 virology;
- Measurement of human immune responses to SARS-CoV-2 and to other viruses;
- Clinical management of COVID-19 clinical disease in different global settings;
- Devising accelerated regulatory pathways to achieve compassionate use/deployment of vaccine under an Emergency Use Authorization (or its EMA equivalent) and to facilitate vaccine licensure;
- The GMP manufacture of virulent viruses under BSL-3 containment.

Collectively, the Advisory Group, whose members are listed in Appendix A, was tasked to consider the feasibility, utility, realistic timelines and approximate costs for the key steps to be taken to establish a closely-monitored experimental challenge model in healthy adult volunteers who would be administered attenuated or fully virulent SARS-CoV-2. The Advisory Group was divided into Subgroups and two of the Subgroups were further divided into two Teams each for the members to address in detail specific procedures to be codified and logistical obstacles to be overcome to perform such challenge studies. The Advisory Group proposed potential practical solutions to overcome or bypass the hurdles that they identified. The Advisory Group took into account not only the safety of the volunteers but also that of the clinical research staff and support staff, and the safety of household members and other close contacts of the volunteers after their discharge.

3.1 Terms of Reference
The Advisory Group was asked to discuss specific issues to be considered in establishing a closely monitored volunteer challenge model of attenuated or fully virulent SARS-CoV-2 virus. Examples of the issues addressed include:

- What level of physical containment is required to assure that there is no inadvertent escape and transmission of this highly virulent pathogen?
- If desirable, can local health authorities establish legal Quarantine of the study site facility (e.g., a physical containment Research Isolation Ward)? Is there a legal basis for Quarantine in the jurisdiction where the challenge study will take place?
- Can the baseline health status of each subject be confidently documented prior to challenge to assure that they have no known predisposing risk factors associated with progression to severe COVID-19 illness?
- Can the follow-up and post-discharge monitoring of every subject be assured?
- What is the risk to household contacts and the larger community if the pathogen were inadvertently to escape containment and be transmissible to non-consented innocent bystanders?
- How will the challenge virus be administered to the volunteers to assure delivery only to the upper respiratory tract (e.g., into the nares by pipette; large-drop aerosol? etc.).

3.2. Logistics, timelines and costs (examples of some specific tasks the Advisory Group discussed)

- Arranging manufacture of a GMP lot of virulent wild type SARS-CoV-2.
  - What SARS-CoV-2 strains (e.g., what clades and sub-clades) should be selected?
  - Where would the GMP batches of challenge viruses be prepared under BSL-3 containment?
  - Would there be a frozen liquid in vial formulation or a lyophilized formulation for challenge studies?
  - Where would the central repository be located for storing the vials of each GMP batch of challenge virus?
  - What would be the conditions of storage of the challenge virus vials at clinical study sites?
  - Would there be vials prepared containing the different inoculum levels to be used in a stepwise dose-escalation to minimize handling in the clinical situation?
- What clinical attack rate should the model aim to elicit and what type of clinical illness [signs and symptoms] is desired?
  - Target clinical attack rate
  - Description of the type of clinical illness to be expected
  - What severity of clinical illness and frequency of occurrence would be considered unacceptable?
- What are the key clinical endpoints?
- Timelines for a stepwise dose-escalation study with either fully virulent or attenuated SARS-CoV-2 virus.
  - Assuming that three different dose levels may have to be tested until a satisfactory attack rate of non-severe clinical illness is attained, what is the timeline for performing such a dose-escalation study?
    ▪ Consider the expected range and median incubation period from inoculation to onset of clinical illness.
    ▪ Take into account the expected duration of clinical illness.
    ▪ Take into account the expected range of duration of shedding.
    ▪ What will be the clinical criteria for discharge?
    ▪ What will be the virus shedding criteria for discharge (how many days of negative RT-PCR)?
- How much time should be set aside to prepare a summary for the Data Safety Monitoring Committee and for them to convene, review the data and provide a yes/no for proceeding to the next higher dose of virus.
- How much time is needed for disinfection and refurbishment of the Research Isolation Ward between volunteer groups at different dose levels.

3.3. Some uses of a model, if established

The Advisory Group will be tasked to identify some specific objectives and uses of challenge trials and to prioritize them. Examples, among others, could include:
• Does an initial clinical SARS-CoV-2 infection (due either to a fully virulent or to an attenuated virus) elicit significant protection against clinical illness following subsequent re-challenge with the same virus circa 6-8 weeks later?
• Is shedding of SARS-CoV-2 significantly diminished following re-challenge with the SARS-CoV-2?
• If clinical protection upon re-challenge is observed, does it correlate with serum IgG or mucosal IgA antibody responses to SARS-CoV-2 spike protein (or to the receptor binding domain of the spike)? Or with CD8 or CD4 cellular immune responses to SARS-CoV-2 antigens? Note that one of the unique opportunities offered by closely monitored experimental challenge studies in healthy adult humans is to identify immunologic correlates of protection that are not easily detectable in large-scale field trials. The uniqueness stems from the fact that not only can extensive and detailed immunologic responses be measured, but these are known at baseline and immediately prior to challenge, as well as following challenge; and these data are available for all vaccinees (or re-challenge veterans) and for all controls.
• Should one or more candidate vaccines be tested in an experimental challenge model that utilizes either virulent SARS-CoV-2 or a partially attenuated strain as the challenge organism? If a fully virulent strain is used, protection against clinical endpoints can be assessed, as well as efficacy in diminishing shedding of virus. If an attenuated strain is used, only efficacy against shedding may be measurable.

3.4. Other related issues

The Advisory Group will not discuss in depth ethical issues related to challenges with fully virulent SARS-CoV-2 as this is being addressed by a larger Ethics Committee of WHO that is considering many COVID-19 ethical issues.

3.5. Deliverables

1) The Advisory Group was asked to provide a report that addresses the points raised above, as examples, as well as additional issues and hurdles that were identified that would have to be overcome.

2) The Advisory Group will be expected to make recommendation on the feasibility of such a model and, if deemed feasible and appropriate, how the model should be used.

4. INTRODUCTION TO THE TASK

Figure 1 shows in schematic form provides an overview of some of the strategic steps and decision trees that must be grappled with in considering the establishment of a closely monitored experimental challenge model of SARS-CoV-2 virus infection and illness in volunteers. The first would be to select whether to begin with a putatively attenuated strain of SARS-CoV-2, such as a live attenuated vaccine candidate strain, or whether to utilize fully virulent strains of SARS-CoV-2. In practical terms this was a moot point when first discussed by the Advisory Group in April 2020, as the only attenuated vaccine strain of which the Advisory Group members were aware was an attenuating approach being pursued by Codagenix and the Serum Institute of India. However, the Advisory Group was not aware of such a strain having progressed to the point where it could be administered in clinical trials. If such a strain were to exist and if it infected volunteers and was shed for several days (including being detectable by tissue culture) in the presence or absence of clinical signs and symptoms, a re-challenge experiment could be designed to determine whether subsequent exposure of the volunteers to the same attenuated strain ~6 weeks later would be followed by shedding of virus compared to a control group of naive volunteers receiving the strain for the first time.

[ PAGE 4 ]

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In the absence of an attenuated SARS-CoV-2 virus being available to use, discussion thereafter focused on the issues associated with challenge of volunteers with a virulent SARS-CoV-2 virus. Some Advisory Group members were concerned that even as the discussions would go forth, clinical studies should not begin until there was a proven therapy shown to be efficacious in reliably arresting the progression of COVID-19 illness form a mild/moderate status to severe, complicated, potentially fatal illness. While that “gate” remained in the background in the discussions, the Advisory Group agreed that they would follow the progress of several therapeutic regimens that were in clinical trials. One that showed some degree of efficacy in hospitalized patients with severe COVID-19 disease was the antiviral drug remdesivir which significantly reduced the days of hospitalization from 15 days to 11 days compared to the placebo control group. While this seems a modest effect, in communities with surging epidemics of COVID-19 disease and a shortage of intensive care beds and ventilators, the ability to discharge patients after an average of 11 days rather than after 15 days frees up many hospital beds. Yet this effect of remdesivir does not offer an obvious “rescue” therapy should a challenged volunteer progress to severe clinical illness. The Advisory Group agreed that within several months there may appear therapies (e.g., Ig or plasma from convalescent patient donor, specific monoclonal antibodies, etc.) in the meantime, there was a consensus to address the specific main tasks required to be completed to initiate a clinical trial should a relevant efficacious therapeutic intervention become available in the meantime.

The Advisory Group next discussed two main uses for a SARS-CoV-2 challenge model once the initial dose/escalation was completed and an acceptable, predictable challenge dose was identified that could be used to answer specific questions. One use discussed was re-challenge of a group of volunteers who excreted SARS-CoV-2 and developed mild illness on an initial challenge 6 weeks earlier, along with a group of naive control volunteers. The hypothesis being tested would be that the immune responses manifested by the re-challenged volunteers following their initial challenge would be protective in significantly diminishing the shedding of SARS-CoV-2 and in significantly preventing clinical illness upon re-challenge compared to naive control volunteers. If significant protection was observed it would be possible to look for an immune response (e.g., IgG anti-spike protein antibodies) that correlated with protection. Many serological tests that are used in population-based surveys to estimate from seroprevalence the proportion of the population that has already encountered the SARS-CoV-2 virus use assays that measure IgG antibody to the SARS-CoV-2 spike protein. Many COVID-19 vaccine candidates are

Commented [KP12]: Could this study be self-controlled, since the initial challenge would be of naïve volunteers?
based on stimulating immune responses to this viral surface protein by which the virus attaches to the ACE-1 receptor on human respiratory tract epithelial cells and cells of other organs and anti-spike IgG exhibits virus neutralizing activity. Nevertheless, many public health officials would like to see more direct proof in humans that anti-spike antibody is a correlate of protection against both COVID-19 disease and viral shedding. A challenge model could provide such information. This information could also be relevant for assessing certain COVID-19 vaccines based on spike protein to determine whether the

The alternative discussed was the use of the model, once established, to assess preliminarily the efficacy of several different COVID-19 vaccines based on somewhat different concepts. For example, several vaccines are based on eliciting immune responses to a stabilized form of the SARS-CoV-2 spike protein, whether encoded by mRNA, DNA or one of several live vectors such as attenuated chimpanzee or uncommon serotypes of human adenovirus. Challenge with SARS-CoV-2 of a group of vaccinees and in a randomly allocated group of control volunteers who received placebo rather than vaccine would potentially allow an assessment of the vaccine in preventing clinical illness and of diminishing shedding of wild virus. If significant protection against endpoints and/or against shedding of wild virus was observed, it might be possible to identify a specific correlate of protection such as a subtype of IgG antibody or multifunctional effector T-cells.

4.1 Formation of Subgroups and Teams

To pursue its work-scope with appropriate concentration and mix of expertise, the members of the Advisory Group were divided into four Subgroups, of which two Subgroups were further divided into two Teams. Each Subgroup was assigned Lead. Thus, the Advisory Group pursued its work through the structure shown below.

WHO Advisory Group on Human Challenge Studies for COVID-19 vaccines
Advisory Group Chair: Myron M. (Mike) Levine

Subgroup on Clinical Trial Issues – Anna Durbin (Lead)
Details of Study Design Team - Anna Durbin (Lead), John J Treanor, Halvor Sommerfelt, Punnee Pitsutthum, Zem Jamrozik, Robert Sauerwein
Infection Control Team - Anna Durbin (Lead), Yasin Arabi, Peter Kremsner, John Treanor, Vicente Estrada, Salim Abdulla

Subgroup on Challenge Virus Strain Issues – Kanta Subbarao (Lead)
Challenge Virus Strain Selection Team – Kanta Subbarao (Lead), Zeng Li Shi, Sudhanshu Vrati

Potential Manufacturers of a GMP Batch of Challenge Virus Team – Kanta Subbarao (Lead), Delese Mimi Darko, Deborah King, Stanley Plotkin, John Treanor

Subgroup on Measurement of Immune Responses Pre- and Post-Challenge – Stanley Plotkin (Lead), Kanta Subbarao, Robert Sauerwein, Rosanna Lagos

Subgroup on Detection of SARS-CoV-2 in Clinical Specimens Post-Challenge – Zeng Li Shi (Lead), Kanta Subbarao, Sudhanshu Vrati

4.2 A Cautionary Two-Stage Approach

In the course of its deliberations, the Advisory Group concluded that following the recommendations of the Subgroup on Clinical Trials issues, the challenge model should be developed in two distinct Stages. The first Stage should take place under high levels of physical and biological containment and legal quarantine not only to protect the volunteers and the clinical trial staff, but also the household and other close contacts of the volunteers after their discharge from the isolation Unit. A High-Level Isolation Unit defines a healthcare facility specifically designed to provide safe, secure, high quality and appropriate care, with optimal infection containment and infection prevention and control procedures for a small number of patients (in this instance, challenged volunteers) who have (or may have) a Highly Infectious Disease (in this instance COVID-19).

The Stage 1 studies would undertake a dose-escalation of several different virus strains to identify a suitable challenge strain, an appropriate challenge dose and a careful assessment of the severity of clinical illness that
occurs and the duration of virus shedding. Performed in this way, the Stage 1 studies could be carried out either in geographic areas where there was little or no currently ongoing transmission of SARS-CoV-2 or in places where there was substantial transmission of COVID-19 disease occurring. The clinical isolation units performing the Stage 1 studies would also have to have ready access to intensive care should the need arise.

Once the model of closely-monitored SARS-CoV-2 experimental infection is established under Stage 1 conditions, the data would be reviewed to consider undertaking specific studies such as challenge/re-challenge to determine if an clinical initial infection confers protection against illness following a second deliberate exposure (versus controls) and to assess the efficacy of a candidate vaccine in preventing clinical illness and/or shedding of virus.

The Advisory Group recognized that very distinct results might be observed during the Stage 1 studies across a spectrum of clinical severity and virus infectivity that would guide the design of potentially larger Stage 2 studies that might involve more volunteers. If the several passages of the selected challenge viruses in tissue culture required to manufacture a GMP batch with sufficient doses at several different dose levels all showed that the viruses appeared to behave as attenuated viruses resulting in only infectivity but no clinical illness or only mild short-lived coryza-like symptoms and signs, it might be possible to consider undertaking Stage 2 challenges in a different type of physical and biological containment (albeit still under legal quarantine). However, even with a challenge model that causes little or no clinical illness and that might only be a model of virus infectivity, the step of direct inoculation of volunteers might still pose an issue with respect to whether or not that has to take place in an BSL-3 environment.

On the other hand, despite multiple passages needed to adapt the viruses to growth in tissue culture, the challenge virus strains may prove to retain considerable virulence such one or more volunteers progress to more severe clinical forms of COVID-19 illness. Some clinical manifestations of concern would include pneumonitis, a need for supplemental oxygen to maintain a physiologic level of arterial O2 saturation, need for a ventilator, highly elevated d-dimer levels accompanied by evidence of clotting in small or large blood vessels, or volunteers exhibiting highly elevated cytokine levels of pro-inflammatory cytokines and evidence of multi-organ inflammatory syndrome.

5. CLINICAL ISSUES

5.1. A Clinical Protocol Synopsis Prepared by the Subgroup on Clinical Trial Issues

The Details of Study Design Team of the Subgroup on Clinical Trial Issues discussed key elements for the development of a SARS-CoV-2 human challenge model. The charge of the Subgroup was to carefully consider how a SARS-CoV-2 challenge study could be conducted safely; what clinical end-points should be defined so that the model can be used successfully for its intended purposes, and what are the clinical and infrastructure supports that need to be in place for the protection of subjects and third parties.

6. ELEMENTS OF A CLINICAL PROTOCOL

6.1. VOLUNTEER SELECTION

Epidemiological data from the current SARS-CoV-2 pandemic demonstrate that adults ≥ 65 years of age are at greatest risk for developing severe COVID-19. However, severe disease can occur in adults of any age including in children. With a decrease in risk of severe disease occurring in younger age groups, adults ages 18 – 25 were deemed to be the most appropriate age group for enrollment. More epidemiologic data would be helpful to better define the risk of severe COVID-19 in this population and to better discern differences in morbidity due to SARS-CoV-2 by gender. Some data suggest that women are at lower risk of severe COVID-19 in ages < 65 years. The general inclusion criteria are discussed below.

[PAGE]
Normal healthy volunteers (exclusion of co-morbidities)
Mental health screening (due to burden of long stay in isolation unit)
Age range: a consensus was reached that volunteers 18 – 25 should be enrolled. This was done by polling the Subgroup members. Members concluded that enrolling subjects older than age 25 years would increase the risk to the volunteer
Gender balance: Some members suggested that it would be prudent to begin enrolling a greater number of women for safety reasons. Others did not support this view. There was agreement that both men and women, in some ratio should participate.

6.1.1. Inclusion/Exclusion Criteria

6.1.1.1. Inclusion Criteria (examples)
1. Adult male or non-pregnant female between 18 and 25 years of age, inclusive.
2. Good general health as determined by physical examination, laboratory screening, and review of medical history.
3. Available for the duration of the study.
4. Willingness to remain in the inpatient Isolation Unit until no longer infectious post-inoculation, which may be 3 weeks or longer.
   a. The number of days spent in the Isolation Unit pre-inoculation can be shortened by testing volunteers for COVID-19 infection by RT-PCR at several time-points prior to admission to the Isolation Unit to ensure that they are not asymptomatically infected. For example, they can be tested on day -14, on day -7 and at time of admission to the Isolation Unit (2 days prior to inoculation). The results of the day -2 sample would be known prior to inoculation with SARS-CoV-2. If a subject was already infected with SARS-CoV-2 during this time, they would not be enrolled in the study.
5. Sufficient understanding of the study and willingness to participate in the study as evidenced by passing a test of understanding and signing the informed consent document.
6. Females only: Female subjects of childbearing potential should be willing to use effective contraception. Reliable methods of contraception include hormonal birth control, condoms with spermicide, diaphragm with spermicide, surgical sterilization, intrauterine device, and abstinence (>6 months since last sexual encounter). All female subjects will be considered as having childbearing potential, except for those who have had a hysterectomy, tubal ligation, or tubal coil (at least 3 months prior to inoculation), or are considered to be post-menopausal, as documented by at least 1 year since last menstrual period.

6.1.1.2. Exclusion Criteria (examples)
A subject will be excluded from the study if any of the following criteria are met:

1. Females only: Currently pregnant, as determined by positive β-human chorionic gonadotropin (HCG) test, or breast-feeding.
2. Evidence of clinically significant neurologic, cardiac, pulmonary, hepatic, rheumatologic, autoimmune, or renal disease based on history, physical examination, and/or laboratory studies.
3. Behavioral, cognitive, or psychiatric disease that, in the opinion of the investigator, affects the subject’s ability to understand and cooperate with the requirements of the study protocol.
4. Screening laboratory values of Grade 1 or above for ANC, ALT, blood glucose, and serum creatinine, as defined in this protocol.
5. Elevated hemoglobin A1c level (HA1c) above laboratory normal limits
6. Any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of a subject participating in the trial, or would render the subject unable to comply with the protocol.
7. Any significant alcohol or drug abuse in the past 12 months that has caused medical, occupational, or family problems, as indicated by subject history.
8. History of a severe allergic reaction or anaphylaxis.
9. History of asthma
10. History of diabetes
11. History of arterial or venous thrombo-embolic disease
12. HIV infection, as indicated by screening and confirmatory assays.
13. Hepatitis C virus (HCV) infection, as indicated by screening and confirmatory assays.
14. Hepatitis B virus (HBV) infection, as indicated by hepatitis B surface antigen (HBsAg) screening.
15. Any known immunodeficiency syndrome.
17. Current use of anticoagulant medications (this does not include anti-platelet medication such as aspirin or non-steroidal anti-inflammatory medications).
18. Use of corticosteroids (excluding topical) or immunosuppressive drugs within 28 days prior to or following inoculation. An immunosuppressive dose of corticosteroids is defined as ≥ 10 mg of a prednisone equivalent per day for ≥ 14 days.
19. Receipt of a live vaccine within 60 days or a killed vaccine within 30 days prior to vaccination.
20. Asplenia.
21. Receipt of blood products within the past 6 months, including transfusions or immunoglobulin, or anticipated receipt of any blood products or immunoglobulin during the 28 days following inoculation.
22. Anticipated receipt of any investigational agent in the 28 days before or after inoculation.
23. Refusal to allow specimen storage for future research.
24. Abnormal chest x-ray that indicates pulmonary disease
25. Abnormal pulmonary function tests that indicate underlying pulmonary disease
26. Abnormal EKG that indicates prolonged Q-T, cardiac arrhythmia, evidence of ischemia or previous infarction, or other cardiac disease that, in the opinion of the investigator affects the subject's safety in participating in the trial

6.2. SIZE OF INITIAL GROUPS
There are numerous unknowns that must be addressed in developing a model for SARS-CoV-2. The range of clinical illness that could be induced by even the lowest dose of virus administered is unknown. Some subjects could not show any symptoms while others could become quite ill. This uncertainty mandates that dose selection proceed with the utmost caution. For this reason, the initial challenge inoculation (proposed as ~1x10^4 TCID50) should involve an initial group of few subjects (1-3) to assess safety of the challenge dose. If the safety profile is acceptable, then the next group could include more subjects (3-5) at the same dose level. Dose escalation to ~1x10^5 TCID50 would proceed with increasing numbers of volunteers if the safety profile is acceptable. Dose escalation should occur to confirm the safety profiles (or lack of symptoms/shedding) and to assess more accurately the incidence of symptoms/endpoints. Dose escalation should occur conservatively. Examples are provided below in Table 2 (bottom of document).

If the symptom profile or virologic profile do not occur in a sufficient number of subjects, then dose escalation could occur. The challenge strain should be evaluated in a sufficient number of subjects before dose escalation to 1.) be confident the dose will not achieve a desirable endpoint in a sufficient number of subjects and 2.) to assess a risk of a serious adverse event occurring at a rate of <5 – 10% (1 – 2 per 20 subjects evaluated). If, after evaluation in a sufficient number of subjects, the lowest dose does not induce a suitable endpoint, dose escalation can occur using the same type of strategy for safety purposes. During initial challenge and/or up-titration, preliminary safety endpoints can be assessed when viral loads and/or symptoms begin to regress (rather than waiting for complete resolution). A DSMB or SMC should be convened to review the safety and virologic profile of each dose and give a recommendation on whether or not dose escalation should proceed.

6.3. ENDPOINTS TO BE ACHIEVED WITH SARS-COV-2 CHALLENGE MODEL.
Whereas much discussion ensued on what would be useful endpoints of a challenge model, a consensus was not achieved. The following is a summary of our discussion. Definition of the appropriate endpoints for a SARS-CoV-2 challenge model is important because it is these endpoints that will allow the model to achieve its stated purpose. This first consideration is, can different challenge models be developed for different purposes? Two such models were discussed. The first was an infection model. The second was an illness model. Some discussion points regarding the pros and cons are presented below. Ideally, the model should produce the defined endpoint in a relatively high proportion of challenged naïve subjects (≥ 70% attack rate) to minimize the number of volunteers.
needed in the study. The primary endpoints are discussed below. There would be other secondary and exploratory endpoints as well.

6.3.1. Infection model:
- The primary endpoint is recovery of challenge virus from the nasopharynx or oropharynx.
- Virus would be quantified, preferably by both PCR and tissue culture.
- This model would presumably be safer and may require fewer volunteers if clinical endpoints cannot be achieved in a sufficient number of young healthy volunteers without inducing more severe disease in others.
- This model may not be able to differentiate between vaccines, if the vaccines do not affect replication of the virus in the upper respiratory tract.
- It is unclear how regulatory agencies would review the “efficacy” of vaccines that demonstrate impact on shedding of virus in the absence of data on prevention of endpoints of clinical illness.
- An infection model in volunteers may be useful for (i) selecting among multiple vaccines for large-scale field trials of clinical efficacy if some vaccines suppress viral replication significantly more than others, based on the assumption that reducing shedding translates to reduced transmission and possible increased indirect (herd) protection; (ii) investigating correlates of protection (e.g., by comparing challenge of naïve vs. recovered), even if this protection is against infection rather than against clinical illness; (iii) investigating viral dose-clinical severity relationships (presumably at lower doses); (iv) possibly helping to estimate transmission risks posed by asymptomatically infected individuals.

6.3.2. Illness Model
- The primary endpoint would be a constellation of clinical signs and/or symptoms that constitute a “case definition”, as is used in the well-established influenza challenge model studies and the endpoint would be a type of “influenza-like” illness.
- The clinical endpoint case definition could evolve as data are collected from the first challenge studies. What signs and symptoms do subjects develop? How long do signs and symptoms last? What proportion of subjects develop signs and symptoms that could collectively define an illness end-point.
- Quantification of virus shedding would be included in the endpoints.
- Careful escalation of administered dose of virus, for example progressing from challenge with $1x10^5$ TCID50 to an inoculum containing $1x10^7$ TCID50 should aim to show the extent to which a spectrum of disease is predictable, at even low doses of virus inoculum. Wide variations in disease severity should prompt a pause in virus dose escalation and should attempt to decipher the reasons for increased severity.
- Advantages of this model include that it may better assess which vaccines should move forward and which should not, since the comparison would be protection against clinical (albeit mild) illness. This may provide data of greater relevance for regulatory authorities. If significant protection of a specific vaccine against clinical illness was demonstrated in the model, this could also reveal one or more immunologic correlates of protection against illness rather than, or in addition to, possibly identifying a correlate of protection against infection.
- Shortcomings of this model include:
  - There may not be a dose-ranging effect with dose-escalation and it may not be possible to define a dose that induces an acceptable clinical case definition.
  - A dose of virus that is accompanied by fairly consistent clinical signs and symptoms of illness in $70\%$ of volunteers may also raise the risk of occurrence of severe adverse events among the volunteers.

It is important to note that in pursuing development of the volunteer challenge model, it may not be possible to achieve an "ideal" model that provides both clinical and virus shedding endpoints yet proves to be safe for
volunteers. Development of the model must proceed iteratively, with reassessment of what type of model can be achieved consistently and safely as dose ranging and dose escalation occur.

6.3.3. Aims of different cohorts included in a challenge model experiment
- Naive participants: (i) develop model of infection against which to test vaccines, passive immunoprophylactic agents (e.g., monoclonal antibody products) and other putative preventive interventions; (ii) risk of transmission (especially during asymptomatic infection).
- Previously exposed participants: risk of re-infection (shedding of virus); risk of developing clinical endpoints; identification of immunological correlates of protection (CoP) against virus shedding or against development of clinical illness following re-challenge.

6.4. Method of administration
There was general consensus to use droplet administration and not nasal spray or aerosol. This was to reduce the likelihood that the challenge virus would be deposited in the lower respiratory tract.

6.5. SAFETY MONITORING DURING INPATIENT STAY
- Safety Procedures during inpatient stay
- At least once a day physical examination including but not limited to nose, throat, pulmonary, cardiovascular, neurological, and skin exam. The frequency would be increased if the volunteer develops clinical signs and symptoms.
- Testing of smell and taste
- Vital signs at least q 6 hours
- Continuous pulse oximetry
- Continuous cardiac monitoring
- Daily pulmonary ultrasound. Should an abnormality be noted, CT Scan of chest should be done
- EKG on admission and repeated as needed
- Safety laboratory studies to include:
  - Complete metabolic panel
  - CBC with differential (this may be checked more frequently than CMP because we would want to document lymphopenia)
  - Troponin
  - CRP
  - D-dimer
  - IL-6
  - PT/PTT
The unit should have a full crash cart on the unit including intubation kits

6.6 DISCHARGE CRITERIA
- Consensus that we must reduce the risk to third parties to as near zero as possible. To this, we anticipate requiring post-challenge inpatient stays of 3 – 4 weeks.
- Three consecutive days of negative naso-pharyngeal swabs by PCR (or culture)
  - Can a correlate between PCR titer and infectious (replicating) virus be established from current clinical cases? If so, discharge could occur sooner. Or if, the studies have the capability of performing virus culture, may be able to discharge the subject when replicating virus is no longer detected. This would require BSL-3 capabilities at the site.
- For volunteers participating in Stage 1 SARS-CoV-2 challenge studies who change their mind and want to leave the study, a legal framework must be in place to retain them on the High-Level Isolation Unit. To address this theoretical scenario, we strongly recommend that the Stage 1 studies to establish the challenge model be performed in High-Level Isolation Units and that, in conjunction with appropriate health and administrative authorities, the Isolation Unit should be placed under legal Quarantine. The Quarantine would extend from the time of inoculation of volunteers with challenge virus until the

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volunteers are no longer shedding virus and will no longer be a potential threat to household and community contacts. In such a situation, the subject can withdraw from the trial and from participating in additional study-related procedures but she/he must remain on the unit until they are no longer shedding infectious virus. One advantage of this approach is that challenge studies with SARS-CoV-2 could proceed in geographic areas and populations where SARS-CoV-2 is no longer circulating. There is an precedent for this approach. In the 1970s and 1980s when challenge models of Classical biotype and El Tor biotype cholera were established in Baltimore, MD, USA, the studies proceeded in the confines of a 22-bed Research Isolation Unit under physical containment and under legal Quarantine. Prior to each challenge study the Baltimore City Health Department would place the Research Isolation Unit under Quarantine from the date and time of challenge until all volunteers were no longer having diarrhea, had received antibiotic therapy and all were culture negative for several days.

6.7. Follow-up
- There should be an explicit plan for follow-up. For instance, monthly follow-up through 6 months than every 3 months up until 12 months following the inoculation. Key follow-up might include early post-discharge neurological examination (i.e. exclude Guillain Barre), longer term serial lung function testing +/- other organ systems if data suggest long term complications among patients. It might also include nasopharyngeal PCR during acute respiratory illness (e.g. to capture episodes of re-infection, if any).
- Follow-up should also include laboratory studies, especially serology. Recruitment for possible re-challenge at 1 year could be considered.
- Follow-up NP/OP swabs may be indicated to evaluate for recrudescence shedding of virus
- Should a subject become positive for SARS-CoV-2 after discharge, specific plans for how that subject will be followed must be in place. Should the subject be re-admitted to the inpatient isolation unit?

6.8. Laboratory studies
- Should include planned sample collection for study of disease pathogenesis, immunological response, CoP. These assays will be discussed by the immunology working group.
- Must be done under guidelines for blood collection limits in ill patients.

6.9. Treatment protocols
- A 10-day intravenous course of Remdesivir has been given Emergency Use Authorization by the FDA for the treatment of severe COVID-19 infection in hospitalized patients in the USA. The protocol must include criteria for the initiation of rescue drugs that have been approved for use to treat SARS-CoV-2, and treatment must be revised criteria as data emerge that identify effective new therapeutic agents. This does not mean all subjects would receive treatment—it would be based on treatment guidelines that would be in place at the time of the challenge.
- In addition, should effective treatments become available that prevent the progression form mild and moderate clinical COVID-19 illness to severe clinical illness, treatment could be initiated once a case definition has been achieved or by a certain day post-challenge if the case definition has not been met.

7. Isolation Units for use in a SARS-CoV-2 challenge
High-level infection control and adequate medical support of subjects are the minimal requirements of any isolation Unit used for SARS-CoV-2 challenge studies. Given the high transmissibility of SARS-CoV-2 and the risks to third parties, including staff, a high-level containment unit would be necessary to conduct COVID-19 human challenge studies. At least until the model or other factors have proven that such controls are not necessary. There are a limited number of high-level isolation units around the world and, for the most part, the number of beds available at each unit is small. However, the units would be suitable for Stage 1 studies. An international review of high-level isolation units was performed by Allison Sykes in

Commented [KP23]: These references do not address this issue specifically for COVID-19. This is a strong statement that I am not sure all members of the group agree with. Would it be worth determining if these are viewed as necessary vs. highly desirable? For example, what if all the staff was previously infected and shown to be seropositive, and also was consented? As noted above, maybe more information about the considerations leading to this conclusion would be useful.
2018. A summary of these units was derived from her report and these units are presented in Table 1. Some of these units were already in place and some were developed in response to the Ebola Zaire outbreak of 2014-2016.

In addition to the above-mentioned considerations, some authorities consulted consider that the step of administration to volunteers of an inoculum of SARS-CoV-2 from a GMP formulation of tissue culture cells infected with SARS-CoV-2 should be performed in BSL-3 containment as challenge of non-human primates or other animal models would have to be done.

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<th># Beds</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High level isolation unit</td>
<td>Charity University Medicine</td>
<td>4+20 resp</td>
<td>Berlin</td>
<td>Germany</td>
</tr>
<tr>
<td>High level isolation unit</td>
<td>Hospital La Paz Carlos 111</td>
<td>2+3</td>
<td>Madrid</td>
<td>Spain</td>
</tr>
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<td>High level isolation unit</td>
<td>HCDGU</td>
<td>7</td>
<td>Madrid</td>
<td>Spain</td>
</tr>
<tr>
<td>High level isolation unit</td>
<td>Newcastle Royal Victoria Infirmary High-Level Isolation Unit</td>
<td>4</td>
<td>Newcastle</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

The USA has a four-tier system for the management of HCoVs (Special Pathogens)

- **Tier 1**: Regional Biocontainment Units. There are 10 and they serve between 2-8 states.
- **Tier 2**: State-designated treatment centers who receive patients from their state prior to transfer to the main center and can also manage patients if the regional ICU is unable to take the patient.
- **Tier 3**: The Assessment Centers who can keep a suspected HCoV case for up to 5 days until diagnosis can be confirmed and transfer organized.
- **Tier 4**: all other hospitals that can assess and isolate the patient for up to 12-24 hours until transfer.

A similar hierarchy is followed in most European countries.

### 7.1. Capabilities Available on the Unit

Units chosen for SARS-CoV-2 challenge studies should be high-level containment units that can house subjects in single rooms. Nursing stations should have full telemetry monitors to view vital signs, hear rhythm, and pulse oximetry. They should have the equipment and monitoring capability of an intensive care unit or step-down unit. Ideally, the challenge inoculum could be stored in a secure, locked, high security freezer in a pharmacy on the unit. If possible, the unit should have an on-site specimen processing area and point-of-care diagnostics for some basic clinical laboratory results. Clinical specimens will have to be sent to the central hospital laboratory for many of the tests. It is likely that some sample processing will need to be done elsewhere (such as PBMC processing).
7.2. **Medical Expertise/Support Care Available on the Unit**

Close clinical monitoring of subjects is critical. Because airborne precautions should be required and will limit what can be brought on and off the unit, careful consideration should be given to what diagnostic equipment is available on the unit to minimize subject transport to and from different testing suites (radiology for example).

- Dedicated portable ultrasound with staff trained in performing the ultrasound and interpreting the results should be available on the unit.
- Oxygen and ventilatory support should be available on the unit. In addition, the site should have the clinical staff and capability to evaluate and manage other complications of SARS-CoV-2 infection such as vascular complication.
- Experienced clinicians should be staffing the unit at all times. The unit should have available critical care facilities and staff either as part of the unit, or transport to an ICU should be readily available.
- The clinical staff and protocols must be in place for initiating advanced care such as intubation or emergency surgery and for transfer to the ICU or other specialty service. Team members should include, in addition to the protocol PI and study team members:
  - Pulmonary / ICU specialist
  - Critical care nursing staff
  - 24-hour physician coverage on the unit (in addition to 24-hour nursing staff)
- Other support services to consider
  - Oxygen in the rooms
  - Continuous pulse oximetry, telemetry
  - Pulmonary U/S on the unit with an experience team member to perform U/S
  - EKG machine
  - IV pumps and fluids
  - Full crash cart including intubation kits
  - Dietary support. Meals can be prepared outside the unit and brought in daily
  - Entertainment on the unit (subjects may have to remain on the unit for weeks)
  - Housing: can more than 1 subject be in a room?

7.3. **Precautions for Staff/Third Parties**

The unit should have dedicated PPE donning and doffing areas. In addition, staff should have regular serology and N-P or D-P swab collection for SARS-CoV-2 detection to detect asymptomatic infection and seroconversion (this could be a sub-study). Other requirements

- Full access to PPE
- Screening of staff to identify those who may have household members at higher risk of COVID-19. They may not be permitted to work on the unit. This would have to conform to institutional guidelines
- Protocols will need to be in place for subjects who decide they do not want to remain in the study. The subject can withdraw from the study but should remain on the isolation unit until it is confirmed that they are no longer shedding the challenge virus. These should be coordinated with local public health authorities regarding enforced quarantine (see below).

7.4. **Mandatory Quarantine to Address Volunteers Who Wish to Leave the Study Before Completion**

Volunteers have the right to "leave the study when they wish." However, they cannot be allowed to physically leave the Isolation Unit until they are no longer infectious as they would pose a potential danger to household and other community contacts. This would be particularly true if the study were to proceed in a geographic area where there is little or no active transmission of SARS-CoV-2 at the time. The one historical method for handling potentially infectious volunteers who want to leave a study and an Isolation Unit was to have the Unit placed under legal Quarantine for the duration of the study form the time of inoculation. A survey taken of the Advisory Group members asking if there were national laws in place allowing the quarantining of subjects against their will revealed that many European countries, Australia and states in the USA have health ordinances that allow the establishment of legal quarantine. Thus, many countries have laws in place allowing for persons to be placed in quarantine if they pose a threat of disease transmission to others.

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Commented (KP24): What is particularly true? I thought everything was either true or false... But this illustrates the point that reasonable people might see gradations of risk where legal quarantine might not be necessary. And it might be difficult to get a court order requiring the legal quarantine. If that were not feasible, would everybody say that the challenge studies should not be done?
7.5. Handling of the SARS-CoV-2 Challenge Virus

The inoculum is a BSL-3 product. Its formulation and presentation should be one that minimizes risk to those who prepare and administer it. Issues around the selection and production of the SARS-CoV-2 challenge virus were discussed by another working group. Issues related to administration of the challenge virus include:

- Reconstitution of a lyophilized vial was deemed to present risks to those who prepare the inoculum. Thus, vials or pre-filled syringes containing frozen inoculum would be preferred.
- One possible practical solution would be to have the inoculum delivered in a single-dose, frozen liquid, ready-to-use syringe at the necessary dose. This would mean it must be produced at the different doses that might have to be given. If this is not feasible, the frozen liquid could be contained in single-dose vials that would have to be withdrawn into a syringe of pipette that would allow 0.5 mL to be delivered into each nostril. These steps would have to be performed in BSL-3 conditions.

7.6. Efficacy Studies

Once a suitable challenge model has been established in the Stage 1 studies, larger studies that incorporate a larger number of volunteers could be contemplated. However, it is important to note that these studies being done to compare directly two candidate vaccines versus a control group of placebo recipients, or to determine the efficacy of a single vaccine would require 40 - 100 subjects to determine significant differences, depending on the questions being addressed. High-level containment units have small bed capacity so that such studies would have to be conducted in multiple units at the same time. This means that these Stage 2 trials must be harmonized between the sites to ensure the results are consistent and reproducible. To reiterate, the Stage 1 dose-finding studies should be performed in a very small number of sites to minimize variability and assure the quality of the results.

8. Consent Form

The Subgroup on Clinical Trials Issues worked extensively to craft a draft Consent Form that they deemed to be appropriate for the Stage 1 dose-escalation viruses, representing the first times that volunteers would be given SARS-CoV-2 viruses. All members of the Subgroup participated, after which other members of the Advisory Group form other Subgroups had an opportunity to provide their inputs. An attempt was made to craft a Consent Form that would, with relatively minor edits, be usable in potential study sites in the USA, Europe, Australia, Asia and other countries where the infrastructure of suitable High Isolation Units existed. This draft Consent Form is attached as Appendix 7.

9. Volunteer Comprehension Test

The Subgroup on Clinical Trials Issues, which includes a number of clinical investigators who collectively have established and undertaken a number of different types of challenge studies over many decades concluded that prospective volunteers should be given a test containing multiple choice and true/false questions to document in an objective manner that they have understood the purpose of the challenge studies, the risks entailed, the procedures they will have to undergo and why, the timeline, the specifics of the Quarantine of the Isolation Unit during the study period, the number and purpose of the follow-up visits, etc. A draft Volunteer Comprehension Test is attached as Appendix 7. The test will contain approximately 30 questions and volunteers will have to attain a grade of 80% or better to be enrolled into the study.
<table>
<thead>
<tr>
<th>Site</th>
<th>Cohort</th>
<th>SARS-CoV-2 test virus</th>
<th>Dose</th>
<th>Number of subjects</th>
<th>Days of acclimation on ward pre-challenge</th>
<th>Study day of virus administration</th>
<th>Estimated days of clinical observation post-challenge</th>
<th>Estimated maximal days of RT-PCR positivity if subjects become infected</th>
<th>Days of Isolation Ward cleaning and disinfection</th>
<th>Cumulative overall study days at a single site with rapid step-wise progression</th>
</tr>
</thead>
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<tr>
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<td>1</td>
<td>#1</td>
<td>Dose level 1</td>
<td>1 - 3</td>
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<td>21(^1)</td>
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<td>~49</td>
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<td>#1</td>
<td>Dose level 1</td>
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<tr>
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<td>149</td>
<td>21</td>
<td>21</td>
<td>3</td>
<td>~199</td>
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</table>

**Timetable for dose level 2 if challenge virus #1 does not elicit mild upper respiratory clinical illness at dose level 1**

<table>
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<tr>
<th>Site</th>
<th>Cohort</th>
<th>SARS-CoV-2 test virus</th>
<th>Dose</th>
<th>Number of subjects</th>
<th>Days of acclimation on ward pre-challenge</th>
<th>Study day of virus administration</th>
<th>Estimated days of clinical observation post-challenge</th>
<th>Estimated maximal days of RT-PCR positivity if subjects become infected</th>
<th>Days of Isolation Ward cleaning and disinfection</th>
<th>Cumulative overall study days at a single site with rapid step-wise progression</th>
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<td>21</td>
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<tr>
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<td>(-2, -1)</td>
<td>149</td>
<td>21</td>
<td>21</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Timetable for dose level 3 if challenge virus #1 does not elicit mild upper respiratory clinical illness at dose level 2**

<table>
<thead>
<tr>
<th>Site</th>
<th>Cohort</th>
<th>SARS-CoV-2 test virus</th>
<th>Dose</th>
<th>Number of subjects</th>
<th>Days of acclimation on ward pre-challenge</th>
<th>Study day of virus administration</th>
<th>Estimated days of clinical observation post-challenge</th>
<th>Estimated maximal days of RT-PCR positivity if subjects become infected</th>
<th>Days of Isolation Ward cleaning and disinfection</th>
<th>Cumulative overall study days at a single site with rapid step-wise progression</th>
</tr>
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<td>#1</td>
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<td>Dose level 3</td>
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</tr>
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<td>#1</td>
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<td>#1</td>
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<td>(-2, -1)</td>
<td>149</td>
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<td>21</td>
<td>3</td>
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<td>149</td>
<td>21</td>
<td>21</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Some centers are reporting PCR positive shedding for 21 – 28 days post-symptom onset; this could be for up to 35 days or more post-inoculation.

**Commented (KP26):** This table may be too pessimistic. If the first few subjects at a dose level don’t get sick or show any sign of infection within 2-3 weeks, it may not be necessary to fill that cohort or perform as much follow-up before escalating. Escalation to new doses could also start at a different facility to reduce cleaning times.
10. SELECTION OF VIRUSES TO BE USED IN CHALLENGE STUDIES

10.1. Points to consider in selecting a SARS-CoV-2 challenge virus strain

10.1.1. Background:

There are two main lineages of SARS-CoV-2 (A and B) that can then be subdivided into a number of component lineages. The bulk of the infections currently world-wide (May 2020) are derived from the B.1 lineage which is associated with the large European outbreak. Currently, most cases across the USA are lineage B.1 following multiple introductions from Europe.

Coronaviruses acquire genetic variation by mutation and recombination. It is important to recognize that mutations can emerge as a consequence of passage in cell culture, as would occur in the preparation of a GMP batch of a SARS-CoV-2 strain for use in challenge studies.

10.1.2. Options for selection of a challenge virus strain.

There are two options for selection of a challenge virus strain:

1. Although this may not be a regulatory requirement, the Advisory Group opines that the biological isolate should be obtained from a COVID-19 subject who does not have known risk factors (e.g., age <50 years, no history of diabetes, hypertension, cardiovascular disease, renal or hepatic disease).
2. Each selected strain will have to be isolated or plaque-purified in a qualified cell line and manufactured and tested under current Good Manufacturing Practices (cGMP) to meet regulatory standards. In at least one jurisdiction, if clinical or virus passage history of the strain is undocumented, plaque purification could address potential concerns regarding adventitious agents.
3. Alternatively, using reverse genetics, a potential challenge virus can be derived that is rescued in qualified cells. The advantage of this approach is that a genetic tag can be introduced into the challenge virus and so it can be tracked. There are a few laboratories globally with expertise to employ this technology. However, the resultant virus will be a genetically-modified organism (a “GMO”), the use of which may be problematic for use in some countries. The Advisory Group was not enthusiastic over this option but believed that it should be included in the report as the approach was raised and discussed.

10.1.3. Criteria in selecting a virus:

- Select one or two viruses from each of the dominant clades.
- Each selected virus should represent as close as possible a consensus sequence for its clade.
- It is not important to select a viruses that has been used in animal models. Rather, it would be preferable to confirm virulence in animal models after the selected virus has been isolated, plaque purified and sequenced.

10.1.4. Advice from experts:

- The B.1 lineage has a mutation in the spike protein (D614G) which is generally thought to be a significant mutation from the molecular perspective but there is debate as to its importance in terms of its effect on pathogenesis and transmissibility. Viruses at the base of the B.1 lineage can be selected that harbor the D614G mutation but that exhibit few other mutations.
- If two variants of SARS-CoV-2 are to be manufactured as potential challenge viruses, one approach would be to manufacture one of the original A viruses (which would not have the D614G mutation), while the other challenge strain would be a B.1 lineage virus. The original A genotype is apparently diminishing in frequency but there are still cases in Europe and the USA (plus many other parts of the world).
- One would aim to manufacture the A1 and B1 viruses from two different A1 and B1 clinical isolates, as one or another individual virus may exhibit lower yields than its counterpart clade virus.

Commented [KP27]: It would be good to provide a reason for this.
A number of groups have observed a notable deletion in the spike protein that accompanies culturing in Vero cells. This deletion removes the furin cleavage site. One expert consultant suggested avoiding viruses with the deletion of the furin cleavage site. However, another expert suggested choosing a purified plaque of S1/S2 deletion mutant that is stable on multiple passages in Vero cells as the challenge virus on the assumption that such a virus might be safer for the unvaccinated control volunteer.

10.1.5. A list of specific sequenced viruses

Prof. Kanta Subbarao, Lead for the Subgroup on Challenge Virus Strain Issues, consulted with Prof. Andrew Rambaut (Institute of Evolutionary Biology, University of Edinburgh, UK) and Prof. Edward Holmes (School of Life & Environmental Sciences and School of Medical Sciences, University of Sydney, Sydney, Australia), requesting that they provide some SARS-CoV-2 strain designations for representative viruses at the base of the B.1 lineage that have the D164G mutation and also a L452R variant. These are close to the base. Their list is shown below as Table 7. Some viruses have a few differences at the beginning and end that may be due to sequencing errors.'

Table 7. A list of potential SARS-CoV-2 challenge virus candidates of Clade B.1 ("European epidemic" clade) and Clade A ("Chinese epidemic" clade)

| Lineage B.1 | Virus ID | Country/Region | Date
---|---|---|---
Italy/1H12/2020 | B.1 | Italy | 1.65 | 2020-03-01
Australia/NSW39/2020 | B.1 | Australia | 1.65 | 2020-03-11
Netherlands/GeIderland_6/2020 | B.1 | Netherlands | 1.65 | 2020-03-09
USA/MI-151/2020 | B.1 | USA | 1.65 | 2020-04-08
USA/MI-134/2020 | B.1 | USA | 1.65 | 2020-04-13
USA/NY-PV08426/2020 | B.1 | USA | 1.65 | 2020-03-18
USA/MI-UN-265/2020 | B.1 | USA | 1.65 | 2020-04-08
Scotland/CVM131/2020 | B.1 | UK | 1.65 | 2020-03-12
Scotland/CVM62/2020 | B.1 | UK | 1.65 | 2020-03-22
Scotland/CVM54/2020 | B.1 | UK | 1.65 | 2020-03-13
Netherlands/Zeewolde_1365080/2020 | B.1 | Netherlands | 1.65 | 2020-03-02
Netherlands/Bfartcmun_1364780/2020 | B.1 | Netherlands | 1.65 | 2020-03-02
Netherlands/Utrecht_11/2020 | B.1 | Netherlands | 1.65 | 2020-03-03
Czech_Republic/IAR_18/2020 | B.1 | Czech_Republic | 1.65 | 2020-03-27
Belgium/BG-036553/2020 | B.1 | Belgium | 1.65 | 2020-03-04
Belgium/VCUH-036548/2020 | B.1 | Belgium | 1.65 | 2020-03-03
Belgium/RS-036677/2020 | B.1 | Belgium | 1.65 | 2020-03-06
Belgium/ANM-036767/2020 | B.1 | Belgium | 1.65 | 2020-03-06
Belgium/FL-036771/2020 | B.1 | Belgium | 1.65 | 2020-03-07
Belgium/GE-036771/2020 | B.1 | Belgium | 1.65 | 2020-03-05
Belgium/MDJS-036879/2020 | B.1 | Belgium | 1.65 | 2020-03-03
Belgium/DCS-036945/2020 | B.1 | Belgium | 1.65 | 2020-03-24
Belgium/CE-036945/2020 | B.1 | Belgium | 1.65 | 2020-03-25
Italy/1H16/2020 | B.1 | Italy | 1.65 | 2020-03-23
Italy/unHMS03/2020 | B.1 | Italy | 1.65 | 2020-02-24
Austria/VIC136/2020 | B.1 | Austria | 1.65 | 2020-03-22
Georgia/IT-147/2020 | B.1 | Georgia | 1.65 | 2020-03-10
Austria/VIC176/2020 | B.1 | Austria | 1.65 | 2020-03-18
Czech_Republic/IAR_21/2020 | B.1 | Czech_Republic | 1.65 | 2020-03-27
Austria/VIC853/2020 | B.1 | Austria | 1.65 | 2020-04-04
Denmark/S53-09/2020 | B.1 | Denmark | 1.65 | 2020-03-03
Austria/VIC845/2020 | B.1 | Austria | 1.65 | 2020-04-04
USA/NY-2NYMC09/2020 | B.1 | USA | 1.65 | 2020-03-18
Australia/QLD9290/2020 | B.1 | Australia | 1.65 | 2020-03-11
Singapore/49/2020 | B.1 | Singapore | 1.65 | 2020-03-08
Austria/VIC992/2020 | B.1 | Austria | 1.65 | 2020-03-15
Iceland/11/2020 | B.1 | Iceland | 1.65 | 2020-03-11
Canada/ON-PH4088/2020 | B.1 | Canada | 1.65 | 2020-03-15
Brazil/SPMP-0/2020 | B.1 | Brazil | 1.65 | 2020-03-04
Italy/FVG-EG0851/2020 | B.1 | Italy | 1.65 | 2020-03-01
Russia/StPetersburg-M145265/2020 | B.1 | Russia | 1.65 | 2020-03-25
Brazil/SPMP-05/2020 | B.1 | Brazil | 1.65 | 2020-02-29
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India/GEK-K318/2020[B.1]India[1.65]2020-03-13
USA/NY-OMP62047/2020[B.1]USA[1.65]2020-03-12
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Australia/VIC114/2020[B.1]Australia[1.65]2020-03-16
Scotland/CVR56/2020[B.1]UK[1.65]2020-03-12
Russia/StPetersburg-R1749365/2020[B.1]Russia[1.65]2020-04-08
Iceland/216/2020[B.1]Iceland[1.65]2020-03-26
USA/NC-MDHS-S2C0133/2020[B.1]USA[1.65]2020-03-17
USA/NC-MDHS-S2C0124/2020[B.1]USA[1.65]2020-03-24
USA/NC-MDHS-S2C0134/2020[B.1]USA[1.65]2020-03-24
Germany/BAV_MV001/2020[B.1]Germany[1.65]2020-04-09

**Lineage A:**

China/WF0018/2020[EPI_ISL_413748]China[2020-02
China/WF0016/2020[EPI_ISL_413746]China[2020-02
China/WF0020/2020[EPI_ISL_413750]China[2020-02
Taiwan/TU021/2020[EPI_ISL_408489]Taiwan[Taipei][2020-03-31
China/WF0015/2020[EPI_ISL_413729]China[2020-02
Belgium/GBH-0302/2020[EPI_ISL_407976]Belgium[Leuven][2020-02-03
Hongkong/210-02/2020[EPI_ISL_410424]China[Hongkong][2020-01-28
Shanghai/Sh0043/2020[EPI_ISL_416332]China[Shanghai][2020-01-30
Shanghai/Sh0013/2020[EPI_ISL_416362]China[Shanghai][2020-01-30
Wuhan/HDCDC-H03/2020[EPI_ISL_412979]China[Wuhan][2020-01-18
China/WF0011/2020[EPI_ISL_413693]China[2020-02
Taiwan/2/2020[EPI_ISL_411926]Taiwan[Taipei][2020-01-24
Australia/HK01/2020[EPI_ISL_407993]Australia[New_South_Wales][2020-01-24
Wuhan/WHA0/2020[EPI_ISL_406801]China[Wuhan]

[PAGE \* MERGEFORMAT]
10.1.6. What will be needed to obtain and ship the candidate challenge viruses and to characterize them before and after manufacture of the GMP batches

- Original clinical material from which the virus was isolated/sequenced so that it is desired to re-isolate the virus can be re-isolated in qualified cells instead of plaque-purifying the virus.
- If re-isolation of the virus is desired, public health officials will have to track back from the list of possible candidate viruses to determine:
  - whether original clinical material from which these sequences were derived are still available;
  - that the clinical history of the patients from whom these viruses were identified meet the criteria listed above;
  - that the laboratory that has the material is willing and able to share it (appropriate consent, MTA etc.).
- If the accompanying clinical and virological information is in a language different from languages read, written, and spoken by key staff in the BSL-3 manufacturer, it is recommended that an official translation should accompany the clinical information and the virological data along with Certificates of Translation to document accuracy.
- Each selected virus isolate will have to be plaque-purified three times.
- Plaque purification should occur in qualified cells under GMP-type conditions, either with control cells subject to the same manipulations or with evaluation for adventitious agents by new generation sequencing (NGS) of the resultant seed conditions that address the potential for introduction of new adventitious agents.
- It will be critical to establish the genetic sequence of each virus strain by NGS both at the commencement and at the completion of the manufacturing process for each strain. This will allow the appearance of mutations to be identified, characterized and documented.
- Each virus strain should be tested for adventitious agents, which may be performed by conventional methods or likely more rapidly by NGS.
- Discussion with regulators of steps (including plaque purification) planned to address potential adventitious agent issues with isolating and manufacturing a challenge strain could facilitate this work. One Advisory Group member with Regulatory Science expertise proposed that, if appropriately done, NGS could also provide evidence to rule out the presence of adventitious agents in the seed. This would potentially expedite the availability of virus for the challenge study. This member recommended that there be a consultation with regulators to discuss this approach.

11. MANUFACTURE OF GMP BATCHES OF SARS-COV-2 VIRUS STRAINS FOR VOLUNTEER CHALLENGE STUDIES

11.1. Points to consider in identifying manufacturers for a GMP batch of SARS-CoV-2 challenge virus

11.1.1. Background:

Manufacture of a SARS-CoV-2 challenge virus pool will require a BSL3 manufacturing facility. The type of formulation and the dosing in the vials should be selected to minimize handling.

11.1.2. Assumptions related to manufacture of GMP batches of challenge viruses:

- Each challenge virus pool will have to be generated under cGMP conditions in a BSL3 facility.
- More than one virus of each clade should be tested by the manufacturer in case growth or yield differs.
- Each virus will likely be passaged about 5-10 times in the manufacturing process.
- The titer and volume should be predefined based on the expected virus dose level 1, dose level 2 and level 3 and the estimated number of volunteers expected to participate in challenge studies.
- Should the engineering and generation of a reverse genetically-derived virus with a genetic bar code to identify the virus be considered. This could be relevant if the GMP manufacturing facility and at least one
or more High Level Isolation clinical testing units reside within the same country and regulatory agencies of that country do not have major issues per se with GMOs.

11.1.3 What will be needed.

- Genetic sequence data by NGS at the start and end of the manufacturing process to document whether mutations have appeared.
- A decision on whether the formulation of the virus will consist of lyophilized material versus frozen liquid and the preferred presentation for the final drug product, e.g., specific dose levels in vials versus in pre-filled syringes.
- Information from prospective manufacturers on how long it will take to manufacture the challenge virus pools.
- Information from prospective manufacturers on how long it will take to fill and finish to achieve the challenge material in a clinical study-ready form such as vials of or pre-filled syringes containing the challenge viruses at “low” (≈1x10^7 TCID_50), “medium” (≈1x10^8 TCID_50), and “high” (≈1x10^9 TCID_50) dose levels.

11.1.4. Questions to ask potential manufacturers:

- Will the manufacturer’s insurance provide indemnification (product liability) for the product or will product liability insurance costs have to be carried by the sponsor?
- Total cost for manufacture of the virus challenge drug product.
- An estimate from the manufacturer on how long it will take to manufacture the virus challenge drug product.

11.1.5. A stability plan to monitor challenge virus potency over time

- In order to assure that there is no substantial loss of viability of the virus in the GMP batches over time, vials or syringes containing the final “drug product” (DP) for each virus will have to undergo periodic testing to monitor the TCID_50 counts of the DP on an agreed upon schedule.
- The stability testing will initially have to be done at the same frequency for all three dose levels of each virus used in the Stage 1 challenge studies. However, once a specific challenge dose level is identified for each challenge virus from the Stage 1 dose-escalation studies, whereas the close monitoring must continue for the chosen challenge dose level, it may be possible to diminish the frequency of stability testing of the other dose levels.

11.1.6. How to bring the challenge virus “drug product” out of BSL3

- World Courier was contacted by Shobana Balasingam of the Wellcome Trust to explore possibilities for this service to perform the tasks and to learn of constraints.
  - World Courier noted that as SARS-CoV-2 virus shipment will need to be flagged with management at World Courier for approval.
  - World Courier would provide a customs invoice for the shipper to fill in and would assist in getting export/import licenses where needed. They would consult with local offices, which will be the rate limiting step. For shipments from a manufacturing site to one or more clinical sites within the US there would likely be no need for paperwork.
- The needed export/import licenses and regulatory agency letters needed to transport the challenge virus drug product across international borders would be investigated on a case-by-case basis. In exploring such cross international border scenarios, the receiving facility would need to contact the relevant national regulatory agencies, as required.
- Shipping -- Once approval to ship has been given, World Courier will provide the 650 packaging, assuming the virus is UN3373 compliant and World Courier will supply the dry ice along with the dry ice box. World Courier can add in a temperature data logger and will top up the dry ice every 24 hours (or at shorter
intervals if required]. There is a cost for the additional dry ice. There shouldn’t be a limit to the number of vials/boxes shipped but this would need to be confirmed at time of booking.

- Cost – World Courier is able to ship globally and the shipment from US to Europe or US to Australia is estimated to be approximately £1000.
  - The size of the dry ice box will not impact cost, neither should the number boxes but this will need to be confirmed with World Courier at the time of booking the shipment.

- Contact – Information on other specific shipping scenarios can be obtained by contacting World Courier as: [ HYPERLINK "mailto:ocs@worldcourier.co.uk" ].

- How long it will take to manufacture and release challenge virus drug product and to get it transported to study sites – This estimate is impacted by two major factors, the manufacturer-specific agenda that the manufacturer largely (but not entirely) controls and specifics of shipping (that in great part depend on the site of manufacture and the site of the clinical trials and the import/export and regulatory rules to be addressed).
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Manufacturer 1</th>
<th>Manufacturer 2</th>
<th>Manufacturer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSL3 and GMP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous experience of production of GMP challenge</td>
<td>Yes</td>
<td>No</td>
<td>No – but growing SARS-CoV-2 currently and still optimizing this</td>
</tr>
<tr>
<td>inoculum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>$600,000 USD</td>
<td>Not known as yet</td>
<td>Not known as yet will depend on quantity required</td>
</tr>
<tr>
<td>Timeline</td>
<td>3-4 months</td>
<td>3-4 months (information provided)</td>
<td>Not known as yet</td>
</tr>
<tr>
<td>Validated GMP cell line exists</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Release testing</td>
<td>Needs to be defined up front – typically sterility, potency and adventitious agent testing</td>
<td>Needs to be defined up front</td>
<td>Needs to be defined up front – typically sterility, potency and adventitious agent testing</td>
</tr>
<tr>
<td>Validated assays available</td>
<td>No. Will need to be transferred or set up (included in timeline)</td>
<td>No. Will need to be transferred or set up (included in timeline)</td>
<td>Plaque assay will be validated shortly</td>
</tr>
<tr>
<td>All assays in house?</td>
<td>Most assays in house, but NGS or any sequencing would be sent to third party.</td>
<td>No – some assays including NGS will need to be outsourced</td>
<td>Most in house</td>
</tr>
<tr>
<td>Capacity</td>
<td>Need to check slot availability</td>
<td>Some capacity in July onwards</td>
<td>Need to check could work it in to the current projects that are ongoing</td>
</tr>
<tr>
<td>Challenge strain</td>
<td>NIH could make some available – they have the Italy strain and others</td>
<td>Needs to be provided</td>
<td>Needs to be provided</td>
</tr>
<tr>
<td>Final Batch size/no of vials</td>
<td>Dependent on titre obtained and volume/vial to be advised</td>
<td>Dependent on titre obtained and volume/vial to be advised</td>
<td>Dependent on titre obtained and volume/vial to be advised</td>
</tr>
</tbody>
</table>

Commented [KP30]: I would not call out manufacturers by name. For this report, just say Manufacturer A, Manufacturer B, etc.
<table>
<thead>
<tr>
<th>Preformed syringes</th>
<th>No – limited</th>
<th>Not known as yet</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>Storage</td>
<td>No storage available</td>
<td>Available</td>
<td>Limited</td>
</tr>
<tr>
<td>Indemnity</td>
<td>Need a clause in the agreement</td>
<td>Need a clause in the agreement/ additional insurance may be needed</td>
<td>Need a clause in the agreement and additional insurance. Approval would need to be sought by the university before agreeing any contract</td>
</tr>
</tbody>
</table>
12. REPORT OF THE SUBGROUP ON MEASUREMENT OF IMMUNE RESPONSES PRE- AND POST-CHALLENGE

12.1. Preface

The subgroup discussed which tests should be done to evaluate immune responses in volunteers experimentally exposed to SARS-CoV-2 (attenuated or fully virulent) under closely-monitored conditions, as well as immune responses to specific vaccines administered prior to volunteers who may then participate in a challenge study. A range of (semi)-innate, humoral and cellular functions were discussed to characterize immune responses and are listed in Table 1. The idea would be to characterize both antibody and cellular responses that could be associated with efficacy, as shown by resistance to challenge. Those responses that appear to be associated with efficacy could then be followed to determine duration of immune memory.

The vaccines to be tested in challenge studies would be prototype vaccines that have already demonstrated preliminary safety and immunogenicity in phase 1 or 2 clinical trials and are available for testing. These may include inactivated virus, purified subunit, mRNA, DNA, and live vector vaccines as prototypes. Candidate vaccines may be those given in one or two doses. In the latter case, the interval between doses will be four weeks and the challenge would be given circa four weeks after the second dose. The protective effect of convalescent plasma and monoclonal antibodies could also be assessed in parallel in challenge studies.

12.2. Principles of immunologic study of volunteer challenges with SARS-CoV-2

12.2.1. Specific volunteer groups to be included in challenge studies:

- Volunteers who lack antibodies to SARS-CoV-2 (seronegatives).
- Volunteers who have antibodies to SARS-CoV-2 (seropositives) consequent to prior natural exposure or to closely-monitored experimental infection.
- Volunteers immunized with candidate COVID-19 vaccines.

12.2.2. Time Points Post-Challenge

Clinical species to measure immune responses will be collected on Days 0, 1, 3, 5, 7, 10, 14, 21, 28 days, 6 months and 12 months, and possibly at later time points to monitor the longevity of the immune responses. See Table 1 for which tests will be performed on which days.

12.2.3. Blood volume constraints

The total volume of blood to be collected for all purposes within the study cannot exceed a total of 500/ml per month. So the various immunologic assays will have to be prioritized to remain within that volume constraint and efforts will have to be taken to minimize the volumes and to optimize the testing. For example, if certain antibody tests on certain timepoints can be performed with plasma, the same sample can provide peripheral blood mononuclear cells (PBMCs) for measurement of cellular responses, while the plasma from that specimen can be utilized for antibody measurements.

12.2.4. Following exposure, protected and infected subjects can be studied for humoral and innate responses:

- Induced (semi)-innate responses in circulation and/or airways
- Induction and duration of humoral responses in circulation and/or airways:
- Specific antibodies (specificity, affinity, isotype, functionality in in vitro assays)
- Composition/activation of B cell populations (blasts, memory, atypicals)

12.2.5. Induction and duration of cellular responses in circulation and/or airways:

[ PAGE 1+ MERGEFORMAT ]
• Composition/activation of T (subset) cell populations including regulatory T cell network
• Functionality ex vivo of induced T (subset) populations (cytotoxicity, cytokines)
• Specificity of induced T (subset) populations
• RNA-seq

12.2.6 Pathology of Cellular Responses

Induced (semi)-innate responses in relation to viral load and clinical signs/symptoms
• Soluble markers of inflammation in circulation and/or airways
• Composition, activation (surface markers) of innate cell populations (e.g., mono (subsets), NK (T) cells, gamma delta T cells, ILC's) in circulation and/or airways
• Ex vivo production of inflammatory markers
  o RNA-seq in identified subsets

12.3. The volunteer challenge model can contribute to identification of

12.3.1. immune mechanisms / immune correlate signatures for:
• Pathology
• Exposure
• Protection
• Disease enhancement

12.3.2. Longevity of immune responses
• Duration of induced immune (protective?) responses
• Induction and duration of immune memory
• Identification of immune targets for clinical vaccine development
• Immune regulation: Induction of immune evasion/suppression/immunopathology
<table>
<thead>
<tr>
<th>Immune effector</th>
<th>Clinical specimen</th>
<th>Antigen (source)</th>
<th>Measure</th>
<th>Assay</th>
<th>Timepoints</th>
<th>Include in studies to address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td>RBD on S1</td>
<td>Binding</td>
<td>IgG, IgM and IgA ELISA (Kramer)</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection Disease enhancement</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td>S1 protein</td>
<td>Binding</td>
<td>IgG, IgM and IgA ELISA commercial or CDC/NIH (Natalie Thornberg/Barney Graham ELISA)</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection Disease enhancement</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td>S1 protein</td>
<td>Binding</td>
<td>IgG subclasses</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td></td>
<td>Neutralizing Ab</td>
<td>Live virus in BSL3 Surrogate sVNT (Linfa Wang/Genscript) in BSL2 Identification of the epitopes inducing neutralizing antibodies</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection Disease enhancement</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td></td>
<td>Neutralizing Ab</td>
<td>Pseudovirion approach (which would be amenable in a BSL-2 lab) reagents are available under MTA from VRC, NIH (Barney Graham) Must be accompanied by neutralization assays using infectious virus</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td>Spike protein</td>
<td>Dimeric IgA</td>
<td>David Anderson, Burnet Instt, Melbourne</td>
<td>Baseline, days 7, 14</td>
<td>Exposure/protection</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum</td>
<td></td>
<td>ADCC Ab</td>
<td>Promega kit</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection Disease enhancement</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Nasal washes (to detect mucosal antibodies)</td>
<td>S1?</td>
<td>IgA subclasses, IgG</td>
<td>ELISA</td>
<td>Baseline, days 7, 14, 21 and 28</td>
<td>Pathology Exposure/protection</td>
</tr>
</tbody>
</table>

[ PAGE ]

*MERGEFORMAT*
| Cellular | PBMC | Stimulation with specific peptides/inactivated virus? | T cells: cTfh | CD4+CXCR5+ICOS+PD-1+ | Thevarajan Nat Med 2020 | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection Disease enhancement |
| Cellular | PBMC | Stimulation with specific peptides/inactivated virus | Activated CD8+ T cells | CD38+HLA-DR+CD8+ | Thevarajan Nat Med 2020 | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection Disease enhancement |
| Cellular | PBMC | S1/ inactivated virus/peptides | B cells: Antibody secreting cells (ASC) | CD3–CD19+CD27hiCD38hi | Thevarajan Nat Med 2020 | Baseline, days 7 | Pathology Exposure/protection |
| Cellular | PBMC | S1/ inactivated virus/ | B cells: Antibody secreting cells (ASC) | IgG, IGA and IgM by ELISPOT | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection |
| Cellular | PBMC | S1 and RBD | Memory B cells | IgG and IgA Bm cells CD3–CD19+ IgG+CD27+ | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection |
| Cellular | PBMC | S1/ inactivated virus/peptides | Th 1/2 orientation | Which cytokines? | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection Disease enhancement |
| Cellular | PBMC | S1/ inactivated virus/peptides | Th17 cells and IL-17 production | Baseline, days 7, 14, 21 and 28 | Pathology Exposure/protection Disease enhancement |
| Cellular | PBMC and serum | S1/ inactivated virus/peptides | Cytokines, especially IL-6 | Baseline and every other day | Pathology Exposure/protection |
| Innate Immune system | serum | CRP protein level | Baseline and Day 1 and 3 minimum | Pathology Exposure/protection Disease enhancement |
| Transcriptomics | Whole blood PAXgene tubes | Transcriptomics | Baseline and every other day | Pathology Exposure/protection Disease enhancement |
13. SUBGROUP ON DETECTION OF SARS-CoV-2 IN CLINICAL SPECIMENS POST-CHALLENGE

13.1. Nucleic acid assay

13.1.1 Sampling

Sampling of every challenged volunteer will take place every day until 14 days after challenge. Recognizing that nasopharyngeal swabs may be both uncomfortable and traumatic to nasal mucosa, these swabs may be interspersed with saliva or oral fluid samples.

Whereas most persons infected with SARS-CoV-2 shed virus for only up to 14 days, it is well recognized that a small proportion of infected individuals may have positive RT-PCR tests for up to 25-28 days. Therefore, we suggest to continue sampling daily until three consecutive negative PCR samples at least two days apart to indicate that the virus is cleared.

13.1.2. Sample types

13.1.2.1. Clinical specimens to be tested will include:

- Induced sputum of the lower respiratory tract (preferred);
- Nasopharyngeal swabs (preferred);
- Bronchoalveolar lavage (BAL) (for severe patients).

13.1.2.2. Detection methods:

- Quantitative PCR targeting at least 2 genes (S and E/N) and with the internal control of a housekeeping gene to monitor the quality of the sample.
- Detection of virus by culture
  - Virus isolation in Vero E6 or Vero cells determined by CPE;
  - Confirmation by IFA or PCR (without CPE)
  - Virus titer quantified by TCID50 or PFU.
- Successful isolation of virus will be correlated with the Ct value from PCR detection.
- Sequencing of the initial subject's virus obtained by culture and of the last positive virus culture by new generation sequencing.
Hi Patrick, Here is the video for the vaccines subgroup. Warm regards, Phil

The vaccines group published many documents on the WHO R&D blueprint website:

Here is the list of peer reviewed publications from the vaccines group:


Dear Research leads and Working Group chairs,

This is a gentle reminder that we are looking forward to your submissions on 14 December.

For those working groups that have co-chairs, the suggestion is to either have one chair send the 1 minute video. The alternative is for co-chairs to have a Zoom call and record their session with the 1 minute achievement.

We look forward to your inputs on Monday.
All the very best,
Patrick

From: LYDON, Patrick
Sent: 06 December 2020 10:48
Subject: WHO Scientific Achievement 2020 – What is yours for your thematic area? [Inputs by 14 December]
Importance: High

Dear ____,

On behalf of Soumya, we are reaching out to you with a time-sensitive request.

On December 21 our Director General (Dr Tedros) will host an end-of-year WHO Press Conference which will include a strong focus on science and research for Covid-19.

In preparation for this, we are inviting each chair of the 9 working groups of the Global Research Roadmap to submit their top achievement or scientific advance for their thematic area. This top achievement or scientific advance needs to be the one that had the greatest impact in the control of the pandemic during 2020.

In addition, we would like to also receive from you, a list of all publications (peer reviewed or not) produced this year that are critical for advancing the science for your thematic area (especially if these were generated with WHO contributions).

Achievements submitted by 14 December will be compiled for Tedros and Soumya to highlight during this end-of-year press conference. Our suggestion for the submission is to produce a 1 minutes video using your smartphone (or other device) describing your top scientific achievement for the year. Depending on the submission, you may be invited to formally present achievements during the 21 December press-conference.

Thank you for your attention and follow-up to this request by 14 December.

All the very best,
Patrick
Patrick Lydon
Research & Development Blueprint Unit – World Health Emergencies (WHE/HEO)
World Health Organization | 20 Avenue Appia | CH-1211 Geneva 27 Switzerland | Office: M1156
📧: lydonp@who.int | ☎️: office +41 22 791 4238 | 📞: mobile (b)(6) | ☀️:skype (b)(6)

Promote health, keep the world safe, and serve the vulnerable
Document produced natively.
1 Privileged & Confidential Coalition for Epidemic Preparedness Innovations From SARS-CoV-2 to Disease X: defining CEPI’s response roadmap Confidential Non-confidential

Document title From SARS-CoV-2 to Disease X: defining CEPI’s response roadmap Document number SAC_01-21_3 Defining CEPI’s response roadmap Agenda item #3 Action □ For information □ For endorsement □

For decision Purposes To inform SAC members of the multiple workstreams to be undertaken by CEPI’s Research and Development group, in order to anticipate and address the greatly accelerated Disease X response timeframes embodied in our CEPI 2.0 strategy. Key considerations are: our research and development roadmap to address three key knowledge gaps: (i) pathogen/strain identification and proliferation, (ii) global manufacturing deficiencies in current products, including enhancing productivity, global manufacturing footprint, thermal stability, and reactivity profile - commencing initiatives to articulate the definition of a Broadly Protective Beta-CoV vaccine from a scientific and regulatory pathway perspective, including the launch of a Call for Proposals with a strong emphasis on immunogen design - Launching a series of dedicated Working Groups to characterize the scientific- and development-oriented strategic and operational needs required to meet the CEPI 2.0 mandate, and in which participation by SAC members is welcomed.

Privileged & Confidential

The next Disease X: Over ninety-five million cases of COVID-19, over two million deaths, a loss of around $21.5 trillion to the global economy in 2020 and unmeasurable disruption to humanity, exemplify beyond any question, the essential nature of preparing for the next outbreak - the next Disease X. However, defining the next Disease X beyond betacoronaviruses remains an enormous challenge. The International Committee on Taxonomy of Viruses (ICTV) maintains a database that recognizes 2,805 mammal-virus associations, including 754 mammal species from 15 orders and 586 unique viral species (every recognized virus found in mammals) from 28 viral families. i Of the 586 mammalian viruses, 263 (44.9%) have been detected in humans, 75 of which are exclusively human and 188 (71.5% of human viruses) zoonotic in origin. No new families have been added to the list since 1988. However, it is estimated that well over a million viruses remain unknown and a significant portion of these may have the ability to infect humans. Therefore, the 263 viruses known to infect people may only represent a fraction of the potential threat iii. Humans are constantly exposed to a huge diversity of viruses. By far the most important nonhuman host taxa are other mammals, with rodents and ungulates most commonly identified as alternative hosts, followed by primates, carnivores and bats. As an example, phylogenetic analysis suggests a likely origin for SARS-CoV-2 (COVID-19) in Rhinolophus spp. bats iv. A minority of the zoonotic viruses (less than 20%) are also known to infect birds; very few have been reported from vertebrates other than mammals or birds. These viruses are genetically diverse and new genotypes, strains and species evolve rapidly, over periods of years or decades. A study using Machine Learning predicts that zoonotic emerging infectious disease risk is elevated in forested tropical regions experiencing land-use changes and where wildlife biodiversity - mammal species richness - is high. However, one must recognize the risk of bias in such analyses. With the inevitable risk of another ‘spill over’ event between a non-human host and a human that results in a pandemic caused by ‘Disease X’, CEPI is planning to address the challenge through the advanced preparation of candidate vaccines that would accelerate even further our future ability to respond to an outbreak. Specifically, two strategic pillars would underpin the overarching goal of preparedness: (i) The generation of ‘banks’ of mRNA-LNP candidate vaccines, expressing immunogens representative of select virus families that pose the greatest significant risk i. Candidate vaccine will be assessed at (i) demonstrate antigen expression in the correct stabilized structural conformation, (ii) preclinical immunological responses and (iii) the generation of immune responses in early clinical studies associated with an acceptable safety profile. ‘Proof-of-concept’ candidate vaccines would then be ‘banked’ across geographical regions to allow rapid responses to outbreaks with an identical or similar virus. Supportive reactive(s) and analytical capabilities would also be distributed accordingly. (2) Prepare and improve vaccine platforms with superior profiles for rapid response. Here, prototypic, well-characterized, disease targets (e.g., Yellow Fever) can be used to drive improvements in the speed of application and production scale of the platform. Live-fire exercises (to test the 100-day response aspiration) can be performed. An expert working group will be convened in the IQ’21 to devise state-of-the-art selection criteria and computational machine learning applications to predict viruses that pose the greatest known or hypothetical risk to transmission to humans, and subsequent human-to-human transmission resulting in significant public disease. Privileged & Confidential leveraging the validation status of the target indication. In the past, Disease X projects have struggled over time to maintain interest. Thus, selecting target indications which will engage developers through to licensure, should also ensure longevity of the Disease X mission. (2) Applying and improving mRNA/LNP technologies Thirty years of discovery, research and development, have recently resulted in the validation of messenger RNA (mRNA) and their Lipid Nanoparticles (LNPs) carriers as a vaccine platform for the prevention of infectious disease, SARS-CoV-2. Pfizer and Moderna have secured emergency use authorization for their mRNA/LNP vaccines in younger and elderly adults and in adults and prescribed in COVID-19. The speed of development was unprecedented with both vaccines: around 300 days from sequence availability to phase 3 interim efficacy results. Millions of doses are destined in 2021 to frontline medical workers, others at risk of COVID-19, and eventually the general population. Globally, over thirty groups are advancing mRNA platforms against COVID-19, in most cases seeking to use LNP formulations for delivery. Moreover, several large vaccine MNCs are pursuing the application of mRNA/LNPs against other infectious diseases, including influenza, rabies, RSV and DAA development. An example of new generation mRNA vaccine platforms are several areas where improvements could result in a superior product profile. The following four main areas require enhancement: 1. Productivity: the current manufacturing process and raw material requirements result in relatively low yields with high cost of goods (COGs). 2. Global manufacturing
footprint: current facilities set-up to manufacture mRNA/LNP vaccines are restricted to the United States, Europe and to a lesser extent in China. 3. Thermal stability: several formulations require -20°C or -70°C storage conditions. 4. Reactogenicity profile: contraindications are emerging following introduction for severe allergic reactions (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components; immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG]). The challenge here resides in finding the right balance between reactogenicity and immunogenicity. Addressing these limitations would allow the rapid utility of mRNA on a truly global scale against COVID-19 and other infectious diseases: namely, a rapidly responsive network of production in all regions, low COGs, sufficient scale, superior tolerability and improved stability for easier distribution. Therefore, CEPI will aim to apply mRNA/LNP technologies, and their improvement, across several areas: Disease X, priority pathogens, Broadly Protective Beta-CoV vaccines and COVID-19 efforts including against clinically relevant SARS-CoV-2 variants. 3. Broadly Protective Beta-CoV vaccines The betacoronaviruses of the greatest clinical importance concerning humans are OC43 and HKU1 (which can cause the common cold) of lineage A, SARS-CoV and SARS-CoV-2 of lineage B, and MERS-CoV of lineage C. MERS-CoV is the first betacoronavirus belonging to lineage C that is known to infect humans. The USAID PREDICT program (2009-2019) identified 113 novel coronaviruses in animals and people in ‘hotspots’ with intensive spillover interfaces, such as live animal markets, caves where bat guano is harvested, and communities that border wildlife habitats. In addition to addressing preparations for the next 4 Privileged & Confidential Disease X, CEPI 2.0 is striving to eliminate the future threat of another beta-coronavirus pandemic. An important first step towards defining the Target Product Profile for such a vaccine, CEPI needs to first articulate the definition of a Broadly Protective Beta-CoV vaccine from a scientific and regulatory pathway perspective. One could aim to generate a vaccine able to protect against the known human betacoronaviruses and their variants. Additionally, one could attempt to protect further against coronaviruses isolated in humans but yet to efficiently transmit from human-to-human. Lastly, one could stretch to derive a vaccine capable of protecting against coronaviruses of concern in animals yet to spill over into humans. A broad consultation is needed to align on the suitable path forward. For humoral immunity, the full-length S protein appears the primary target with which one could derive a broadly protective immunogen, or immunogens. Our growing understanding of the four classes of monoclonal antibody that neutralize and bind to the S protein, combined with a growing knowledge of the antibody repertoire elicited by S-based vaccines, will provide invaluable direction for immunogen design able to broadly protect against betacoronaviruses. CEPI is planning to initiate a new call for Proposals with a strong emphasis on immunogen design. As exemplified in the H1N1-1 field, monoclonal antibody investigations could direct immunogen selection in terms of identifying broadly protective conserved epitopes across the betacoronavirus targets. In addition, computational methods to derive consensus sequences, such as the COBRA approach for influenza, could also advance candidate immunogens of interest. Indeed, efforts to derive broadly protective influenza vaccines can inform the scientific approach. 4. Working Groups In order to prepare for our transition to CEPI 2.0, our R&D group will initiate in the 1Q ‘21 a series of dedicated Working Groups to prepare the necessary scientific and development plans, as well as operational needs, required to launch our new mandate in 2022. Ten working groups have been identified, with multiple overlapping dependencies as follows: 1. mRNA / LNP - state-of-the-art platforms 2. One Health (focus on RVF) 3. Disease X 4. Priority Pathogens - new annual method of evaluation 5. Broadly Protective Beta-Coronavirus (BPBC) 6. Machine Learning & Digital Transformation 7. Mabs for Core Portfolio & beyond (with AHEAD100) 8. Manufacturing innovations/capacity 9. Enabling science priorities 10. Advanced clinical development CEPI welcomes SAC member involvement in these Working Groups in order to secure the best scientific guidance for our path to CEPI 2.0. i Ollivier et al. 2017, Nature 22975 ii Woolhouse et al. 2021, Phil. Trans. R. Soc. B (2012) 367, 2864-2871 iii EcoHealth Alliance, report. iv Latinne et al. 2020, Nature Communications volume 11, Article number: 4235. v Allen et al. Nature Communications, 8, 1124.
Nicely done!

Steven Buchsbaum
[b66]@me.com
www.bermuda-associates.com

On May 18, 2020, at 8:41 AM, David Ecker <DEcker@ionisph.com> wrote:

Dear government (and former government) colleagues,
As you may know, I have been advocating for “agnostic diagnostics” as a national surveillance strategy for more than a decade. I published the same general concept in Scientific American in 2014. I hope the idea will gain some momentum now, and maybe a champion.


Cheers,
Dave

David J. Ecker PhD
Janus-I Science
1396 Poinsettia Ave
Vista, CA 92081

VP of Strategic Innovation
Ionis Pharmaceuticals
2855 Gazelle Court
Carlsbad, CA 92010
Our proposal can greatly help. You can rely on standardized test, no bias, high volume
Ed scolnick
Earhardt, Ainsley [Ainsley.Earhardt@foxnews.com]; Kilmeade, Brian [Brian.Kilmeade@foxnews.com];
brian.williams@nbcul.com; Dana Perino [dana.perino@foxnews.com]; Mark Cuban Chabensky [mcuban@ax.tv];
Edward M. Henry III [ed.henry@foxnews.com]; Mike.Emanuel@foxnews.com; greg.palkot@foxnews.com;
peter.gaynor@fema.gov; david.miller@foxnews.com; Steve Doocy [Steve.Doocy@foxnews.com];
peter.doocy@foxnews.com; Jacob Paul Tapper [jake.tapper@turner.com]; Randal Howard Paul
[press@paul.senate.gov]; Stephen K Bannon [pschweizer@breitbart.com]; Stephen K Bannon
[bsannon@breitbart.com]; steve@breitbart.com; larry@breitbart.com; General John R Allen Brookings President
[jallen@brookings.edu]; Willard Mitt Romney [Mrromney@solamerecapital.com]; Hon Senator Willard Romney
[liz_johnson@senate.gov]; Hon Senator Willard Romney [liz_johnson@senate.gov]; Michael S Lee
[brecken_denler@lee.senate.gov]; Michael Shumway Lee [connell.carroll@lee.senate.gov]; Harris Kimberly Faulkner
[harris Faulkner@foxnews.com]; William George Hemmer [bill.hemmer@foxnews.com]; Alina.Kabaeva@nm-g.ru;
Kari, Jonathan D. [Jonathan.D.Kar1@abc.com]; John D Roberts [john.roberts@foxnews.com]; John Glover Roberts Jr
[rebecca.lawson@supremecourt.uk]; John R Bolton [john.bolton@ai.org]; Geoffrey.Okamoto@treasury.gov;
Geoffrey William Seiji Okamoto [McCourtAlumniboard@georgetown.edu]; Okamoto Geoffrey
[geoffrey.okamoto@imf.org]; Kristalina Georgieva [Kristalina.Georgieva@imf.org]; Sasha.Chavin@icij.org;
mannanbrown@icfc.org; PMejlak@icfc.org; David Malpass [DMalpass@icfc.org]; gerry.rice@imf.org; BWalker@imf.org;
Seema.Verma@hhs.gov; Seema.Verman@census.gov; KarenAldana@census.gov; Ceballos, Kelly (CMS)
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(FYDIBOHF235PDLT/cn=Recipients/cn=e68a916dfd4324e8bbee678c21d69a25e3-3HHS-Kelly.C); Smith, Aaron (CMS)
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(CMS) [/o=Exchange.Labs/o=Exchange.Administrative Group
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(CMS) [/o=Exchange.Labs/o=Exchange.Administrative Group
(FYDIBOHF235PDLT/cn=Recipients/cn=633e7a0706fe479ab77c466a55f03cb-HHS-elizabeth); Brookhart, Julie R (CMS)
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(FYDIBOHF235PDLT/cn=Recipients/cn=91f11a5f3fe406ca61b299eb0a4c88bb-HHS-Julie.B]; Myers, Gregory (CMS)
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(FYDIBOHF235PDLT/cn=Recipients/cn=14d1c9445e634157a2842f06d0a180c8b-HHS-nicole.j]; Jackson, Karen E (CMS)
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(FYDIBOHF235PDLT/cn=Recipients/cn=be9bafef245aae491baa1c01e7e03ad9e4-HHS-Brady.B]; Kimberly.Brandt@cms.hhs.gov; Kouzoukas, Demetrios (CMS) [/o=Exchange.Labs/o=Exchange.Administrative Group
(FYDIBOHF235PDLT/cn=Recipients/cn=87cab5d1c3fe48409195c03dd897988d-HHS-Demetri]; Main, Jennifer (CMS)
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(FYDIBOHF235PDLT/cn=Recipients/cn=3ca2a127f2851485a9e0be9dfe7f90ca4-HHS-Jennifer); FDA Commissioner
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Affairs [/o=Exchange.Labs/o=Exchange/Administrative Group
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(FYDIBOHF235PDLT/cn=Recipients/cn=fb77660891384232a7cd9086fcb1a3b-Anna.Abram]; nafeyan@mit.edu;
Scott Gottlieb [scott.gottlieb@ai.org]; Jay Robert Inslee [david.postman@gov.wa.gov];
david.postman@gov.wa.gov; kelly.wicker@gov.wa.gov; Feng Zijian@chinadcdn.cn; George.Gao@chinadcdn.cn;
Trevor Mundel@gatesfoundation.org; TrevorM@gatesfoundation.org; Dan.Wattendorf@gatesfoundation.org;
DanW@gatesfoundation.org; Melinda@gatesfoundation.org; Bill@gatesfoundation.org;
Morgan.Ortagus@state.gov; eds19@worldbank.org; eds05@worldbank.org; Alison.Morris@nbcul.com;
Janelle.Rodriguez@nbcul.com; Peter.Alexander@nbcul.com; dorriesn@parliament.uk;
jacob.reesmogg.mp@parliament.uk; rishi.sunak.mp@parliament.uk; Hon Alexander Boris de Pfeffel Johnson

FDACBER-2020-5341-0004316
Subject: Mika re:- Depopulator Stanley Johnson, Satanic Masks (mark of the beast) Remdesivir, & Chief Jesuit Inquisitor Anthony Fauci +more Corona Virus Fakery

Full Interview: Biden Denies Sexual Assault Allegation From Tara Reade | Morning Joe | MSNBC
https://www.youtube.com/watch?v=seu_C08yAAM

Hey Mika,

Watching your interview with Joe Biden and have to say you are a very good interviewer. Please, can you consider the attached links for further investigation by your production team who may deem them newsworthy?

Meanwhile, wishing you and Joe a great May Day week-end.

Regards,
Freemasonic Thumbs up from Stanley and Boris

Johnson and Symonds announced birth of baby son they will be the first couple that occupy 10 Downing Street as an unwed couple -
The PM was allowed to be at Carrie's bedside despite some hospitals telling dads to keep their distance because of coronavirus risk. Visiting family members, even newborn grandchildren, is not an excuse to leave the home, according to the Government's own advice. Boris' siblings, Jo, Rachel and Leo Johnson, also won't be able to meet their newborn nephew for the same reason. It might be that the only member of the Johnson clan able to meet the new baby is the couple's dog, Dilyn, who was rescued from a shelter last year and living with them in the Downing Street flat.

Stanley Johnson claims he predicted Covid-19 pandemic in novel published 40 years ago
https://www.amazon.com/Marburg-Virus-Stanley-J…/…/043437704X

Boris Johnson's father, Stanley Johnson has been writing books promoting depopulation for almost fifty years now; starting with 'Life without Birth: A Journey Through the Third World in Search of the Population Explosion' published all the way back in 1970. He's also a former employee of the World Bank and the European Commission; two of the most prominent promoters of 'Carbon' taxation; which would increase the cost of both food and fuel, exponentially. Resolving, they hope, the 'population issue'.

https://twitter.com/Wyrdo_Mk2/status/1240283863173169158
http://www.stanleyjohnson.org/contact/
Matt Hancock's a mediocre minister says Janet Street Porter

Matt is the MP for West Suffolk and was appointed the Secretary of State for Health and Social Care on 9 July 2018. Matt's own profession of faith is very profound, nor very interesting. It's certainly very Anglican, in that he doesn't take orders on it from anyone. And not just Anglican, he would say it's very Church of England. Matt's wife and children are Catholic, and their common faith as a family is a source of strength.

IF YOU'VE EVER BEEN VACCINATED" YOU MUST SEE THIS
https://www.youtube.com/watch?v=Zxf6vK8mEs
Bill Gates Is Funding Coronavirus Vaccine Candidates That Would Compete With Chloroquine, And Dr. Fauci’s Agency Is Co-Partnering On The Project

Chief Jesuit Inquisitor Anthony Fauci +more Corona Virus Fakery, Fauci gives his stamp of approval on a drug that will cut recovery time to 11 days from 15 days, (that's really worth it ain't it Tony?)
https://en.wikipedia.org/wiki/Remdesivir

In this sign ye shall conquer   https://en.wikipedia.org/wiki/College_of_the_Holy_Cross
How the Jesuits push the Measles Vaccinations
(Jesuit College Preparatory School of Dallas offers young men an excellent, Catholic education in the classical Jesuit tradition with the purpose of forming a community of men with high moral principles and service to others.)


Michael McCaul
AKA Michael Thomas McCaul
Born: 14-Jan-1962
Birthplace: Dallas, TX
Jesuit, Roman Catholic - https://www.nndb.com/lists/758/000094476/
https://en.wikipedia.org/wiki/Michael_McCaul
Michael Thomas McCaul Sr. (born January 14, 1962 = He graduated from Jesuit College Preparatory School of Dallas
McCaul is also pushing for "sufficient manufacturing to meet the demand for COVID-19 vaccines.
President Trump in the Oval Office on Friday flanked by, from left, Vice President Pence; Daniel O’Day, the Gilead Sciences C.E.O.; and Stephen Hahn, the F.D.A. commissioner. Erin Schaff/The New York Times

May 01, 2020
Gilead’s Investigational Antiviral Remdesivir Receives U.S. Food and Drug Administration Emergency Use Authorization for the Treatment of COVID-19


Satanic Masks (mark of the beast) & the push for a vaccine for a fake virus (psst..it's the vaccine that will kill you, not the virus)

https://www.youtube.com/watch?v=BEaX_3lhky0
Photo:- A Mask wearer dons a mask depicting the satanic red star -

(b)(6)
Subject: Borge- re yr Selected US President Donna J Trump & UK Prime Minister Boris de Pfeffel Johnson (to run the 2020 Corona Psyop)

To: The Managing Board, chaired by the Forum's President, Børge Brende

Dear Borge,

Saw your twitter feed and noted your comments about vaccines here:-

Børge Brende @borgebrendeApr 26 President World Economic Forum -
#Vaccines one of the greatest medical advances of the past 150 years, have saved hundreds of millions of lives.
#WorldImmunizationWeek is more important than ever — #vaccines are vital for protecting all of us. Now it is paramount to accelerate progress on a #COVID19 vaccine.
Your above quote belies your ex-member Stanley Johnson (father of Boris)

Rachel Johnson with father Stanley (right) with her brother Prime Minister Boris Johnson (middle right)

stance on Depopulation
As you may be aware Stanley Johnson says he predicted the present Corona Virus Psyop - in his book the

Marburg Virus -

The mother of Ebola is the Marburg Virus, the precursor to the Corona Virus 2020
https://www.bitchute.com/video/VgjodSVXac9t/

UK Prime Minister's father, Stanley Johnson claims he predicted Covid-19 pandemic in novel published 40 years ago entitled, The Marburg Virus!
https://www.amazon.com/Marburg-Virus-Stanley-Johnson/dp/043437704X
as well as Prince Charles's stance on depopulation - (Son of Prince Phillip who wants to be reincarnated as a

![VIRUS](image)

speaking of which I noted when the prince met with Klaus Schwab they were in close proximity :

![Prince and Klaus](image)

Hopefully Klaus got tested after it was established the Prince came down with the Corona Virus?
Also, I find it astonishing that your World Economic Forum has so much power, even to the extent of selecting presidents and prime ministers, who are presently in place in the UK in the form of US Citizen Alexande

Boris de Pfeffel Johnson

and Donald John Trump

both of whom have very similar styles of speaking and leading, and they look a lot alike too... as you will note by this photo:-
Proof Flip Flopper Fake President Trump was selected precisely for this moment in time, to run this fake psyop Corona Virus pandemic,

Operation Warpspeed - Trump on Injecting America
https://www.youtube.com/watch?v=ThmgMa3ITHQ

++++++++++++++
by his bosses at the World Economic Forum - where the head of the International Monetary Fund Kristalina Ivanova Georgieva-Kinova has just been made a Trustee -


Kristalina Ivanova Georgieva-Kinova
Managing Director of the International Monetary Fund Georgieva started her career at the World Bank Group in 1993. From 2004 to 2007 she was the institution's director and resident representative in the Russian Federation, based in Moscow. https://en.wikipedia.org/wiki/World_Bank_Group

Trump says we're mobilising our military to distribute the vaccine, by the end of the year - and now we're going to Pennsylvania, where we're opening up and the people want their freedom back, and they're going to get their freedom back -

(as soon as we pump them up with the vaccine) sic

https://www.youtube.com/watch?v=qZCqG3zvxg

I attach some further links for your investigations to follow up on your twitter feed and will be watching out for your twitter comments, meanwhile it does seem to me that in this world presently,
HELL IS EMPTY
AND
ALL THE DEVILS
ARE HERE.

WILLIAM SHAKESPEARE

UN = World Government / Jacob Rothschild standing, Kissinger seated right.
The Jesuits; a complete history of their open and secret proceedings from the foundation of the order to the present time
https://archive.org/details/jesuitscompleteh00grieiala

American red Cross vampires blood drinkers in plain sight
https://www.youtube.com/watch?v=Jhpd2IIRfjs
--WHO and Queen announce children will be taken from homes  
https://www.youtube.com/watch?v=ws3CVXS5qdQ

Red Cross urges Americans to donate blood to prevent shortage during coronavirus scare  
There's great concern about a slowdown in donations during the outbreak.

The super rich are injecting blood from teenagers to gain ‘immortality’  
the super-wealthy are now pumping themselves with the blood of young people in an attempt to prevent themselves from ageing.  
“It's like plastic surgery from the inside out.”

there are dangers of unnecessarily exposing people to the potential risks of blood transfusions, which include hives, lung injury and fatal infections

https://www.bbc.co.uk/bbcthree/article/347828f8-6e7f-4a9b-92ab-95f637a9dc2e?fbclid=IwAR1jivIXsvdlx_YDjkClZefBYUTnBfV3sXryNHm0pQymDMHn-3Vq7L1YEVKI

Blood plasma from Covid-19 survivors

https://www.bbc.co.uk/bbcthree/article/347828f8-6e7f-4a9b-92ab-95f637a9dc2e?fbclid=IwAR1jivIXsvdlx_YDjkClZefBYUTnBfV3sXryNHm0pQymDMHn-3Vq7L1YEVKIimproved

https://www.eveningexpress.co.uk/news/blood-plasma-from-covid-19-survivors-improved-symptoms-of-severely-ill-patients/?fbclid=IwAR3kgNYI93OJOyLohJ3TW7cx23lYJgVWMHPyXIIVhztxxkA9ZmPjyFd92V0
UK Health Secretary Matt Hancock and the Covid-19 trial tests -
UK 'leading world's largest Covid-19 treatment trials'

https://www.dailymail.co.uk/news/article-8256409/Health-Secretary-Matt-Hancock-shares-photo-taking-clinical-trial.html
Jesuit Trained Andrew Mark Cuomo gets a lot of masks sent to him, but he doesn't want to wear one! -
Why they don't want you talking on YouTube about the Corona Virus -
https://www.youtube.com/watch?v=m8nCjNk3djc

Photo:- A Mask wearer dons a mask depicting the satanic red star -
Satanic Masks (mark of the beast) & the push for a vaccine for a fake virus (psst..it's the vaccine that will kill you, not the virus)
https://www.youtube.com/watch?v=BE\_X\_3Ihky0

**Herd Management - The Mask of Death**
https://www.youtube.com/watch?v=W\_YFH545Q-RM

--This Nasty Piece of work at WHO wants to break up families and even take your kids away if you let him---

Ryan is also pushing for trace and track and isolate -
---He advocates a very rapid way to get those infected people out of their homes... now we need to look and find those families where members of that family may be sick..and remove them, and isolate them.."!

https://www.youtube.com/watch?v=SCLUUV-\_MBwY

Michael Joseph Ryan (born 1965) is an Irish Catholic former trauma surgeon. Ryan claims to be an expert at WHO, but in fact he only has practical experience in intervention epidemiology gained from schools that no longer exist!..

Irish Catholics are an ethnoreligious group native to Ireland that are both Catholic and Irish. Irish Catholics have a large diaspora, which includes more than 10 million Americans. The run the police force in Boston, New York and throughout the Eastern Seaboard. [https://en.wikipedia.org/wiki/Irish_Catholics](https://en.wikipedia.org/wiki/Irish_Catholics)

Photo: - Jesuit trained Robert Redfield, CDC Director, and Roman Catholic Tedros Adhanom Ghebreyesus, WHO Director-General, practice a dry run Ebola hoax , when they met in the Democratic Republic of the Congo to discuss the then international Ebola response.

**The CDC , Dr Fauci and The Order of The Jesuits**

[https://www.bitchute.com/video/KdWK6x18A5qa/](https://www.bitchute.com/video/KdWK6x18A5qa/)

Robert Ray Redfield Jr. (born July 10, 1951 is an American virologist. He is the current Director of the Centers for Disease Control and Prevention, and the current Administrator of the Agency for Toxic Substances and Disease Registry, having served in both positions since March 2018. He attended Jesuit Georgetown University School of Medicine, and was awarded his Doctor of Medicine in 1977.

The Poisoned Needle

https://archive.org/details/1_ThePoisonedNeedle(mode/2up)
Hey Lester,

Saw you reporting about the Senate testimony of Drs. Fauci and Redfield and really am astonished at his persistence to continue the lock down. But then I saw a youtube clip and some articles about the Red Cross and blood donations and perhaps that might be one of his motivations. Also one about ex-black panther Bobby Lee Rush now in his mid seventies, introducing his TRACE 666 bill. I attach the relevant links for your further investigations

and wish you a pleasant rest of week and week-end.

Warm Regards: **(b)(6)**
#NOTINAMERICA - https://twitter.com/PgigiL/status/1259218157140574209
H.R. 6666 a devil of a COVID-19 government surveillance plot
Mark of the beas for a beastly, monstrousy unconstitutional bill.
-----A House resolution from Illinois Democrat Rep. Bobby Rush that would put Big Government in charge of tracking citizens’ movements as they relate to COVID-19 mitigation efforts — even sending health bureaucrats to “individuals’ residences,” “as necessary,” as the legislation states — has a most apt number: 6666.
-----After all, what’s more devilishly un-American than launching one of the most massive government surveillance programs of private citizens in U.S. history, all under the guise of protecting people from the coronavirus?
--Rush as Black Panther member: - We consider ourselves as being the vanguard of the revolution,”

-----LET'S NOT FORGET HIS SO CALLED BLACK PANTHER FRIENDS DIE IN A AMBUSH EXCEPT FOR HIM HE IS A CHICAGO CONGRESSMAN ???? FUNNY HOW THAT HAPPENS!!!666 MR. RUSH!!!! CAN WE SAY 6IX9INE WASN'T THE FIRST!!!
https://www.youtube.com/watch?v=WTUFIRd32FM

Rush co-founded the Illinois chapter of the Black Panthers.
https://www.nndb.com/people/297/000040177/
H.R. 6666 -- Rush Introduces Bipartisan Legislation to Fund $100 Billion Coronavirus Testing and Contact Tracing Effort
May 1, 2020
Press Release
--WASHINGTON — Today, U.S. Representative Bobby L. Rush introduced H.R. 6666, the COVID-19 Testing, Reaching and Contacting Everyone (TRACE) Act. This bipartisan bill would establish a grant program run by the Centers for Disease Control and Prevention (CDC) to fully mobilize coronavirus testing and contact tracing efforts. Grantees would include Community Health Centers, School Based Health Centers, academic
medical centers, non-profits, and other entities who would hire and train individuals to operate mobile testing units, as well as outreach in hot spots and medically underserved areas.

Sponsor Bobby Lee Rush (born November 23, 1946)


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The Jesuit Culling Masters, Redfield, Fauci & Cuomo

Fauci Clashes In Tense Moment At Senate Hearing | he wants lockdown extended

Why they don't want is talking on You Tube about the Corona Virus -
https://www.youtube.com/watch?v=m8nCjNk3djC

but why they still want your blood - despite the Virus -

American red Cross vammpires blood drinkers in plain sight
https://www.youtube.com/watch?v=JhpR2lRfjs

--WHO and Queen announce children will be taken from homes
https://www.youtube.com/watch?v=ws3CVXS5qdQ

Red Cross urges Americans to donate blood to prevent shortage during coronavirus scare
There's great concern about a slowdown in donations during the outbreak.

The super rich are injecting blood from teenagers to gain ‘immortality’
the super-wealthy are now pumping themselves with the blood of young people in an attempt to prevent themselves from ageing.

“It’s like plastic surgery from the inside out.”
there are dangers of unnecessarily exposing people to the potential risks of blood transfusions, which include hives, lung injury and fatal infections
UK Health Secretary Matt Hancock and the Covid-19 trial tests -
UK 'leading world's largest Covid-19 treatment trials'

https://www.dailymail.co.uk/news/article-8256409/Health-Secretary-Matt-Hancock-shares-photo-taking-clinical-trial.html
Jesuit Trained Andrew Mark Cuomo gets a lot of masks sent to him, but he doesn't want to wear one! - Why they don't want you talking on You Tube about the Corona Virus - https://www.youtube.com/watch?v=m8nCjNk3djc

Photo:- A Mask wearer dons a mask depicting the satanic red star -
Satanic Masks (mark of the beast) & the push for a vaccine for a fake virus (psst. it's the vaccine that will kill you, not the virus)
https://www.youtube.com/watch?v=BEzX_3lhky0

Herd Management - The Mask of Death
https://www.youtube.com/watch?v=WyFH545Q-RM
Photo: - Jesuit trained Robert Redfield, CDC Director, and Roman Catholic Tedros Adhanom Ghebreyesus, WHO Director-General, practice a dry run Ebola hoax, when they met in the Democratic Republic of the Congo to discuss the then international Ebola response.
This email has been checked for viruses by Avast antivirus software.

www.avast.com
Dear Ana Maria,

These are very good points.

I think that the CEPI meeting as planned will be fully complementary to the global research forum.

Best regards,

Paul-Henri

Provenance: Courrier pour Windows 10

De: HENAO RESTREPO, Ana Maria
Envoyé le: jeudi, 5 mars 2020 09:24
À: Robert Chen; philip.krause@fda.hhs.gov; Simon Funnell; William Dowling; Cesar Munoz-Fontela; GSELL, Pierre
Cc: qinchuan; kanta.subbarao; Perlman, Stanley; rbaric; braham; Arnaud Didierlaurent; Paul Henri Lambert; Steve Black; Corry Dekker; Gaof@im.ac.cn; Andrew Pollard; StanleyPlotkin@vaxconsult.com; Marco.Cavaleri@ema.europa.eu; Gruber, Marion; [o=ExchangeLabs/ou=Exchange Administrative Group (FYDIOBH23SPDLT)/cn=Recipients/cn=5d220ee1a49746899d88f8077e08486-Weirj]; albert.osterhaus@tiho-hannover.de; rouch@bcm.edu; gary.kobinger@phac-aspc.gc.ca; sktseng; rodewaldl@chinadc.c.cn; Flor Munoz; brian.ward@mcgill.ca; eva.vanbraeckel@ugent.be; Svein Rune Andersen; Jakob Cramer; SPEAC Executive Board [eb@speac-cepi.net]; Imanol Urcola Lecuona [imanol@wedo-projects.com]

Objet: RE: URGENT: Save The Date: CEPI-BC meeting on preventing disease enhancement with COVID-19 vaccines

Dear Bob,

Many thanks for the kind invitation.

Given the urgency and the public health imperatives it is important not to duplicate efforts.
We would like to refer to the outcomes of the recent GLobal Research Forum for COVID-19, the discussions in our vaccine expert groups among others.

Also the same pool of experts is invited numerous times.

Any chance that this meetings and efforts focus on aspects not being yet included by other forums?

Perhaps a mapping of questions and complementarias is pertinent?

I am copying Phil Krause we is the Chair our Vaccine expert group and the colleagues who are coordinating the animal model and enhanced disease expert group deliberations.

Thanks for consider including them in these deliberations.

Kind regards,

Ana Maria

Sent from my iPhone

On 4 Mar 2020, at 20:55, Robert Chen wrote:

Dear Colleague,

The Coalition for Epidemic Preparedness and Innovation (CEPI) has funded several programs to develop a vaccine against COVID-19. CEPI has partnered with the Brighton Collaboration (BC) to support the safety assessment of its vaccine candidates. Some prior coronavirus vaccine candidates vs. SARS and MERS have shown enhanced disease (ED) can occur in immunized animals upon subsequent exposure to live virus. To better understand and hopefully prevent this phenomenon with COVID-19 vaccine candidates, CEPI and BC are organizing an urgent internal scientific consensus meeting (Draft Agenda attached; your suggestions welcome).

To cut the challenges, cost, and risk associated with traveling, we plan to hold this meeting on March 12-13, 2020 using an internet conference platform for 5 hours duration on two successive days at the following times on both days:

23:00-04:00+1 (Melbourne)
20:00-01:00+1 (Beijing)
12:00-17:00 GMT (London)
08:00-13:00 EDT (New York)
05:00-10:00 PDT (San Francisco)

You will receive a calendar invite shortly from Imanol Lecuola of WEDO, the meeting logistician shortly. Please accept if you are interested and available to attend as a speaker, moderator, peer reviewer, or observer (you're in last two category unless listed in draft agenda as a speaker or moderator).
We anticipate the meeting outcomes to be presented and published in multiple scientific and policy forums subsequently. We look forward to your reply on your availability and your contribution towards a fruitful meeting. We’ll follow up with more details as soon as we can. Please let me know if you have any questions.

Best regards,

Robert (Bob) Chen MD MA  
Scientific Director, Brighton Collaboration  
email: (b)(6)@gmail.com

JAKOB CRAMER  
Head of Clinical Development  
CEPI

<Draft agenda.Acc Assess ED.4Mar20211_with annexes.pdf>
Dear Colleague,


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Best regards,

Robert (Bob) Chen MD MA
Scientific Director, Brighton Collaboration

email: (b)(6)@gmail.com

JAKOB CRAMER
Head of Clinical Development
CEPI
Accelerated assessment of the risk of disease enhancement with COVID-19 vaccines
A Coalition for Epidemic Preparedness Innovation (CEPI)/Brighton Collaboration (BC) scientific working meeting

Background

- The Coalition for Epidemic Preparedness and Innovation (CEPI) has funded several programs to develop a vaccine against COVID-19. CEPI has partnered with the Brighton Collaboration (BC) to support the safety assessment of its vaccine candidates.
- Pre-clinical studies of various SARS vaccine candidates have indicated a risk of enhanced disease after challenge with SARS-CoV in previously immunized animals (mice, NHPs).
- The mechanism of enhancement appears to be linked either with the induction of an inappropriate immune response (Th2 dominance) associated with the accumulation of eosinophils in lung lesions, or with an enhanced lung inflammation associated with the formation of virus-antibody immune complexes and a cytokine storm.
- To better understand and hopefully prevent this phenomenon with COVID-19 vaccine candidates, CEPI and BC are organizing an urgent internal scientific consensus meeting.

Tentative agenda (GMT, London)

<table>
<thead>
<tr>
<th>Day 1: March. 12, 2020</th>
<th>Total Minutes</th>
<th>Session</th>
</tr>
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<tbody>
<tr>
<td>12:00-12:20 GMT</td>
<td>20</td>
<td>1 Preliminaries</td>
</tr>
<tr>
<td>12:00-12:10</td>
<td>10</td>
<td>1.1 Welcome &amp; Introductions Melanie Saville (CEPI) Bob Chen (BC)</td>
</tr>
<tr>
<td>12:10-12:15</td>
<td>5</td>
<td>1.2 Scope and objectives of the meeting: Jakob Cramer (CEPI)</td>
</tr>
<tr>
<td>12:15-12:20</td>
<td>5</td>
<td>1.3 Videoconference logistics - TBD</td>
</tr>
<tr>
<td>12:20-14:15</td>
<td>115</td>
<td>2</td>
</tr>
<tr>
<td>12:20-12:40 Talk</td>
<td>20</td>
<td>2.1 Lessons from SARS animal models - relevance for COVID-19</td>
</tr>
<tr>
<td>12:40-12:45 Q&amp;A</td>
<td>5</td>
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</tr>
<tr>
<td>12:45-13:05 Talk</td>
<td>20</td>
<td>2.2 Lessons from SARS animal models- relevance for COVID-19</td>
</tr>
<tr>
<td>13:05-13:10 Q&amp;A</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>13:10-13:20 Q&amp;A</td>
<td>10</td>
<td>2.3 Joint Q&amp;A with Kanta Subbarao and Stanley Perlman</td>
</tr>
<tr>
<td>13:20-13:30 Talk</td>
<td>10</td>
<td>2.4 Mouse model of COVID 19 using hACE2 transgenic mice Qin Chuan (Pekin Union Medical College)</td>
</tr>
<tr>
<td>13:30-13:35 Q&amp;A</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>13:35-14:15</td>
<td>40</td>
<td>2.5 Drafting guidance on COVID-19 animal models; moderator: Paul-Henri Lambert (Geneva Centre of Vaccinology)</td>
</tr>
<tr>
<td>14:15-14:20</td>
<td>5</td>
<td>3 Break</td>
</tr>
<tr>
<td>14:20-16:45</td>
<td>145</td>
<td>4 Potential implication of IgG mediated pathology for vaccine design. Should one focus on ACE2-binding epitopes (RBD) to reduce the risk of enhanced antibody-mediated immunopathology?</td>
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<tr>
<td>14:20-14:40 Talk</td>
<td>20</td>
<td>4.1 Structure and function of CoV spike protein</td>
</tr>
<tr>
<td>Time</td>
<td>Duration</td>
<td>Session #</td>
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</tr>
<tr>
<td>14:40-14:55 Q&amp;A</td>
<td>15</td>
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</tr>
</tbody>
</table>
| 14:55-15:15 Talk  
15:15-15:30 Q&A | 20  
15       | 4.2       | Immunogenicity and neutralizing efficacy of truncated spike antigens  
**Barney Graham** (NIH)                                                   |
| 15:30-15:50 Talk  
15:50-16:05 Q&A | 20  
15       | 4.3       | Which immunological/inflammatory markers should we monitor during a  
first Phase 1 trial, including impact of adjuvants?  
**Arnaud Didierlaurent** (Geneva Centre of Vaccinology)                      |
| 16:05-16:45 | 40       | 4.4       | Drafting guidance on COVID-19 immunological markers;  
moderator: **Corry Dekker** (Stanford/BC)                                    |
| 16:45-17:00 | 15       | 5         | Summary, Prepare for Day 2  
**Bob Chen** (BC)                                                            |

**Day 2:**  
March 13, 2020

<table>
<thead>
<tr>
<th>Time</th>
<th>Duration</th>
<th>Session #</th>
<th>Content</th>
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<tbody>
<tr>
<td>12:00-12:20</td>
<td>20</td>
<td>5</td>
<td>Preliminaries</td>
</tr>
</tbody>
</table>
| 12:00-12:10 | 10       | 5.1       | Welcome & Introductions  
**Melanie Saville** (CEPI)  
**Bob Chen** (BC)                                                  |
| 12:10-12:15 | 5        | 5.2       | Scope and objectives of the meeting:  
**Jakob Cramer** (CEPI)                                            |
| 12:15-12:20 | 5        | 5.3       | Videoconference logistics - TBD                                         |
| 12:20-13:50 | 90       | 6         | Review draft guidance on COVID-19 animal models                          |
| 12:20-12:30 | 10       | 6.1       | Summary draft guidance by moderator  
**Paul-Henri Lambert** (Geneva Centre of Vaccinology)                     |
| 12:30-13:50 | 80       | 6.2       | Peer review with web audience guided by moderator & videoconference  
coordinator                                                        |
| 13:50-14:00 | 10       | 7         | Break                                                                   |
| 14:00-15:30 | 90       | 8         | Review draft guidance on COVID-19 immunological markers                  |
| 14:00-14:10 | 10       | 8.1       | Summary draft guidance by moderator  
**Corry Dekker** (Stanford/BC)                                           |
| 14:10-15:30 | 80       | 8.2       | Peer review with web audience guided by moderator & videoconference  
coordinator                                                        |
| 15:30-16:00 | 30       | 9         | Next Steps:  
**Melanie Saville** (CEPI)                                           |
Annex 1: times for the teleconference by Time Zone
12-13 March 2020, Teleconference (2 sessions, 5-hour each)

<table>
<thead>
<tr>
<th>MEETING TIME</th>
<th>TIMEZONE</th>
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<tbody>
<tr>
<td>08:00-13:00</td>
<td>EDT (New York)</td>
</tr>
<tr>
<td>07:00-12:00</td>
<td>CDT (Chicago)</td>
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<tr>
<td>05:00-10:00</td>
<td>PDT (San Francisco)</td>
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<tr>
<td>12:00-17:00</td>
<td>GMT (London)</td>
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<tr>
<td>13:00-18:00</td>
<td>CET (Brussels)</td>
</tr>
<tr>
<td>20:00-01:00+1</td>
<td>CST (Beijing)</td>
</tr>
<tr>
<td>23:00-04:00+1</td>
<td>AEDT (Melbourne)</td>
</tr>
</tbody>
</table>
### Annex 2: tentative agenda (EDT, New York)

<table>
<thead>
<tr>
<th>Day 1: March. 12, 2020</th>
<th>Total Minutes</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00-8:20 EDT</td>
<td>20</td>
<td>1</td>
<td>Preliminaries</td>
</tr>
<tr>
<td>8:00-8:10</td>
<td>10</td>
<td>1.1</td>
<td>Welcome &amp; Introductions Melanie Saville (CEPI) Bob Chen (BC)</td>
</tr>
<tr>
<td>8:10-8:15</td>
<td>5</td>
<td>1.2</td>
<td>Scope and objectives of the meeting: Jakob Cramer (CEPI)</td>
</tr>
<tr>
<td>8:15-8:20</td>
<td>5</td>
<td>1.3</td>
<td>Videoconference logistics - TBD</td>
</tr>
<tr>
<td>8:20-10:15</td>
<td>115</td>
<td>2</td>
<td>Lessons from animal models for zoonotic coronaviruses I and II</td>
</tr>
<tr>
<td>8:20-8:40 Talk 8:40-8:45 Q&amp;A</td>
<td>20 5</td>
<td>2.1</td>
<td>Lessons from SARS animal models - relevance for COVID-19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Review of SARS animal models: young and old mice, mouse adapted virus, hamsters, NHP and ferret model</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Outcomes observed in vaccine studies for SARS in mice, hamster and NHP</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Kanta Subbarao (U of Melbourne)</td>
</tr>
<tr>
<td>8:45-9:05 Talk 9:05-9:10 Q&amp;A</td>
<td>20 5</td>
<td>2.2</td>
<td>Lessons from SARS animal models- relevance for COVID-19</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- SARS hACE2 Tg mice model: immunologic aspects and hypothesis related to eosinophils and/or enhanced pathology</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Relevant findings from MERS models</td>
</tr>
<tr>
<td>9:10-9:20 Q&amp;A</td>
<td>10</td>
<td>2.3</td>
<td>Joint Q&amp;A with Kanta Subbarao and Stanley Perlman</td>
</tr>
<tr>
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<td>9:35-10:15</td>
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<td>Drafting guidance on COVID-19 animal models; moderator: Paul-Henri Lambert (Geneva Centre of Vaccinology)</td>
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<td>Break</td>
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<td>20 15</td>
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<td>Structure and function of CoV spike protein Ralph Baric (UNC)</td>
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<tr>
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<td>20 15</td>
<td>4.2</td>
<td>Immunogenicity and neutralizing efficacy of truncated spike antigens Barney Graham (NIH)</td>
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<tr>
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<td>20 15</td>
<td>4.3</td>
<td>Which immunological/inflammatory markers should we monitor during a first Phase 1 trial, including impact of adjuvants? Arnaud Didierlaurent (Geneva Centre of Vaccinology)</td>
</tr>
<tr>
<td>12:05-12:45 Talk</td>
<td>40</td>
<td>4.4</td>
<td>Drafting guidance on COVID-19 immunological markers; moderator: Corry Dekker? (Stanford/BC)</td>
</tr>
<tr>
<td>12:45-13:00</td>
<td>15</td>
<td>5</td>
<td>Summary, Prepare for Day 2 Bob Chen (BC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 2: March 13, 2020</th>
<th>Total Minutes</th>
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<tbody>
<tr>
<td>8:00-8:20</td>
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<td>5</td>
<td>Preliminaries</td>
</tr>
<tr>
<td>8:00-8:10</td>
<td>10</td>
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</tr>
<tr>
<td>8:10-8:15</td>
<td>5</td>
<td>5.2</td>
<td>Scope and objectives of the meeting: Jakob Cramer (CEPI)</td>
</tr>
<tr>
<td>8:15-8:20</td>
<td>5</td>
<td>5.3</td>
<td>Videoconference logistics - TBD</td>
</tr>
<tr>
<td>Time</td>
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<tr>
<td>8:20-9:50</td>
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<td>6.1</td>
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<td></td>
<td></td>
<td>Summary draft guidance by moderator <strong>Paul-Henri Lambert</strong> (Geneva Centre of Vaccinology)</td>
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<td>8:30-9:50</td>
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<td>6.2</td>
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<td></td>
<td></td>
<td>Peer review with web audience guided by moderator &amp; videoconference coordinator</td>
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<td>9:50-10:00</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Next Steps: <strong>Melanie Saville (CEPI)</strong></td>
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# Annex 3: tentative agenda (CDT, Chicago)

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<th>Day 1: March. 12, 2020</th>
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<tr>
<td>7:00-7:10</td>
<td>10</td>
<td>1.1</td>
<td>Welcome &amp; Introductions <strong>Melanie Saville</strong> (CEPI) <strong>Bob Chen</strong> (BC)</td>
</tr>
<tr>
<td>7:10-7:15</td>
<td>5</td>
<td>1.2</td>
<td>Scope and objectives of the meeting: <strong>Jakob Cramer</strong> (CEPI)</td>
</tr>
<tr>
<td>7:15-7:20</td>
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<td>2.1</td>
<td>Lessons from SARS animal models - relevance for COVID-19</td>
</tr>
<tr>
<td>7:40-7:45 Q&amp;A</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:45-8:05 Talk</td>
<td>20</td>
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<td>Lessons from SARS animal models- relevance for COVID-19</td>
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<td>8:05-8:10 Q&amp;A</td>
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</tr>
<tr>
<td><strong>Kanta Subbarao</strong> (U of Melbourne)</td>
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</tr>
<tr>
<td>8:10-8:20 Q&amp;A</td>
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<td>2.3</td>
<td>Joint Q&amp;A with <strong>Kanta Subbarao</strong> and <strong>Stanley Perlman</strong></td>
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<tr>
<td>8:30-8:35 Q&amp;A</td>
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<td></td>
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<tr>
<td>8:35-9:15</td>
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## Annex 4: tentative agenda (PDT, San Francisco)

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### Day 2: March 13, 2020

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<td>2.4 Mouse model of COVID 19 using hACE2 transgenic mice</td>
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<td>2:15-2:30 Q&amp;A</td>
<td>15</td>
<td><strong>Barney Graham</strong> (NIH)</td>
</tr>
<tr>
<td>2:30-2:50 Talk</td>
<td>20</td>
<td>4.3 Which immunological/inflammatory markers should we monitor during a first Phase 1 trial, including impact of adjuvants? <strong>Arnaud Didierlaurent</strong> (Geneva Centre of Vaccinology)</td>
</tr>
<tr>
<td>2:50-3:05 Q&amp;A</td>
<td>15</td>
<td>4.4 Drafting guidance on COVID-19 immunological markers; moderator: <strong>Corry Dekker</strong>? (Stanford/BC)</td>
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<tr>
<td>3:05-3:45</td>
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<td>5 Summary, Prepare for Day 2 <strong>Bob Chen</strong> (BC)</td>
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<th>Day 2: March 13, 2020</th>
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<tr>
<td>23:00-23:20</td>
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<td>5 Preliminaries</td>
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<tr>
<td>23:00-23:10</td>
<td>10</td>
<td>5.1 Welcome &amp; Introductions <strong>Melanie Saville</strong> (CEPI) <strong>Bob Chen</strong> (BC)</td>
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<td>5.2 Scope and objectives of the meeting: <strong>Jakob Cramer</strong> (CEPI)</td>
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<tr>
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<td>6 Review draft guidance on COVID-19 animal models</td>
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<td>00:50-01:00</td>
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<td>01:00-02:30</td>
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<td>02:30-03:00</td>
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## Annex 7: tentative agenda (CET, Brussels)

### Day 1: March 12, 2020

<table>
<thead>
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<th>Session</th>
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<td>Preliminaries</td>
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<tr>
<td>13:00-13:10</td>
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<td>1.1</td>
<td>Welcome &amp; Introductions <strong>Melanie Saville</strong> (CEPI) <strong>Bob Chen</strong> (BC)</td>
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<td>Scope and objectives of the meeting: <strong>Jakob Cramer</strong> (CEPI)</td>
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<td>1.3</td>
<td>Videoconference logistics - TBD</td>
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<tr>
<td>13:40-13:45 Q&amp;A</td>
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<tr>
<td>13:45-14:05 Talk</td>
<td>20</td>
<td>2.2</td>
<td>Lessons from SARS animal models- relevance for COVID-19</td>
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<tr>
<td>14:05-14:10 Q&amp;A</td>
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<tr>
<td>14:10-14:20 Q&amp;A</td>
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<td>2.3</td>
<td>Joint Q&amp;A with <strong>Kanta Subbarao</strong> and <strong>Stanley Perlman</strong></td>
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<tr>
<td>14:20-14:30 Talk</td>
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<td>2.4</td>
<td>Mouse model of COVID 19 using hACE2 transgenic mice</td>
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<tr>
<td>14:30-14:35 Q&amp;A</td>
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<td><strong>Qin Chuan</strong> (Pekin Union Medical College)</td>
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<tr>
<td>14:35-15:15</td>
<td>40</td>
<td>2.5</td>
<td>Drafting guidance on COVID-19 animal models; moderator: <strong>Paul-Henri Lambert</strong> (Geneva Centre of Vaccinology)</td>
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<td>15:15-15:20</td>
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<td>3</td>
<td>Break</td>
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<tr>
<td>15:20-17:45</td>
<td>145</td>
<td>4</td>
<td>Potential implication of IgG mediated pathology for vaccine design. Should one focus on ACE2-binding epitopes (RBD) to reduce the risk of enhanced antibody-mediated immunopathology?</td>
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<tr>
<td>15:20-15:40 Talk</td>
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<td>4.1</td>
<td>Structure and function of CoV spike protein</td>
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<td>15:40-15:55 Q&amp;A</td>
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<td><strong>Ralph Baric</strong> (UNC)</td>
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<td>15:55-16:15 Talk</td>
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<td>4.2</td>
<td>Immunogenicity and neutralizing efficacy of truncated spike antigens</td>
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<tr>
<td>16:15-16:30 Q&amp;A</td>
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<td><strong>Barney Graham</strong> (NIH)</td>
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<td>16:30-16:50 Talk</td>
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<td>17:45-18:00</td>
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<td>Summary, Prepare for Day 2 <strong>Bob Chen</strong> (BC)</td>
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### Day 2: March 13, 2020

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<td>Time</td>
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<td>13:30-14:50</td>
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<td>Peer review with web audience guided by moderator &amp; videoconference coordinator</td>
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<td>Break</td>
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<tr>
<td>16:30-17:00</td>
<td>30</td>
<td>9</td>
<td>Next Steps: <strong>Melanie Saville</strong> (CEPI)</td>
</tr>
</tbody>
</table>
Dear Bob,

Many thanks for the kind invitation.

Given the urgency and the public health imperatives it is important not to duplicate efforts?

We would like to refer to the outcomes of the recent GLocal Research Forum for COVID-19, the discussions in our vaccine expert groups among others.

Also the same pool of experts is invited numerous times.

Any chance that this meetings and efforts focus on aspects not being yet included by other forums?

Perhaps a mapping of questions and complementarities is pertinent?

I am copying Phil Krause we is the Chair our Vaccine expert group and the colleagues who are coordinating the animal model and enhanced disease expert group deliberations.

Thanks for consider including them in these deliberations.

Kind regards,

Ana Maria

Sent from my iPhone
On 4 Mar 2020, at 20:55, Robert Chen <(b)(6) @gmail.com> wrote:

Dear Colleague,


Some prior coronavirus vaccine candidates vs. SARS and MERS have shown enhanced disease (ED) can occur in immunized animals upon subsequent exposure to live virus. To better understand and hopefully prevent this phenomenon with COVID-19 vaccine candidates, CEPI and BC are organizing an urgent internal scientific consensus meeting (Draft Agenda attached; your suggestions welcome).

To cut the challenges, cost, and risk associated with traveling, we plan to hold this meeting on March 12-13, 2020 using an internet conference platform for 5 hours duration on two successive days at the following times on both days:

23:00-04:00+1 (Melbourne)
20:00-01:00+1 (Beijing)
12:00-17:00 GMT (London)
08:00-13:00 EDT (New York)
05:00-10:00 PDT (San Francisco)

You will receive a calendar invite shortly from Imanol Lecuola of WEDO, the meeting logistician shortly. Please accept if you are interested and available to attend as a speaker, moderator, peer reviewer, or observer (you're in last two category unless listed in draft agenda as a speaker or moderator).

We anticipate the meeting outcomes to be presented and published in multiple scientific and policy forums subsequently. We look forward to your reply on your availability and your contribution towards a fruitful meeting. We'll follow up with more details as soon as we can. Please let me know if you have any questions.

Best regards,

Robert (Bob) Chen MD MA
Scientific Director, Brighton Collaboration
email: (b)(6) @gmail.com
JAKOB CRAMER
Head of Clinical Development
CEPI

<Draft agenda.Acc Assess ED.4Mar20211_with annexes.pdf>
Dear All,

Please find below today’s agenda -

CC: William Dowling [william.dowling@cepi.net]; Mark Page [Mark.Page@nibsc.org]

Subject: [COVID-19] 12th Assay call - today’s agenda -
1. Miao XU, Deputy Director, Institute for Biological Products Control, National Institutes for Food and Drug Control (NIFDC) – Establishment and Validation of a pseudovirus neutralization assay and development of national antibody standard

2. Kathy Rowlen, CEO&CSO, InDevR, Establishment and Validation of a Multiplex CoV serology assay

3. And other Updates and general discussion

Thanks for your continuous support all.

Kind regards

Pierre-Stéphane Gsell
Technical Officer
R&D Blueprint | Health Emergencies Programme | 1156
World Health Organization | Avenue Appia 20 | 1211 Geneva 27 | Switzerland
Desk: +41.22.791.50.74 | Mob: [MASKED] gsellp@who.int
Hi John,

Thank you for the updates.

Have a nice weekend,

Zhiping

---

From: Balog, John  
Sent: Friday, August 16, 2019 10:10 AM  
To: Ye, Zhiping <Zhiping.Ye@fda.hhs.gov>  
Subject: Winnipeg update

Hello Dr. Ye.  
Here is the latest I’ve seen on the CA NML at Winnipeg.

Regards, jb


Weaponizing Medicine: China’s Latest Theft a Potential Biological Weapon  
Christopher Burgess / Aug 15, 2019  
On the heels of finding that the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) had its level 3 and 4 biological research labs sanctioned by the Centers for Disease Control and Prevention, we learn that many of those same viruses that USAMRIID was researching are on their way to China, courtesy of a Canadian laboratory.

In early July 2019, Xiangguo Qui, a Chinese scientist at the National Microbiology Laboratory in Winnipeg, was dismissed and her ties with the University of Manitoba cut. What makes this somewhat unusual is that Qui is recognized globally as one of the leading researchers on infectious diseases. Furthermore, Qui is credited with being instrumental in creating a new drug for treating the Ebola virus. Despite her accomplishments, the CBC reports that Qui, her husband Keding Cheng, and her students were “forcibly dispatched from the facility on July 5.

In response to pathogen samples being sent to China, the National Microbiology Laboratory spokesperson commented:
“To advance scientific work worldwide, the National Microbiology Laboratory routinely shares samples of pathogens and toxins with partner laboratories in Canada and in other countries. These transfers follow strict protocols.”

from canada To china, with love: Henipavirus and Ebola

The Royal Canadian Mounted Police are investigating the sharing of Ebola, as well as a second pathogen, a henipavirus, which in real life kills 100% of those infected. While the lab claims this is normal and is part of the global research into deadly pathogens, the potential transfer of knowledge to China may be advancing their biological weapons program.

In a research paper published by the National Institutes of Health, National Library of Medicine, the authors note, “Continued outbreaks of Henipaviruses in South Asia and Australia cause severe and lethal disease in both humans and animals. Together, with evidence of human to human transmission for Nipah virus and the lack of preventative or therapeutic measures, its threat to cause a widespread outbreak and its potential for weaponization has increased.”

Providing the henipavirus to China would seem to feed the weaponization narrative. One could also argue that given the proximity of the henipavirus outbreaks in South Asia, research into treatment is a high priority for China.

Intellectual property theft of the virus?

The Ebola treatment drug, ZMapp, in which Qui had a collaborative hand, has already been cloned (pun intended) by a Chinese company, even though the the experimental drug was under patent. The Chinese firm, Mabworks, admitted they had duplicated the drug without authorization, and then continued working with researchers in Canada.

Digging into Qui’s dismissal, coupled with the obtuse and contradictory statements coming out of named and unnamed sources to the Canadian press, the worst case scenario is that Qui, her husband and research students made possible an unauthorized transfer of technology and deadly pathogens to China. They facilitated the theft of research and pathogen strains by China. The other end of the spectrum has Qui being investigated for administrative lapses which exposed intellectual property to a foreign entity in an unauthorized manner, though without malice or interest in advancing China’s biological weapons program, nor putting coin into her own pocket.

Bottom line?
China now has samples of the henipavirus and research from the Canadian National Lab, which may be useful in advancing China’s biological weapons program, occurring at a time the USAMRIID’s defensive biological research lab is shut down.

"OLE Object: Picture (Device Independent Bitmap)" | "OLE Object: Picture (Device Independent Bitmap)"

"File: Balog_John.vcf"