Summary of Discussions between NASEM and CAS on COVID-19, 13Oct 2020

1. CAS (George Gao) provided an overview of the COVID-19 vaccine efforts underway in China. Key points were as follows:
   a. 7 different vaccine approaches are underway (list was shared)
   b. Range from classic inactivated vaccines to live, attenuated candidates
   c. Vaccine underdeveloped based on modified “cold adapted” influenza vaccine as a live, attenuated vaccine for COVID-19 following nasal administration.
   d. Several candidates are in Phase 3 clinical trials (Brazil, Argentina and UAE mentioned, but perhaps other locations as well)

2. Human monoclonal antibody candidates are being developed for clinical use
   a. Multiple candidates are under study
   b. Collaborations with Lilly to create a 2 monoclonal antibody cocktail was mentioned. This product is in clinical trials (now on hold) in the USA.
   c. Several questions were raised:
      i. Protective efficacy of candidates
      ii. Impact on/activity in lungs
      iii. Duration of maby protection
      iv. Possibility of antibody dependent enhancement
      v. Possible impact on vaccination

3. A general discussion of the value and challenges associated with the creation of a universal coronavirus vaccine similar to ongoing discussions about a possible universal vaccine for influenza.
   a. Comment (Stanley Perlman) about the possibility of including T cell epitopes as a component of a universal coronavirus vaccine given demonstrated cross-reactivity among recognized coronaviruses.

4. NAS (Nancy Connell) shared an overview of the USA “Warp Speed” vaccine development efforts underway.
   a. 4 vaccine platforms are being developed with 2 candidates supported in each platform technology (list shared)
   b. Most candidates will require a prime/boost administration
   c. mRNA candidates will require an ultralow temperature cold chain that will be demanding to implement
   d. Many are in Phase 3 clinical trials with the mRNA candidates most advanced
   e. Selection of technologies was based in part on ease of production
   f. Results of clinical studies may be available incrementally with the mRNA candidates farthest along; results known perhaps by Nov-Dec 2020; others at roughly 2 month intervals with the replicating live vaccine results available in late 2021.
   g. Vaccine production is underway concurrent with clinical trials, with approximately 100 M doses of mRNA vaccine available around the end of 2020. Manufacturing costs provided by USG (BARDA).

5. Discussion of challenges associated with USA vaccine development and roll-out strategy.
   a. Key questions: is the candidate safe, is it effective in preventing infection/disease, and what is the duration of protection (Harvey’s comments)
b. How to manage multiple “successful” candidates with differing vaccination schedules and other requirements

c. How to detect adverse events

d. If EUA is granted early, those receiving placebo with receive the vaccine, leading to challenges in interpretation late onset adverse events (Ralph’s comment)

e. For all candidate vaccines (USA and China), what is the strategy for select segments of the population—children, elderly, high risk occupations, others—still being addressed in China; Just released NASEM report on equitable distribution of vaccine discussed by Nancy and slide of 4 tiers of those to be vaccinated shared.

6. Review of vaccination efforts for animal diseases caused by coronaviruses (Linda Saif)

   a. Linda gave a comprehensive review of several vaccine development efforts, especially those associated with swine (list provided)

   b. Challenges encountered in producing protective vaccines for piglets

   c. Difficulties in generating mucosal immunity/IgA

7. Discussion of lessons learned from animal coronaviruses and how they might foretell problems with COVID-19 vaccination

   a. Relevance of past infection versus naïve populations on response to vaccines

   b. Mention of evidence of naturally occurring recombination of coronaviruses infecting swine in Europe.
Greetings,

Thank you for joining the dialogue session last night. I have attached the slides from the three presentations.

FYI CAS has invited two additional CCDC experts to the session tonight.

Dr. Huaqing Wang, PI, Immunization program, Chinese Center for Disease Control and Prevention
Dr. Zundong Yin, Director of National Immunization Program, Chinese Center for Disease Control and Prevention

Looking forward seeing and hearing from you all in a few hours.
Session 2: Wednesday October 14, 9-11 PM ET / 6-8 PM PT in U.S.
Meeting Link: https://nasem.zoom.us/j/98420889232?pwd=NFJJ2LF1eWgx0xOZH0zQWxMbnJPdz09
Password: 375761

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

Greetings,

I have attached what should be the final agenda for the U.S. China dialogue meeting sessions on Tuesday, October 13 and
Looking forward to seeing/talking to you all on Tuesday and Wednesday evening.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

***

Session 1: Tuesday, October 13, 9-11 PM ET / 6-8 PM PT in U.S.
Meeting Link: https://nasem.zoom.us/j/29754903815?pwd=OUV2R38PdDdbDdZ724Gd4VjJoUT09
Password: 833624

Session 2: Wednesday October 14, 9-11 PM ET / 6-8 PM PT in U.S.
Meeting Link: https://nasem.zoom.us/j/98420889232?pwd=NFJkZ1eWgxTDZHQ3QWxMbnJPDz09
Password: 375761

From: Rusek, Benjamin
Sent: Friday, October 9, 2020 5:43 PM
To: 'relman@stanford.edu' <relman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffin@jhmi.edu' <dgriffin@jhmi.edu>; 'peggy@hbaf.net' <peggy@hbaf.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidfranz@gmail.com)'; <davidfranz@gmail.com>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenthal@nas.edu>; 'antoinette_baric@med.uncc.edu' <antoinette_baric@med.uncc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSsharples@nas.edu>
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links
Importance: High

Greetings,

We are looking forward to the two virtual bio dialogue sessions set to take place on Tuesday, October 13 (9-11 PM ET / 6-8 PM PT) and Wednesday, October 14 (9-11 PM ET / 6-8 PM PT) next week. Like in previous sessions we expect that the Chinese expert participants will lead the discussion on the majority of the topics and that the format will be more of a discussion among the participants instead of a series of formal presentations. I have attached an agenda that includes the Zoom connection links for both days along with the U.S. participant list. If I get the Chinese participant list before the session I will send that out to you all.

Feel free to respond to this email with any thoughts, points of emphasis or issues that you would like to discuss among the U.S. group before the sessions. Also let me know if you have any questions or concerns.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Rusek, Benjamin
Sent: Monday, September 21, 2020 9:01 PM
Subject: Virtual U.S. China dialogue meeting October 13 and 14

Importance: High

Greetings,

I hope you all had a good summer and are staying safe and healthy. The Chinese Academy of Sciences has agreed to hold another (4th) virtual bio dialogue meeting with NASEM on 1) vaccine development and delivery and 2) immunity, testing and diagnostics. The agreed topics for the session are below. We have reserved Tuesday, October 13 (9-11 PM ET / 6-8 PM PT) and Wednesday, October 14 (9-11 PM ET / 6-8 PM PT) to discuss the topics on the agenda.

We hope you are able to participate. Please let me know if you are available and if so save the dates and times on your calendar. We will get back to you with more information and a detailed agenda for the sessions soon.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

***

Vaccine development and delivery

Human
1) Current status of CoVid-19 vaccine development in China and the U.S.
2) Chinese vaccination of military personnel and other Chinese populations
3) Vaccination of pediatric populations
4) Active surveillance strategies for monitoring adverse events observed after vaccination (as well as immunogenicity)
5) Adapting current vaccine platforms to novel mass vac strategies and other mass vaccination strategic issues
6) Progress on a universal influenza vaccines
7) Vaccine for enterovirus D68

Animal
1) Status of corona virus vaccination for animals - kinds of vaccine, efficacy, complications, etc
2) ASF in China and ASF vaccine progress
3) New swine coronavirus
4) Vaccination strategy for H5N1 avian influenza and domestic poultry

Immunity, testing and diagnostics
1) Correlates of immunity including the possibility of background immunity from circulating “common cold” coronaviruses
2) Chinese diagnostic testing strategies for testing large populations quickly
3) Antibody and antibody testing topics, importance of T-cell responses
4) Long-term sequela following CoVid-19 infection—lung function, neurologic issues, others
Greetings,

I have attached the American version of the agenda for the 3rd U.S. China virtual dialogue meeting on immunity and related topics set to take place on Tuesday night, June 9 from 9:00-11:00 PM ET (9-11 AM the next morning, Beijing time).

As you can see we have incorporated George Gao’s questions into the agenda, we hope that Harvey Fineberg can provide information on and lead the discussion of 1) serologic investigation in the U.S. 2) strategy in the U.S. for the second half of this year 3) vaccine availability in the U.S. and that Ralph Baric can do the same re progress in the development of vaccine in the U.S. (especially mRNA vaccine).

We have also listed delegation member names after the other Immunity questions. Like previously, folks are listed simply so someone is responsible for getting an answer from the Chinese to each question during the discussion. I will send a version to CAS without those names listed but will let them know who we have asked to answer George’s questions.

Please let us know if you have any thoughts or comments on the agenda or this plan. I will send you the Zoom link later tonight or tomorrow morning.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Rusek, Benjamin
Sent: Monday, June 1, 2020 10:03 AM
To: 'elman@stanford.edu' <elman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>
subject: 'antonette_baric@med.unc.edu' <antonette_baric@med.unc.edu>; andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; 'davidfranz@gmail.com' <davidfranz@gmail.com>; 'Nancy Connell' <NancyConnell@jhu.edu>

Subject: RE: 3rd Virtual U.S. China dialogue meeting on COVID-19 Tuesday, June 9, 9-11PM ET

Importance: High

Greetings,

Good news, just heard back from CAS. They agreed to hold the 3rd dialogue meeting on the proposed immunity topics on Tuesday, June 9 from 9:00-11:00 PM ET (9-11 AM the next morning, Beijing time). Please hold that time on your calendar.
CAS let us know that George Gao wants to add the following questions to the discussion:

- Could any US participant introduce the progress in the development of vaccine in the US, especially mRNA vaccine?
- How is the overall situation of serologic investigation in the US?
- What is the COVID-19 prevention and control strategy in the US for the second half of this year? When do you expect COVID-19 vaccine to be available in the US?

We will send out a new agenda and Zoom link for the meeting later in the week.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975
Vaccine development

Future hope
Major forms of coronavirus vaccine

- Virus-like particle (Nano-particle)
- Inactivated
- Live attenuated
- Protein subunit
- Viral vectored

1. Inactivation
2. Attenuation
3. mRNA inactivation
4. DNA
5. Protein subunit
6. Viral vectored
7. Virus-like particle (Nano-particle)
全球新冠疫苗研发现况（截至2020年9月9日，全球有180种候选疫苗）

- 35种进入人体临床试验，9种进入临床III期
  - 非复制病毒载体（4）：Ad5, ChAdOx1, Ad5+ Ad26, Ad26
  - RNA（2）：mRNA-1273, mRNA-BNT162b
  - 灭活疫苗（3）：中生北京所、中生武汉所、科兴
  - DNA：INO-4800等
  - 蛋白亚单位：NVX CoV2373等

- 145种在临床前研究阶段，主要技术路线：
  - 蛋白亚单位（51）
  - 非复制病毒载体（19）
  - 复制型病毒载体（19）
  - RNA（17）, DNA（12）
  - 病毒样颗粒（12），灭活（9）
  - 减毒（3）
<table>
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<tr>
<th>企业</th>
<th>疫苗类型</th>
<th>临床试验</th>
<th>目标人群</th>
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<th>进展</th>
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<td>Ad5载体疫苗</td>
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<td>18-60岁</td>
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<td></td>
<td></td>
<td>II期</td>
<td>≥18岁</td>
<td>1</td>
<td>完成</td>
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<tr>
<td></td>
<td></td>
<td>III期</td>
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<td>1</td>
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<td>I + II期</td>
<td>≥6岁</td>
<td>2</td>
<td>阿联酋、秘鲁、摩洛哥、</td>
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<tr>
<td></td>
<td></td>
<td>III期</td>
<td>≥18岁</td>
<td>2</td>
<td>阿根廷、埃及</td>
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<td>灭活疫苗(Vero)+铝佐剂</td>
<td>I + II期</td>
<td>≥3岁</td>
<td>2</td>
<td>已完成</td>
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<tr>
<td></td>
<td></td>
<td>III期</td>
<td>≥18岁</td>
<td>2</td>
<td>巴西、印尼</td>
</tr>
<tr>
<td>北京科兴</td>
<td>灭活疫苗(Vero)+铝佐剂</td>
<td>I + II期</td>
<td>18-59岁;≥60岁</td>
<td>2</td>
<td>以色列</td>
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<td></td>
<td></td>
<td>III期</td>
<td>18-59岁, ≥60岁</td>
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<td>I + II期</td>
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<td>18-55岁;≥55岁</td>
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<td>进行中</td>
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<td>四川大学华西医院</td>
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<td>重组蛋白疫苗（CHO）</td>
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<td>4月10日</td>
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- Hot Spot: ChAdOx1腺病毒载体疫苗 (AZD1222)

  ➤ 由牛津大学与阿斯利康合作开发

  - 腺病毒载体疫苗
  - 以复制缺陷型猴腺病毒为载体，包含SARS-CoV-2的全长结构表面糖蛋白（S蛋白）的腺病毒载体疫苗
  - 该平台尚未用于已批准的疫苗，但已在针对其他病毒（包括埃博拉病毒）的实验性疫苗中进行了测试。

  ➤ 临床试验分期：Ⅲ期临床试验

  - 美国、英国、巴西、南非

  - 18-55岁健康成人

  ※阿斯利康与深圳康泰公司签署了技术转让的合作协议

AZD1222因疑似不良反应暂停临床试验

- 9月8日，阿斯利康表示一个英国受试者出现一种无法解释的疾病
- 该公司该疫苗在全球临床试验都暂停，旨在确保受试者安全
- 9月10日，阿斯利康CEO Pascal Soriot在电话会议中表示
  - 患上无法解释疾病的受试者是否为横贯性脊髓炎仍正在检查
  - 今年7月也曾发现一名疫苗接种者出现了神经系统症状，一度暂停临床试验，后被诊断患有多发性硬化症，独立审查小组结论为多发性硬化症与疫苗接种无关

9月12日，英国恢复了阿斯利康牛津新冠病毒疫苗AZD1222的临床试验
横贯性脊髓炎

- 脊髓局限性炎性病变过程，导致运动、感觉和自主神经功能障碍
  - 疼痛、肌肉无力、瘫痪、感觉问题或膀胱和肠道功能障碍
- 横贯性脊髓炎的确切病因不清楚
  - 一些影响脊髓的病毒、细菌和真菌感染可能导致横断性脊髓炎

### Table 1  Cases of transverse myelitis following vaccination

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Vaccine</th>
<th>Age (years)</th>
<th>Time from vaccination</th>
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<td>Bre49</td>
<td>2007</td>
<td>Rabies</td>
<td>25</td>
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<td>2007</td>
<td>Typhoid</td>
<td>19</td>
<td>5 days</td>
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<td>Kelly56</td>
<td>2006</td>
<td>OPV + DT + Hib</td>
<td>0.5</td>
<td>7 days</td>
</tr>
<tr>
<td>Riet-Romero43</td>
<td>2006</td>
<td>OPV</td>
<td>0.7</td>
<td>17 days</td>
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<td>2004</td>
<td>Measles or Rubella</td>
<td>9</td>
<td>16 days</td>
</tr>
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<td>Kulkami51</td>
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<td>Rubies</td>
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*41.5, average of all four cases presented by Shaw et al.33*
Johnson & Johnson: Ad26
Virus vectored vaccine strategy: Ad5-COVID-19
CanSino Biological Inc. with Beijing Institute of Biotechnology

Approved for IND in China on 17th, March, 2020

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

In May, Lancet published the data for phase I clinical trials

Safety and immunogenic for both humoral and cellular responses
Virus vectored vaccine strategy: Ad5-COVID-19
CanSino Biological Inc. with Beijing Institute of Biotechnology

Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial

In Jul., Lancet published the data for phase II clinical trials

NCT04526990; NCT04540419

Currently under Phase III overseas multi-center clinical trials

Safety and immunogenic for both humoral and cellular responses
鼻喷流感载体新冠肺炎疫苗

- 由厦门大学、香港大学和北京万泰生物药业股份有限公司共同研发
- 核心技术是CA4-DeINS1，是将California/04/2009(H1N1)流感病毒株的NS1基因敲除后再经低温适应获得的减毒且温度敏感的双重减毒流感载体，缺失NS1可显著增强T细胞免疫应答
- 该疫苗是在CA4-DeINS1内插入新冠病毒RBD基因片段研制而成的活病毒载体疫苗，是目前已获准开展临床试验的新冠肺炎候选疫苗中唯一采用鼻腔喷雾接种方式的疫苗

1月27日启动研发 8月27日获批临床 9月1日启动一期临床
鼻喷流感载体新冠肺炎疫苗

该疫苗在动物模型中呈现出对流感病毒和新冠病毒的双重保护效果：
✓ 小鼠实验显示：对甲型H1N1流感病毒的致死性感染保护率为100%。
✓ hACE2小鼠和仓鼠实验显示：攻毒对照组肺组织出现中至重度病理损伤且体重明显下降，疫苗免疫可明显减轻肺组织病理损伤，体重无明显下降。

该疫苗通过模拟呼吸道病毒天然感染途径激活局部和全身性免疫应答，在动物体内可诱导出较强的RBD特异性细胞应答，尤其以肺组织局部T细胞应答为突出特征，同时可检测到RBD特异性抗体应答，包括粘膜局部的IgA。

该疫苗于9月1日启动一期临床试验，已完成63名受试者接种，显示出良好安全性：
✓ 正常年龄组 (18-59岁) 不良反应发生率为28.13% (9/32)，其中2级2人，1级7人。
- Inactivated vaccine, BBIBP-CorV
- Protein subunit vaccine
Seed virus selection for COVID-19 vaccine

3 virus strains isolated from broncho-alveolar lavage samples or throat swabs of 3 hospitalized patients

- 19nCoV-CDC-Tan-HB02
- 19nCoV-CDC-Tan-Strain03 (CQ01)
- 19nCoV-CDC-Tan-Strain04

Lu et al., Lancet, 2020
Zhu et al., NEJM, 2020

Wang et al., Cell, 2020
Flowchart of preparing the inactivated COVID-19 virus vaccine, BBIBP-CorV

Wang et al., Cell, 2020
Time-course of the BBIBP-CorV vaccine development
- Inactivated vaccine, BBIBP-CorV
- Protein subunit vaccine
Overview of the protein subunit COVID-19 vaccine

* A universal design of betacoronavirus vaccines

Dai et al., 2020, Cell

* The first protein subunit COVID-19 vaccine approved for clinical trials in China and the second in the world
Rational design of tandem repeat RBD single chain dimer

- A generalizable strategy to design vaccines against MERS, COVID-19, SARS and other CoV diseases

- RBD-sc-dimer induced significantly higher NAbs compared to conventional monomer

Dai et al., 2020, Cell
Clinical trials of the first protein subunit vaccine in China

On 19 June 2020, vaccine was approved by the NMPA to enter Phase I clinical trials in China

On 10 July 2020, vaccine enters Phase II clinical trials in China

<table>
<thead>
<tr>
<th>Platform</th>
<th>Type of candidate vaccine</th>
<th>Developer</th>
<th>Coronavirus target</th>
<th>Current stage of clinical evaluation/regulatory status</th>
<th>Same platform for non-Coronavirus candidates</th>
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<td>Inactivated</td>
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<td>Protein Subunit</td>
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<td>Aihui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences</td>
<td>SARS-CoV2</td>
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www.who.int
Isolation of RBD-specific memory B cells in a convalescent patient

- Two mAbs-containing supernatant blocks the interaction between soluble COVID-19 virus RBD and 293T-hACE2 cells, respectively.
- Both CA1 and CB6 are specific to interact with COVID-19 virus S protein.

Shi et al., 2020, Nature
Isolation of RBD-specific memory B cells in a convalescent patient

- PBMCs from a convalescent patient
- Memory B cells
- SARS-CoV-2 RBD
- RBD-specific B<sub>m</sub> cells
- RT-
- Coding sequences
- Expression

- Two mAbs-containing supernatant blocks the interaction between soluble COVID-19 virus RBD and 293T-hACE2 cells, respectively.
- Both CA1 and CB6 are specific to interact with COVID-19 virus S protein

Shi et al., 2020, Nature
Binding affinity between mAbs and RBD

- The binding affinity between mAbs and RBD are stronger than that between the receptor and RBD
- CA1 and CB6 bind to the overlapped epitopes

<table>
<thead>
<tr>
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<th>$k_a$ (1/Ms)</th>
<th>$k_d$ (1/s)</th>
<th>$K_D$ (M)</th>
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<td>7.29E-04</td>
<td>0.82E-09</td>
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<td>ACE2/RBD</td>
<td>3.82E+04</td>
<td>5.15E-03</td>
<td>133.3E-09</td>
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</table>

Shi et al., 2020, Nature
CB6 and CA1 can effectively neutralize COVID-19 virus

Shi et al., 2020, Nature
CB6 and CA1 can effectively neutralize COVID-19 virus

- CB6 competes with the receptor to interact with the same residues of COVID-19 virus RBD
- Both of CB6 heavy chain and light chain sterically hinder the interaction of COVID-19 virus RBD with hACE2

Shi et al., 2020, Nature
CB6-LALA to eliminate the potential ADE effect

ADE (Antibody-Dependent Enhancement)

- Increased entry into Fcγ receptor-bearing cells
- Increased virus production

No detectable ADE effect for CB6-LALA in vitro

Unpublished data
CB6-LALA protects NHPs from COVID-19 virus infection

A human neutralizing antibody targets the receptor binding site of SARS-CoV-2

CB6 decreased the viral loads in the throat swabs in NHPs at both prophylactic and treatment settings

CB6 reduced the infection-related lung damage of challenged NHPs at both groups

Shi et al., 2020, Nature
Multiple neutralizing MAbs could prevent the escape mutations

- The protection efficiency of MAbs in hACE2 mice model post infection with COVID-19 virus
- Structural analysis of B38 and COVID-19 virus RBD complex and the epitope comparison between B38 and hACE2

Wu et al., 2020, Science
A pair of noncompeting human neutralizing MAbs against COVID-19 virus

- H4 and B38, a pair of noncompeting human neutralizing MAbs, synergistically prevent COVID-19 virus infection
- The neutralizing activity of bispecific antibody Bi-15 against COVID-19 pseudovirus is 10 times stronger than those of parental monoclonal antibodies

Wu et al., 2020, Science

Unpublished data
CB6 advanced into clinical trials in both China and America

- On 5 June 2020, CB6 was approved by the NMPA to enter Phase I clinical trials in China
- On 8 June 2020, CB6 was approved by the FDA to enter Phase I clinical trials in America

<table>
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</table>
Correlations of neutralizing MAbs with protection

Reach of neutralizing MAbs to lung

Lasting time of neutralizing MAbs in vivo

Antibody-dependent enhancement (ADE) effect

Best Immunization programs and the pro and con of all the vaccines

Stratified/prioritized vaccination program
流感病毒
躲也躲不过的敌人

THANK YOU
Emerging coronaviruses of humans and animals: Immunity and vaccines

Linda J. Saif

Food Animal Health Research Program
Department of Veterinary Preventive Medicine
College of Food, Agricultural, Environmental Sciences
The Ohio State University/OARDC, Wooster, Ohio US
7 Human Coronaviruses — Respiratory infections
6 Swine and 1 Bovine CoV — Enteric/respiratory infections

**Human CoVs**

➢ **Endemic—Common Cold** (Population has immunity, but lasts only ~1yr)
  - Alpha-CoVs- HC 229E, NL63
  - Beta-CoVs- HC OC43, HC HKU1

➢ **Epidemic/Pandemic-- Pneumonia**
  (Naïve population, no immunity)
  - Beta-CoVs- SARS, MERS, SARS-CoV-2

**Bovine CoVs**

➢ **Endemic—Respiratory/Diarrhea**
  - Beta-CoV- BCoV

**Porcine CoVs**

➢ **Endemic--Gastroenteritis**
  - Alpha-CoVs- TGEV, PEDV

➢ **Endemic--Respiratory**
  - Alpha-CoV- PRCV

➢ **Endemic--Encephalomyelitis**
  - Beta-CoV- HEV

➢ **Epidemic-- Diarrhea**
  (Naïve population, no immunity)
  - Alpha-CoV- SADS
  - Delta-CoV- PDCoV

Bovine and most human CoVs belong to the *betacoronavirus* genus; most swine CoVs belong to the *alphacoronavirus* genus.
Questions Addressed: SARS-CoV-2 and Porcine and Bovine CoVs

➢ How does SARS-CoV-2 cause disease compared with a porcine and bovine respiratory CoV?

➢ What are the unknowns/gaps for SARS-CoV-2 vaccines and lessons learned based on porcine and bovine CoV vaccines?

  -- What are the correlates of protection?
  -- What are the lessons for immunity from similar next Gen platform swine experimental CoV vaccines?
  -- What are the correlates of immunity based on immunity to bovine respiratory CoV infections?
Porcine respiratory CoV (PRCV) mutant of TGEV

- TGEV causes fatal diarrhea in baby pigs
- PRCV--S gene deletion mutant of TGEV (621 – 682 bp, N-terminus) emerged in 1980s
- TGEV and PRCV share APN receptor; tissue tropisms differ due to loss of SA binding (gut mucins) by PRCV Spike (Schultze et al 1996)
- Lost of enteric tropism and virulence

**Similarities to SARS CoV-2 respiratory infections**

- PRCV infects epithelial cells of upper/lower respiratory tract and type I and 2 pneumoctyes (Jung/Saif et al 2007 JVI)
- Most infections mild or subclinical— walking pneumonia like > 50% asymptomatic COVID-19 cases (Long, QX et al 2020 Nat Med)
- Atypical pneumonia in most pigs resembles SARS-CoV-2 lesions (Saif, Jung, 2020 JCM): **PRCV as a BSL2 respiratory CoV model for COVID-19**
Lessons from Swine Coronavirus Veterinary Vaccines

Swine Enteric/Respiratory Coronaviruses: TGEV/PRCV

- Only 2-3X attenuated oral enteric CoV vaccine induced gut/milk IgA Abs: Correlate of immune protection (Chatta, Roth, Saif 2015 ARAB; Langel/Saif et al 2020 Pathogens)
  
  GALT-Mammary gland SIgA axis

  Mother
  Gut IgA Ab- Immunity against CoV

  Suckling piglet
  Milk IgA Abs-Passive immunity

  Weaned piglet
  Gut IgA Ab-Active immunity: Prevent disease and infection

- Repeated PRCV infections induce IgA Abs and immunity to TGEV (Sestak/Saif et al 1996 AJVR)
  
  BALT-Mammary gland SIgA axis

PRCV as naturally occurring TGEV vaccine

Saif ©
COVID-19 Vaccines

AN ARRAY OF VACCINES

Virus
- Inactivated
- Weakened

Viral vector
- Replicating
- Non-replicating

Nucleic acid
- DNA
- RNA

Protein-based
- Protein subunit
- Virus-like particles

Number of vaccines in development

* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

(Modified E Callaway Nature 30 April 2020)
Lessons from Molecular Vaccines for Swine CoVs

➢ Molecular next Gen vaccines have advantages (if safe & effective)
   -- Provide a platform for rapid production of vaccines for new emerging diseases
   -- Backbone constructs to insert key antigens for new viruses with established manufacturing

Will these unproven vaccines be effective to prevent disease and shedding (transmission)?

Recombinant vector vaccines:

PRCV respiratory vaccine
— Recominant experimental human adenovirus (Ad)+PRCV S1

Enteric CoV vaccines — PEDV
— PEDV - Recombinant experimental human Ad5+PEDV S1
— PEDV- iPEDV+ (PED RNA)vaccine—Viral Replicon Particle (VRP)=
  VEEV based replicon vaccine encoding PEDV S replicon RNA
  • Non-replicating single cycle RNA in DCs
Recombinant Vector Vaccines: rAd vaccines for porcine CoVs

<table>
<thead>
<tr>
<th>Antigen/ Vector</th>
<th>Route</th>
<th>Challenge</th>
<th>VN Ab</th>
<th>Protection against</th>
</tr>
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<tbody>
<tr>
<td>PRCV respir. H Ad5 /S_{A+D} (1220aa) (A+)</td>
<td>Oronasal 1x</td>
<td>PRCV</td>
<td>Yes (low)</td>
<td>NT Partial (shorter)</td>
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<td>H Ad5 Control</td>
<td>Oronasal 1x</td>
<td>PRCV</td>
<td>No</td>
<td>NT None</td>
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<table>
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</thead>
<tbody>
<tr>
<td>H Ad5/S1 PEDV</td>
<td>IN 1X</td>
<td>PEDV</td>
<td>(PreC) No</td>
<td>Partial No</td>
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<tr>
<td>Control</td>
<td>--</td>
<td>PEDV</td>
<td>(Post) Yes (3x)</td>
<td>No No</td>
</tr>
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</table>

(Callebaut et al, J Gen Virol 1996; 4-wk-old pigs)

(Crawford et al, Virus Res 2016; 8 and 20-wk-old pigs)

The human Adeno-S vaccine 1x elicited only partial respiratory immunity to PRCV and marginal enteric immunity to PEDV: multiple doses needed?
Lessons from Molecular Vaccines for Swine CoVs

Recombinant vector/virus and subunit vaccines:

**Enteric CoV vaccines — TGEV and PEDV**

— TGEV-S recombinant vaccine—ineffective in naïve pigs, but effective as booster vaccine after 1x oral attenuated vaccine *(Shoup/Saif et al, 1997; Park/Saif et al, 1998)*

— PEDV -PED RNA (iPEDV+) vaccine—Viral Replicon Particle (VRP) VEEV+ PEDV S replicon RNA
  • 1-3X IM doses in pregnant sows showed low efficacy (only 14-22% less mortality vs controls) in piglet protection in manufacturer’s studies *(Crawford et al 2016)* and only 3% less in an independent study *(Greiner et al 2015)*
  • Low milk VN Ab titers (50%+,<80) vs milk (100%,>320) of wt PEDV orally inoculated sows *(Sherba et al 2016)*

— PEDV - Recominant live attenuated virus vaccine developed by introduction of attenuating mutations into infectious clone *(Lead PI: Dr Q. Wang, OSU)*
Strategy to generate safe attenuated CoV vaccines using iclones

PEDV

➢ Target genes that encode innate immune response modulators (nsp1, nsp16) and virus replication (nsp14), non-essential sequences of S protein and the accessory gene ORF3

➢ Introduce at least 2 distinct mutations into separate genes that attenuate the virus to increase genetic stability

Three Clinical Syndromes Occur for Bovine Beta-CoV A Infections

Enteric Infections
Calf diarrhea
- Diarrhea, dehydration
- Intestinal villous atrophy

Winter dysentery
- Bloody diarrhea ± upper respiratory infection
- Intestinal villous atrophy

Respiratory Infections
Calf respiratory disease
Bovine respiratory disease complex (Shipping Fever)
- Cough, nasal discharge, pneumonia

Age Groups/Vaccines
Birth to 4 wks of age
IM inact or atten virus vaccine in pregnant cow
Adults, but not calves
No Vaccine

2 wks to 6 months
6-9-mo-old feedlot cattle
No Vaccine

BCoVs are endemic, pneumoenteric, age effects for clinical syndromes (Saif, Jung 2020 JCM)
Some SARS-CoV-2 patients have diarrhea, shed virus in stools
Lessons from BCoV respiratory infection: Correlates of protective immunity in calves

- Strong correlation between serum antibody titers to BCoV and respiratory disease and IgA antibody titers in nasal secretions and nasal shedding in field studies

Calves (Heckert/Saif et al, 1990, 1991)

- Calves (birth to 20 weeks) shed BCoV repeatedly in nasal secretions, often subclinically (short lived mucosal immunity?)

- Calves with IgA antibodies (titer >100) in nasal secretions did not show recurrent BCoV nasal shedding

- Correlation between serum antibody titers to BCoV at 24hrs of age and subsequent number of respiratory sick days

Develop COVID-19 vaccines that elicit both systemic and mucosal immunity?
Lessons from BCoV respiratory infections: Correlates of protective immunity in feedlot cattle

- In Feedlot cattle BCoV serum antibody titers may be a marker for respiratory protection
  - Antibody isotype (IgG, IgA) and neutralizing titer in serum of cattle at arrival in feedlots were correlated with protection against respiratory disease, pneumonia or BCoV shedding (Cho/Saif et al, 2001; Lin et al, 2001; Hasoksuz/Saif et al 2002; Thomas/Saif et al, 2005)

**Strategy:** Use vaccines to boost memory antibody responses to BCoV to rapidly increase antibody titers

- Calves vaccinated IN with an attenuated BCoV vaccine at entry to feedlots had reduced risk for treatment for shipping fever pneumonia (Plummer et al, 2004)
Challenges for COVID-19 Vaccines

- Rapidly deployed nucleic acid or viral vector vaccines may be a 1st generation vaccine to reduce mortality in high risk groups
  - May not prevent nasal shedding (NHP: ChAdOx1, BioRxiv; Inact vaccine, Sci)
  - May require annual booster doses to maintain immunity (common cold CoVs)

- 2nd generation (more potent, efficacious) vaccines (attenuated) may be needed to prevent severe disease and reduce shedding

- Many vaccines have reduced efficacy in elderly (or those with chronic diseases)
  - Require higher dose like flu vaccines, better adjuvants or multiple doses
  - Animal models may not reflect vaccine responses in these high risk groups

- Vaccines will be used in two populations: naïve vs recovered individuals with variable levels of pre-existing immunity
  - Efficacy/adverse effects (ADE?) may vary
Antibody produced in response to a COVID-19 vaccine

COVID-19 vaccines in the US: an update

13 OCT 2020
Nancy Connell
Professor and Senior Scholar
Johns Hopkins Center for Health Security
Draft landscape of COVID-19 candidate vaccines

2 October 2020 | Publication

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>LIMITED</th>
<th>APPROVED</th>
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<tr>
<td>29</td>
<td>14</td>
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- Vaccines testing safety and dosage
- Vaccines in expanded safety trials
- Vaccines in large-scale efficacy tests
- Vaccines approved for early or limited use
- Vaccines approved for full use

NY Times Oct 12, 2020
Preserving the Scientific Integrity of Getting to COVID-19 Vaccines: From Clinical Trials to Public Allocation

Moncef Slaoui
Chief Advisor
Four platforms, 2 vaccines in each

- Parameters for choice
  - Speed of development
  - Likelihood of efficacy
  - Expected safety profile
  - Scaleup of manufacturing
  - Capacity of owners to execute
- 1. mRNA vaccine
- 2. non-replicating live vectored
- 3. adjuvanted recombinant protein
- 4. live replicating vectored vaccine
  - Oral? Single does?
mRNA vaccines

• Who?
  Moderna
  BioNtech/Pfizer/Fosun Pharma

Previous uses?
  none

MF and dose availability:
  single digit millions Nov
  10s millions – Dec
  100s million - Jan

• Structures
  • mRNA encoding Spike protein
  • Encapsulated in lipid nanoparticles – to survive attack by blood cells
  • Pass through cell membranes
  • Chemicals – ease of manufacture
  • Ultracold chain required
Non-replicative live vector

• Who?
  Johnson & Johnson
  Oxford/Astrazeneca

• Previous use?
  Ebola

• MF and dose availability
  Oxford 10s millions Jan
  J&J 6-8 weeks behind

• Mechanism:
  • Virus infects one cell – induced viral immune response
  • Carries S protein gene
  • Immunity to vector?
    • J&J: Adenovirus Ad26 (obscure)
    • Oxford/AZ: (ChAdOx1) (chimp)
Adjuvanted recombinant protein

- **Who?**
  - Novovax
  - Sanofi/GSK

- **Previous use?**
  - multiple

- **MF and dose availability:**
  - Doses available 1st Q 2021
  - Novovax: NC and TX
  - Sanofi: MA and NJ

- **Mechanism**
  - Each protein and expression system is different
  - Novovax: nanoparticle with adjuvant
  - Sanofi: based on flu vaccine technology ("FluBlock")
Four waves of roll-out

- RNA vaccines: November/December
- Non-replicating live vectors: January/February
- Adjuvanted proteins: March-April
- Replicating live vectors: mid-late 2021
Equitable allocation of COVID-19 vaccine

- Four-phased equitable framework, for state, tribal, local and territorial authorities (demand exceeds supply)
- Use existing programs;
- Promotion campaign with risk communication and engagement;
- Support of equitable global allocation
FIGURE: A Phased Approach to Vaccine Allocation for COVID-19

**Phase 1**
- "Jumpstart Phase"
  - High-risk health workers
  - First responders

**Phase 1a**
- People of all ages with comorbid and underlying conditions that put them at significantly higher risk
- Older adults living in congregate or overcrowded settings

**Phase 1b**
- People of all ages with comorbid and underlying conditions that put them at moderately higher risk
- People in homeless shelters or group homes for individuals with disabilities, including serious mental illness, developmental and intellectual disabilities, and physical disabilities or in recovery, and staff who work in such settings
- People in prisons, jails, detention centers, and similar facilities, and staff who work in such settings
- All older adults not included in Phase 1

**Phase 2**
- K-12 teachers and school staff and child care workers
- Critical workers in high-risk settings—workers who are in industries essential to the functioning of society and at substantially higher risk of exposure
- People of all ages with comorbid and underlying conditions that put them at moderately higher risk
- People in homeless shelters or group homes for individuals with disabilities, including serious mental illness, developmental and intellectual disabilities, and physical disabilities or in recovery, and staff who work in such settings
- People in prisons, jails, detention centers, and similar facilities, and staff who work in such settings
- All older adults not included in Phase 1

**Phase 3**
- Young adults
- Children
- Workers in industries and occupations important to the functioning of society and at increased risk of exposure not included in Phase 1 or 2

**Phase 4**
- Everyone residing in the United States who did not have access to the vaccine in previous phases

**Equity is a crosscutting consideration:**
In each population group, vaccine access should be prioritized for geographic areas identified through CDC’s Social Vulnerability Index or another more specific index.
• *Fauci:* I could say... as a public health person, as a scientist, it will end. We will get through this for absolutely certain. We’ve already suffered through a lot of pain—a lot of economic and personal pain and inconvenience. But it will end. It will end because the public health efforts will succeed ultimately. And science will get us through this. We will get a vaccine. We will get therapies for early disease and for late disease. So the only message that I think we can jointly tell the American public and the global public is that we will get through this. Hang in there. It will end, we promise you.

Anthony Fauci, August 2020
Greetings,

Thanks again for participating in the China bio dialogue sessions last week. And thank you Peter and others who sent me feedback and thoughts on the future of the dialogue. Additional thoughts and comments are welcome.

Re next steps: The general plan is to try and hold another two night session in 2-3 months, when we have more information to share on vaccines, durability of immunity and the evaluation and uses of different types of tests. More discussion on the origin or “natural history” of the virus focused on preventing future outbreaks (since George Gao seems to be open to it) might be possible as well.

PS I have attached the ppt on learning from Covid patients from the dialogue.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Monday, October 19, 2020 12:21 AM
To: Rusek, Benjamin <BRusek@nas.edu>; 'elman@stanford.edu' <elman@stanford.edu>; rbaric_email.unc <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perelman@uiowa.edu' <stanley-perelman@uiowa.edu>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhm.edu' <dgriffi6@jhm.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidfranz@gmail.com)' <davidfranz@gmail.com>
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Subject: Some bullets following our US-China dialogue discussion on Friday

3-month follow-up-JP Weng.pdf

Importance: High

Thanks for a good discussion on Friday Ben,

I fully support a continued dialog and noted, as did some of those on the call, that George Gao and others were more open in their discussion of investigations into animal reservoirs of SARS-CoV-2 – i.e. discussion about the origin. We discussed ways we could frame a future topic that would allow us to talk about some important issues around the ‘natural history’ of SARS-CoV-2, that might also be comfortable for our Chinese colleagues. Here are a couple of bullets along the lines you asked me for:

1. Summary of recent findings re. the ability of SARS-CoV-2 to infect other species of animals in the lab, and in the wild, around the world (e.g. mink farm infections Europe and US, experimental infections of ferrets & raccoon dogs, risk
2. From the natural history of the virus, what do we know about the diversity of alpha and beta CoVs in wildlife reservoirs, and in potential intermediate hosts in various countries in Asia.

3. What information can we identify from the receptor binding domain of SARS-related CoVs that might help us predict future potential for emergence of CoVs from other countries

I think a good strategy would be to have the US side give the opening slide deck so that we sort of set the parameters and open up some of the discussion that I’m sure would lead to interesting information. I’d be happy to help on the first 2 points, and I’m sure Ralph could talk to the 3rd point. Linda and Stanley have a great deal of knowledge and could provide supporting comments...

Cheers,
Peter

**Peter Daszak**
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*EcoHealth Alliance develops science-based solutions to prevent pandemics and promote conservation*

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**Subject:** RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links

Greetings,

Thank you for participating in the China bio dialogue sessions on Tuesday and Wednesday this week. We have scheduled a short hotwash session so the American participants can discuss the virtual dialogue discussions (from this week and earlier this year) and your get your ideas on future topics and other issues.

The session will take place tomorrow from 5:30-6:30 PM, Zoom link is below. Sorry for the short notice, if you can’t make it tomorrow feel free to weigh in by email.
PS I have asked CAS for the ppts from last night, will send those out as soon as I get them.

Kind regards,

Ben

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