Viral load of SARS-CoV-2 in clinical samples

An outbreak caused by a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in Wuhan in December, 2019, and has since spread within China and to other countries. Real-time RT-PCR assays are recommended for diagnosis of SARS-CoV-2 infection.

However, viral dynamics in infected patients are still yet to be fully determined. Here, we report our findings from different types of clinical specimens collected from 82 infected individuals.

Serial samples (throat swabs, sputum, urine, and stool) from two patients in Beijing were collected daily after their hospitalisation (patient 1, days 3-12 post-onset; patient 2, days 4-15 post-onset). These samples were examined by an N-gene-specific quantitative RT-PCR assay, as described elsewhere. The viral loads in throat swab and sputum samples peaked at around 5-6 days after symptom onset, ranging from around $10^4$ to $10^9$ copies per mL during this time (figure A, B). This pattern of changes in viral load is distinct from the one observed in patients with SARS, which normally peaked at around 10 days after onset.

Sputum samples generally showed higher viral loads than throat swab samples. No viral RNA was detected in urine or stool samples from these two patients.

We also studied respiratory samples (nasal [n=1] and throat swabs [n=67], and sputum [n=42]) collected from 80 individuals at different stages of infection. The viral loads ranged from 641 copies per mL to $1.34 \times 10^{12}$ copies per mL, with a median of $7.99 \times 10^4$ in throat samples and $7.52 \times 10^6$ in sputum samples (figure C). The only nasal swab tested in this study (taken on day 3 post-onset) showed a viral load of $1.69 \times 10^9$ copies per mL.

Overall, the viral load early after onset was high ($1 \times 10^6$ copies per mL). However, a sputum sample collected on day 8 post-onset from a patient who died had a very high viral load ($1.34 \times 10^{11}$ copies per mL). Notably, two individuals, who were under active surveillance because of a history of exposure to SARS-CoV-2-infected patients showed positive results on RT-PCR a day before onset, suggesting that infected individuals can be infectious before they become symptomatic.

Among the 30 pairs of throat swab and sputum samples available, viral loads were significantly correlated between the two sample types for days 1-3 (R²=0.50, p=0.022), days 4-7 (R²=0.93, p<0.001), and days 7-14 (R²=0.95, p=0.028).

From 17 confirmed cases of SARS-CoV-2 infection with available data (representing days 0-13 after onset), stool samples from nine (53%; days 0-11 after onset) were positive on RT-PCR analysis. Although the viral loads were less than those of respiratory samples (range 550 copies per mL to $1.21 \times 10^{10}$ copies per mL), precautionary measures should be considered when handling faecal samples.

Figure: Viral dynamics of SARS-CoV-2 in infected patients

Viral load (mean [SD]) from serial throat swab and sputum samples in patient 1 (A) and patient 2 (B). (C) Viral load (median [IQR]) in throat and sputum samples collected from 80 patients at different stages after disease onset. (D) Correlation between viral load in throat swab samples and viral load in sputum samples.
We declare no competing interests. This work was supported by the Theme-based Research Scheme (UGC, Hong Kong).

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Beijing Center for Disease Prevention and Control, Beijing 100013, China (YP, DZ, PY, QW); Beijing Research Center for Preventive Medicine, Beijing, China (YP, DZ, PY, QW); School of Public Health, Capital Medical University, Beijing, China (YP, PY); and School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region 999077, China (LLMP)


14/02/2020, 17:43

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd. nd many countries in the world with meaningful numbers of secondary transmissions. The scale is much larger than SARS for example (where it had many introductions and no known onward transmission)
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:45

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd. would predict far more than that given the R0 estimates in the 2-3 range (80-90%). Making more realistic assumptions about mixing, perhaps a little help from seasonality, brings the numbers down
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:48

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd.lation, and in 1918 30%. Those likely had R0 less than COVID-19. Below is from stacks.cdc.gov/view/cdc/11425 pic.twitter.com/EMwjEpA49s
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:49

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Different in some fundamental way from elsewhere that we are mistaken in expecting further outbreaks to have basic aspects in common. No reason I know of to think that but a formal possibility
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:53

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd. ("dispersion in R0") which could mean that many locations outside Wuhan could "get lucky" and escape major onward transmission. hopkinsidd.github.io/nCoV-Sandbox/D...
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:55

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd. me to prepare. Maybe in a few, but seems unlikely that is the case in all, especially countries with stretched health systems.
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:56

Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd. We currently expect. That doesn't help Southern Hemisphere, and is not consistent with behavior in China (preprint in queue from □@MauSantillana□ et al.)

From: Caneva, Duane

Sent: Sunday, February 16, 2020 9:39 AM

To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; DeBord, Kristin (OS/ASPR/SPPR) <Kristin.DeBord@hhs.gov>; Phillips, Sally (OS/ASPR/SPPR) <Sally.Phillips@hhs.gov>; David Marcozi (b)(6)@som.umd.edu; Hepburn, Matthew J (CIV USAROY (VA)) <matthew.j.hepburn.civ@mail.mil>; Lisa Koonin (b)(6)@gmail.com; Wargo Michael <Michael.Wargo@hcahealthcare.com>; Walters, William (STATE.GOV) <walterswa2@state.gov>; HARVEY, MELISSA <melissa.harvey@hq.dhs.gov>; WOLFE, HERBERT <herbert.wolfe@hq.dhs.gov>; Eastman, Alexander <alexander.eastman@hq.dhs.gov>; EVANS, MARIEFRED <mariefred.evans@associates.hq.dhs.gov>; Callahan, Michael V., M.D. (b)(6)...@mgh.harvard.edu; UTMB.EDU (b)(6)...@email.unc.edu; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>; Yeskey, Kevin <kevin.yeskey@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Redd, John (OS/ASPR/SPPR) <John.Redd@hhs.gov>; Hassell, David (Chris) (OS/ASPR/IO) <David.Hassell@hhs.gov>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Tracey Mcnamara (b)(6)...@westernu.edu; Dean, Charity A (CDPH) <Charity.Dean@cdph.ca.gov>; Caneva, Duane <duane.caneva@hq.dhs.gov>; Richard Hatchett <richard.hatchett@cepi.net>; Lawler, James V. (b)(6)...@unmc.edu; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; Martin, Gregory J (MartinGJ@state.gov) <MartinGJ@state.gov>; Borio, Luciana <LBorio@iqt.org>; Hanfling, Dan <DHanfling@iqt.org>; McDonald, Eric <Eric.McDonald@sdcounyt.ca.gov>; Wade, David <david.wade@hq.dhs.gov>; TARANTINO, DAVID A <david.a.tarantino@cbo.dhs.gov>; Baric, Ralph S (b)(6)...@email.unc.edu; WILKINSON, THOMAS <thomas.wilkinson@hq.dhs.gov>; Hassell, David (Chris) (OS/ASPR/IO) <David.Hassell@hhs.gov>; David Gruber (david.gruber@dshs.texas.gov) <david.gruber@dshs.texas.gov>; KAUSHIK, SANGEETA <sangeeta.kausihk@hq.dhs.gov>

Subject: Red Dawn Breaking, COVID-19 Collaborative, Feb 16 start
Purpose: This is a new Red Dawn String to cut down the size from the previous string, opportunity to provide thoughts, concerns, raise issues, share information across various colleagues responding to COVID-19.

Including all from previous string plus a few additional folks.

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Clinical outcomes of 402 patients with COVID-2019 from Zhongnan Hospital, Wuhan, China

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| Complete List of Authors: | Wu, Yingjie  
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Peng, Zhiyong  
Xiao, Shu-Yuan; University of Chicago Medical Center, Pathology; Wuhan University Zhongnan Hospital, Pathology |
| Keywords: | COVID-19; SARS-CoV-2, Mortality, Pneumonia |

Abstract: The SARS-CoV-2 outbreak is causing widespread infections and significant mortality. Previous studies describing clinical characteristics of the disease contained small cohorts from individual centers or larger series consisting of mixed cases from different hospitals. We report analyses of mortality and disease severity among 402 patients from a single hospital. The cohort included 297 patients with confirmed and 105 with suspected diagnosis. The latter group met the criteria for clinical diagnosis but nucleic acid tests results were initially interpreted as suspicious. Data were compared between genders and among different age groups. The overall case fatality is 5.2%. However, patients 70 years of age or older suffered a significantly higher mortality (17.8%), associated with more patients having severe or critical illness (57.5%). Patients 50 years of age or older had a mortality of 8.0%, and those younger than 50 years, 1.2%. Male patients had a mortality of 7.6% versus 2.9% in females.
February 24, 2020

Dear Editor,

We would like to submit our manuscript titled “Clinical outcomes of 402 patients with COVID-2019 from Zhongnan Hospital, Wuhan, China” for consideration of publication in Emerging Infectious Disease. We report comparative analyses of mortality and disease severity among 402 patients from a single center, and attempt to shed light on relevance of patient demographics and other factors to clinical outcomes.

All the authors have contributed significantly to the study and agree with the content of the manuscript. This study was approved by the Ethics Board of Zhongnan Hospital of Wuhan University (No. 2020012). The authors also declare that the content has not been published or submitted for publication elsewhere.

We hope after careful review you’d find this paper to be of sufficient value to the clinical infectious disease community, and suitable for the journal.

Yours sincerely,

Shu-Yuan Xiao, MD
Professor of Pathology
E-mail: [b][6]@uchicago.edu
Clinical outcomes of 402 patients with COVID-2019 from Zhongnan Hospital, Wuhan, China

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Abstract

The SARS-CoV-2 outbreak is causing widespread infections and significant mortality. Previous studies describing clinical characteristics of the disease contained small cohorts from individual centers or larger series consisting of mixed cases from different hospitals. We report analyses of mortality and disease severity among 402 patients from a single hospital. The cohort included 297 patients with confirmed and 105 with suspected diagnosis. The latter group met the criteria for clinical diagnosis but nucleic acid tests results were initially interpreted as suspicious. Data were compared between genders and among different age groups. The overall case fatality is 5.2%. However, patients 70 years of age or older suffered a significantly higher mortality (17.8%), associated with more patients having severe or critical illness (57.5%). Patients 50 years of age or older had a mortality of 8.0%, and those younger than 50 years, 1.2%. Male patients had a mortality of 7.6% versus 2.9% in females.

Key words

Coronavirus; fatality; mortality; COVID-19; SARS-CoV-2; diagnosis; epidemiology

Introduction

In December 2019, a cluster of “atypical” pneumonia cases with then unknown causes occurred in several hospitals in Wuhan, Hubei Province, China[2]. Most of the initial patients had fever, fatigue and non-productive cough, and showed a characteristic ground glass shadow on chest CT imaging of the lungs. Some of these
patients could be linked to a local fresh seafood market, Huanan Seafood Market, although others could not. A coronavirus was subsequently isolated and genomically sequenced. It was found that the viruses share nucleotide sequence homology of 79.5% to SARS-CoV and 85-96% to bat SARS-like coronavirus bat-SL-CoVZC45 at the whole genome level[3]. The virus was initially named 2019-novel coronavirus (2019-nCoV) on January 12, and subsequently, SARS-CoV-2 on February 11. Disease caused by the infection is now designated coronavirus infected disease 2019, or COVID-19. The outbreak thus represents a new emerging viral disease due to species “jumping” of an animal virus to humans. Currently, human-to-human transmissions of the virus have reached an unprecedented magnitude, in community, healthcare facilities, and at homes[4], and spread to entire China and some parts of the world.

Initially, recognition and diagnosis of the disease, namely COVID-19, were based on the characteristic clinical, laboratory and radiological findings, with exclusion of other known respiratory agents. Soon after, definitive diagnosis required the detection of viral sequence by a nucleic acid test, reverse-transcriptase polymerase chain reaction (RT-PCR). Most previous reports on clinical case studies were based on this definition. However, it became evident that a significant portion of cases showed negative viral detections in pharyngeal swab specimens, although tested repeatedly, but clinically fit the diagnosis. The possible causes of this discrepancy are several, including but not limited to (1) not all patients with the lower respiratory tract involvement shed virus from the upper respiratory tracts, at least early on; (2) there
might be insufficient consistency in sampling; (3) the sensitivity and specificity of the nucleic acid tests had not been sufficiently investigated[5]. Strictly following this criterium had prevented many patients from receiving timely care, particularly early on when availability of enough test kits could not meet the demand of the large number of symptomatic patients. The clinicians and authorities recognized these problems and made prompt changes to the diagnostic guidelines, so that patients meeting the criteria for clinical diagnosis in Hubei Province were treated as COVID-19 patients. In the updated version of the guidelines for clinical diagnosis and management of COVID-19 by the National Health Commission of China, definition for clinical diagnosis does not require a nucleic acid test result.

There have been several studies describing the clinical characteristics of SARS-CoV-2 infected patients[1, 6, 7], including symptoms, lab tests and radiographic features. These were smaller series, from 41[6] to 138 confirmed cases[1]. Some of the larger series consisted of mixed cases submitted from hospitals of varying sizes and settings[7]. Analysis of larger series with cases from a single center and expanding a longer period of time should offer more accurate information about the overall clinical outcomes, mortality and morbidity, because these cases would have followed more or less uniform diagnostic algorithms and had received more consistent treatment regimens. The results should have less interference from uncontrollable factors such as inconsistency in reporting from individual hospitals. In addition, patients included in these prior studies all had diagnosis confirmed by the nucleic acid tests for pharyngeal swab specimens. For the reasons described above,
some patients not included due to suspicious nucleic acid test results may represent more mild illness, thus causing bias in clinical outcome analysis. Therefore, it is important to include cases with typical clinical presentations and course, even though “suspicious” result on nucleic acid tests, in studies of clinical outcomes and disease characteristics. In the current study, we analyzed data on 402 patients from a single hospital from December 2019 to February 2, 2020, with emphasis on mortality in these patients, in hope to understand characteristics related to clinical outcome in a more uniform clinical setting.

Material and Methods

Patients

Patients presented to our hospital and had nucleic acid tests showing “positive” or “suspicious” results from December 2019 to February 2, 2020 were included in this study. Electronic medical charts were reviewed. Patients demographics, status of nucleic acid tests, time of presentation and or illness, length of symptoms, and so on, were recorded. The clinical severity status (ie, common/mild, severe, or critical) and death were monitored up to February 2, 2020, the final date of follow-up.

All patients met the criteria for clinical diagnosis given by The National Health Commission of China (NHCC) Guidelines on novel coronavirus pneumonia for diagnosis and disease severity triage (5th Edition). Briefly, diagnosis was based on
epidemic exposure, plus two of the following clinical findings: fever, radiographic features, normal or lowered white blood cells (WBC) or reduced lymphocyte count.

**Interpretation of results for real-time Reverse Transcription Polymerase Chain Reaction Assay for SARS-CoV-2**

The real-time Reverse Transcription Polymerase Chain Reaction using the laryngeal swabs were performed as reported previously[1]. Initially, results of “positive” nucleic acid tests were defined as 2 amplification sites in quantitative RT-PCR, while the “suspicious” results were defined as one of the two sites had a positive signal. Along with accumulating experience and knowledges about this disease and the test, both scenarios were considered as “positive” subsequently. Therefore, all cases in this study that had been classified as “suspicious” were in fact positive cases. In addition, they all met the criterial for clinical diagnosis. In the following analysis, we keep the label of “suspicious” but also analyzed the initially confirmed cases in a separate group, side-by-side.

**Severity Group Designation**

The common (mild) cases were those only had fever, respiratory symptoms, and pneumonia on chest radiography. Severe cases need to meet one of the following criteria: (1) respiratory distress, RR>=30/min; (2) resting blood oxygen saturation <=93%; or (3) arterial blood oxygen partial pressure (PaO2)/FiO2 =<300 mmHg.

Critical cases meet one of the following: (1) respiratory failure needing mechanical oxygenation; (2) shock; or (3) development of other organ failure, requiring intensive
care unit (ICU) care. Around 70-80% of patients were mild, and 20-30% were severe or critical.

**Statistical Analysis**

Categorical variables were described as frequency rates and percentages. Proportions for categorical variables were compared using the $\chi^2$ test. All statistical analyses were performed using GraphPad Prism (GraphPad Company, San Diego, CA, USA) version 6.0 software. P-value “< 0.05” was considered with statistical significance.

This study was approved by the Ethics Board of Zhongnan Hospital of Wuhan University (No.2020012).

**Results**

**Case fatality analysis of SARS-CoV-2 infected patients**

As showed in Table 1 and Figure 1A, the fatality of all confirmed and suspected COVID-19 patients was 5.2%, while fatality of confirmed cases was 5.7%. Male patients had higher fatality (7.6%) than females (2.9%) among all patients (P=0.04) (Figure 1B), while in confirmed cases, fatality in males was 8.8% and female 2.7% (P=0.03) (Figure 1C). The classification of case fatalities among different age groups were shown in Table 1 and Figure 1D and E. Fatalities in patients younger than 30 years of age, 30 to 49, 50 to 69, 70 and older were 0, 1.5%, 3.6% and 17.8% respectively among all suspected and confirmed patients (Figure 1D). The
fatalities of patients under 30, from 30 to 49, from 49 to 69, 70 and older, were 0, 1.0%, 4.2% and 20.0%, respectively, among confirmed patients (Figure 1E). Taking 50 years old as a cutoff in confirmed cases, the mortality in patients over 50 years old was 14.3% in males and 4.5% in females (Table 1).

Severity of illness among gender and age groups

As showed in Table 2 and Figure 2, the overall severity rate (proportion of severe and critical severe cases, or SR) of confirmed and suspected cases was 35.1%, while the SR of confirmed cases was 27.3%. Male patients had a higher SR (38.9%) than female (31.4%) among suspected and confirmed patients, but the difference was not statistically significant (Figure 2B). In confirmed cases, male patients also had a higher SR than females without statistical significance (Figure 2C). The SR for patients under the age of 2 years, from 2 to 29, from 30 to 49, from 50 to 69 and over 70 was 0, 10.3%, 26.3%, 37.0% and 57.5% respectively, among all suspected and confirmed patients (Figure 2D). Which indicate that elder patients have higher severity rate than younger patients among all suspected and confirmed patients. The severity rate of patients under 2, from 2 to 29, from 30 to 49, from 50 to 69, 70 and over was 0, 11.1%, 17.3%, 28.8% and 52.7% respectively among all confirmed patients (Figure 2E). These results indicated that elder patients had higher severity rate than younger patients among all confirmed patients.

Discussion
From late December, 2019 to February, 2020, the number of COVID-19 patients is increasing in an astonishing speed. The symptoms of this disease include but are not limited to fever, cough, myalgia, diarrhea, dyspnea[1, 6]. Pathologically the lungs exhibit marked proteinaceous exudation and macrophages in alveolar spaces, as well as fibrin plugs in early phase [8], and hyaline membrane formation, reactive hyperplasia desquamation of alveolar epithelium [8, 9]. In addition to pneumonia, patients may also suffer injuries in the heart, liver and kidneys. Up till February 2, the mortality of this disease in Wuhan is 5.5%, and in Hubei is 3.2%, while in the region outside of Hubei is 0.1% (China National Health Commission official website).

This study included COVID-2019 patients from Zhongnan Hospital, one of the largest tertiary teaching hospitals in Wuhan, Hubei province. From late December, 2019 to early January, 2020, before large scale isolation measures were implemented, many departments in the hospital experienced cross-infection among patients and to the medical staff, due to unrecognized infectious patients and lack of proper protection. Many patients in incubation period came to the hospital for illnesses other than respiratory symptoms or fever[1]. After being designated as the specialized hospital, special isolation wards were built in each department[7]. The period from which we collected the clinical data was before the prevention was in full implementation. Indeed, the overall mortality and the rate of severe cases in the study are higher than the national figures. There may be several causes for the higher mortality in Wuhan compared to other cities. First, the rapid transmission of the virus and increase of patient volume quickly overwhelmed medical resources in Wuhan,
leaving many patients to receive care later in the clinical course. Secondly, there were a large number of patients who had mild or transient symptoms who never received diagnosis nor nucleic acid tests, and were not counted as COVID-19 patients, making the denominator of mortality smaller than real.

We analyzed the mortality and proportion of the severe cases in gender and different age groups. Our cohort of 402 cases included patients of all ages, the youngest were a 1-month old girl and 6-month old boy, the oldest were a 94-year-old woman and a 96-year-old man. Most patients were between 30 and 80 years (87%) old, the median and average ages were 54 and 53 years, respectively. The highlights of findings are: (1) most deaths occurred in patients 70 years of age or older; (2) male patients had a mortality significantly higher than females (3 times); (3) no death occurred in patients 30 years of age or younger. It was shown that the higher mortality coincided with higher proportion in older age group having severe or critical illness. Patients with ages over 50 years were more susceptible to develop severe illness, particularly those in their 7th decades. This is likely related to the fact that the majority of them had preexisting systemic illness. This finding is similar to that of influenza and SARS.

The difference in mortality between male and female genders is unknown. There appears that the severity distribution is equal between male and female groups. However, further analysis showed that mortality in severely ill male patients is higher than severely ill female patients. Some investigators reported that some chronic diseases are more common in males, such as hypertension[10], atherosclerosis, and
chronic heart diseases[11]. But prevalence of these chronic diseases seems to be related to estrogen and equalize when women undergo menopause. Another possibility is that, expression of ACE2, the major receptor for the SARS-CoV-2, is higher expressed in males than in females[12]. But the study only included 8 individuals, with only 2 males (one Asian). Therefore, it is still a puzzle what roles ACE2 played in the pathogenesis of this catastrophic viral disease. Whether there is difference in viral load in males and in females, or whether more severe organ injury occurred in males, is still unknown. All these possibilities need further pathological and pathogenesis study. In addition, in a mouse models, it was found that males were more susceptible for SARS-CoV infection, although the result turned out that estrogen may have played a role[13].

Of note, we presented data in two different groups, one including the confirmed and suspected, and the other just the confirmed cases. As we know, during the outbreak case definitions had been changed, and application and interpretation of nucleic acid tests were not uniform for some period of time [14]. We believe it is best to see both the overall (including both confirmed and suspected) and confirmed group. Other than the individual figures in the results, the final conclusion remains the same in terms of comparisons between genders, and among different age groups. We strongly believe that all the suspected cases represent real COVID-19 patients, as they met the criteria for clinical diagnosis. Furthermore, as described in Methods, the interpretation of nucleic acid test subsequently removed the suspect category.
In conclusion, analysis of a cohort of 402 COVID-19 patients from a single center revealed an overall mortality of 5.2% and 17.8% mortality in patients 70 years of age or older. Male patients had a mortality 3 times that of female. No death occurred to patients age younger than 30. Causes for difference between male and female are currently unknown.

References:


Table 1. Case fatalities by age and gender among patients with suspected and confirmed diagnosis for SARS-CoV-2 infection

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Fatality rate (%) : The proportion of died patients.
Table 2. Portion of severe and critical cases by gender and age among patients with suspected and confirmed diagnosis of SARS-COV-2 infection.

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*Include severe and critical cases.
Figure 1. Case fatality analysis of SARS-CoV-2 patients. (A) Fatality of confirmed or suspected cases. (B) Male versus female patients among all suspected and confirmed patients. (C) Male versus female patients, confirmed cases only. (D) Fatality by age groups among suspected and confirmed patients. (E) Fatality by age group among confirmed patients. *P<0.05; ***P<0.001.
Figure 2. Clinical severity classification among SARS-CoV-2 patients by gender and age groups. (A) Overall severity classification in all cases versus confirmed cases. (B) Severity classification in male versus female patients among all patients. (C) Severity classification in male versus female patients among confirmed patients. (D) Severity classification by age groups among all patients. (E) Severity classification by age among confirmed patients. ns. no significance; *P<0.05, **P<0.01.
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Dr F,

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Subject: RE: WHO advance team on coronavirus on way to China - Tedros tweet

Date: 2020/02/09 18:34:48
Priority: Normal
Type: Note

(b)(5)
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Subject: FW: WHO advance team on coronavirus on way to China - Tedros tweet

Many thanks, Bernard! I know I’ll be asked, so I will pass your email up the chain...

Take care and thanks again!

From: SCHWARTLANDER, Bernhard F. <schwartlanderb@who.int>
Sent: Sunday, February 9, 2020 5:59 PM
To: Grigsby, Garrett (HHS/OS/OGA) <Garrett.Grigsby@hhs.gov>
Cc: SIMONSON, Stewart <simonsons@who.int>
Subject: Re: WHO advance team on coronavirus on way to China - Tedros tweet

Hi Garrett,

We have three people on the way to Beijing who will work with our Chinese counterparts on finalizing the TOR and composition of the joint WHO - China mission. As you are much aware, the US has given us a number of names who will be able and willing to join such a mission. We have received similar proposals from other countries and will now match the “long list” of experts with the required specific expertise.

We are hoping to have more clarity over the coming days and will obviously keep you in the loop. The overall number will be kept at a level to make sure that the team is fully operational.

With my warmest wishes

Bernhard

Dr Bernhard Schwartländer
Chef de Cabinet
World Health Organization

On 9 Feb 2020, at 23:24, Grigsby, Garrett (HHS/OS/OGA) <Garrett.Grigsby@hhs.gov> wrote:

Bernard,

Hope you had a good weekend.

I’m reaching out to get more clarity on the WHO experts team issue – please see article below. I’ve heard everything from an advance group of one or two individuals to 15 people discussed in the article. I haven’t heard any word about US people, and I was just with Dr Redfield late this afternoon and he was in the dark too.

Any additional information will be deeply appreciated.

Thanks!

From: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>
Sent: Sunday, February 9, 2020 5:03 PM
UPDATE 1-WHO advance team on coronavirus on way to China - Tedros tweet

Stephanie Nebehay
By Stephanie Nebehay

GENEVA, Feb 9 (Reuters) - An advance team of international experts led by the World Health Organization (WHO) has left for Beijing to help investigate China’s coronavirus epidemic, the Geneva-based agency said on Sunday.

WHO director-general Tedros Adhanom Ghebreyesus, who made a trip to Beijing for talks with President Xi Jinping and Chinese ministers in late January, returned with an agreement on sending an international mission.

But it has taken nearly two weeks to get the government’s green light on its composition, which was not announced, other than to say that WHO veteran Dr. Bruce Aylward, a Canadian epidemiologist and emergencies expert, was heading it.

“I’ve just been at the airport seeing off members of an advance team for the @WHO-led #2019nCoV international expert mission to #China, led by Dr Bruce Aylward, veteran of past public health emergencies,” Tedros said in a tweet from Geneva.

Dr. Sylvie Briand, who accompanied Tedros last month and stayed behind for talks with top Chinese health officials, told Reuters last week that they were discussing a list of experts with China.

“Because it is a joint mission, they need to be on board, it’s not just an international group going there. We have about 15 people,” said Briand, director of Global Infectious Hazard Preparedness at WHO.

China raised the death toll from the coronavirus outbreak to 811 on Sunday, passing the number killed globally by the SARS epidemic, as authorities made plans for millions of people returning to work after an extended Lunar New Year break.

The virus, which has spread to two dozen countries, has killed some 2% of more than 37,550 cases worldwide, with 99 percent of infections in China, WHO figures show.

The WHO declared the outbreak a global emergency on Jan. 30, days after the Chinese central government imposed a lockdown on 60 million people in Hubei province and its capital Wuhan, epicentre of the virus that emerged in December in a seafood market.

Tedros said on Saturday that he hoped the team would include experts from the U.S. Centers for Disease Control (CDC).

“It has to be meaningful on the ground,” Lawrence Gostin, professor of global health law at Georgetown Law, said in an interview in Geneva this week.

Gostin called for a “genuine partnership with transparent flows of information and accountability for the response”, adding that there should be a strong CDC presence.

“CDC has got no peer in terms of its experience and technical expertise in dealing with international outbreaks,” he said.

“But the other benefit is the smart diplomacy, what it could signal is that despite all of our differences in ideology, trade, politics, that when faced with a common threat to humanity, we come together as a human community to tackle it,” Gostin said.
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Daily Cumulative 2019-nCoV Hospitalization Rate per 100,000 Wuhan and Hubei

- Wuhan Cum Hospitalization Rate per 100,000
- Hubei Cum Hospitalization Rate per 100,000

Days since Onset of Symptoms 1st Case
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CC:

Subject: FW: Are we at the point that Pence et al. should be announcing steps outlined in this paper?

Date: 2020/03/08 19:55:22

Priority: Normal

Type: Note

Team:

(5)

Thanks,

Tony

Paper attached.

Dalton, Craig and Corbett, Stephen and Katelaris, Anthea, Pre-Emp tie Low Cost Social Distancing and Enhanced Hygiene Implemented before Local COVID-19 Transmission Could Decrease the Number and Severity of Cases. (March 5, 2020). Available at SSRN: https://ssrn.com/abstract=3549276 or http://dx.doi.org/10.2139/ssrn.3549276
Pre-emptive low cost social distancing and enhanced hygiene implemented before local COVID-19 transmission could decrease the number and severity of cases.

Dalton CB¹, Corbett SJ², Katelaris AL³.

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Summary

China appears to have constrained transmission of COVID-19 outside of Hubei Provence through rapid and intensive containment and mitigation interventions. Most countries only attempt social distancing and hygiene interventions when widespread transmission is apparent. This gives the virus many weeks to spread with a higher basic reproduction number (R₀) than if they were in place before transmission was detected or widespread. Pre-emptive, low cost, hygiene enhancement and social distancing in the context of imminent community transmission of novel coronavirus COVID-19 should be considered. Early interventions to reduce the average frequency and intensity of exposure to the virus might reduce infection risk, reduce the average viral infectious dose of those exposed, and result in less severe cases who are less infectious. A pre-emptive phase would also assist government, workplaces, schools, and businesses to prepare for a more stringent phase. Countries, and subregions of countries, without recognised COVID-19 transmission should assume it is present and consider implementation of low cost enhanced hygiene and social distancing measures.

Rationale for Pre-emptive Interventions

It is estimated that approximately two thirds of COVID-19 cases exported from China from 1st to 13th of January have gone undetected globally.¹ Most of these exported cases will be mild and may only be detected after several hundred cases have accumulated and severe or fatal cases are recognised 5 to 8 weeks later, as has likely occurred in the recent COVID-19 outbreaks in Iran, South Korea, Italy, and Seattle in the USA.²

The spread of novel coronavirus COVID-19 transmission globally has been very rapid. The basic reproduction number is estimated at between 2 to 3.³⁴ The mode of transmission is thought to be droplet and contact infection, although opportunistic or close range airborne infection may be involved.⁴

The transmission dynamics of the early cases of COVID-19 were significantly different to those during the SARS epidemic. In particular the proportion of cases from healthcare settings was low and the proportion with no known risk exposures was high.⁴ Another significant factor is that viral loads in nasopharyngeal and respiratory secretions are highest soon after symptom onset in COVID-19 cases⁵ compared to a peak of around 10 days in SARS cases,⁶ making transmission before entering health care facilities more likely.
Even though the understanding of transmission dynamics is at an early stage, they do suggest that the step-wise introduction of stringent measures will be necessary to control this epidemic and highlights the importance of early community control.

Quarantine, city “lockdowns”, complete childcare, school, university and work closures, and cancellation of mass gatherings/events have significant social and economic impact and are unlikely to be implemented until significant transmission is confirmed – when it may be less effective. However, there are a range of lower level, potentially cost neutral, pre-emptive interventions that could be considered when transmission is only suspected or anticipated. Here we explore whether low cost pre-emptive enhanced hygiene and social distancing should be implemented prior to confirmation of community transmission in countries without, or with minimal, confirmed person-to-person transmission of COVID-19.

The purpose of pre-emptive interventions is to slow the transmission of disease and limit the impact on health services, particularly hospitals and intensive care units, to ensure access to high level care when needed.

The concept of pre-emptive deployment is based upon the following assumptions which require further exploration and are elaborated upon below:

1. Community wide COVID-19 transmission may be occurring undetected or may only be recognised after containment is no longer feasible.
2. Interventions implemented after community wide transmission is detected will be less effective.
3. Reducing the force of infection, particularly early, will delay the epidemic peak, blunt the epidemic peak, spread cases over a longer time, and help to limit the potential for critical care services to be overwhelmed, which may be lifesaving.\(^7\)^\(^8\)
4. Enhanced hygiene and social distancing interventions should:
   a. Decrease the total number of cases per week but extend duration of the epidemic
   b. Decrease the severity of cases through reducing viral inocula.

Figure 1 below illustrates the concept of limiting the peak in cases so that health services are less likely to be overwhelmed (red dashed line) and there is less unmet health service need. Unmet need may include inability to admit patients to a hospital or to provide hospitalised patients in critical condition access to intensive care. Interventions to reduce infection lead to longer, but less peaked, epidemics. A slower evolution in the epidemic also allows time for health care staff to provide better care, for recovery of infected health care workers, for learning and adapting to the evolving situation by administrators, and for vaccines and treatments to be developed. Although we have not validated this principle for COVID-19 epidemics it is sufficiently validated in simulations for influenza that it would appear a reasonable assumption in response to this emergent disease.\(^9\)
Figure 1: Intended impact of enhanced hygiene and social distancing measures on the COVID-19 pandemic adapted from Fong.8

Enhanced hygiene and social distancing measures may reduce both numbers of cases and severity of cases through several mechanisms.

We suggest that a pre-emptive implementation of low cost interventions prior to detection, but in imminent expectation of community transmission should be considered because it may decrease both the total numbers of cases and severity of cases. This principle applies equally well to subregions of countries that have not as yet detected community transmission events.

The basic reproductive number (R0) is the average number of secondary cases of an infectious disease that arise from cases in a totally susceptible population, and reflects the epidemic potential of a pathogen.10 R0 is a function of the number of contacts an infectious person has, the risk of transmission per contact, and the duration of infectiousness.

Social distancing mostly acts on the first factor, by reducing the number of contacts each person makes. Hygiene measures mostly act on the second factor, as they reduce the risk of transmission if a contact occurs. There are epidemiological observations from the outbreak in China that might indicate the effectiveness of pre-emptive implementation of the measures in the community. The WHO-China Joint Mission on COVID-19 determined that widespread community transmission and outbreaks occurred in Wuhan prior to the implementation of comprehensive control measures.4 However in other parts of China, community transmission has been limited and most transmission has occurred in families. For example, among 344 clusters involving 1308 cases (out of a total 1836 cases reported) in Guangdong Province and Sichuan Province, 78%-85% have occurred in families.4 This is likely due to the intense quarantine and social distancing measures implemented in areas outside Hubei prior to the establishment of widespread community transmission.

Community wide interventions may decrease the average viral exposure dose encountered in the community. People exposed to a higher viral dose (inoculum) are more likely to become infected and suffer more severe disease. Animal models for other coronavirus infections demonstrate that increased viral inocula lead to more severe disease and higher viral loads in the lungs and other organs/fluids.11 The Amoy Gardens SARS outbreak in 2003
provided evidence that cases with presumed higher exposure to the index case had higher nasopharyngeal viral loads and more severe illness. Modelling of the 2009 influenza pandemic also supported a hypothesis that severe illness was due to a higher infectious dose of the virus mediated by the number of simultaneous infectious contacts. Viral loads in severe MERS cases were higher than those in a mild group and the patients in the severe group had more prolonged viral shedding in respiratory secretions, beyond 21 days after the onset of symptoms, whereas viral RNA was no longer detected by 21 days in the mild group.

Therefore, it is proposed that early measures that lower the number of contacts, the likelihood of transmission, and average viral infective dose in an area of new transmission could have a multiplier effect leading to less cases, and less severe cases who are less infectious. This early reduction of the R0 would result in fewer cases overall and have a significant negative multiplier effect on the overall impact of the epidemic, including the number of deaths (Figure 2). The higher case fatality rate in Wuhan, compared with other provinces in China may partially relate to health-care resource availability and shortages in the face of overwhelming community transmission, as well as greater severity of disease due to higher infection doses. These interventions will be particularly important for people over 60 years of age and those with underlying medical conditions.

Figure 2: Conceptual model of how pre-emptive interventions with a negative multiplier effect could impact an impending epidemic
Low cost Hygiene and Social Distancing Interventions

Box 1. Workplace Interventions

- No handshaking policy
- Promote cough and sneeze etiquette (but focus is on excluding ill staff)
- Videoconferencing as default for meetings
- Defer large meetings
- Enforced sanitisation of hands at entrance
- Regular hand sanitation schedule reminders via email
- Lunch at desk rather than in lunch room
- Gamifying hygiene rules e.g. to discourage touching face
- Ill* people stay at home and ill workers immediately isolated
- Hold necessary meetings outside in open air if possible
- Staff with ill household contacts should stay at home**
- Disinfect high touch surfaces regularly and between users
- Work from home where possible and consider staggering of staff where there is no loss of productivity from remote work
- Consider opening windows and adjusting air conditioning***
- Limit food handling and sharing of food in the workplace
- Assess staff business travel risks****
- Enhance hygiene and screening for illness among food preparation (canteen) staff and their close contacts.
- Analyse the root cause of crowding events on site and prevent through rescheduling, staggering, cancelling.

Box 1. Notes: **"ill" person refers to someone with an undiagnosed respiratory illness or fever, who is not yet under investigation for COVID-19 but nevertheless could be an unrecognised case. ** This could be costly unless used judiciously while awaiting exclusion of COVID-19 in the case and should be introduced based on likelihood of local transmission. *** Evidence that low temperature and low humidity in air conditioned environments may enhance the survival of coronaviruses such as SARS.15 **** Sites such as the CDC travel risk assessment site may be useful https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html

Box 2. School Interventions

- Supervised sanitisation of hands at entrance and at regular intervals
- Defer activities that lead to mixing between classes and years.
- Promote cough and sneeze etiquette (but focus on excluding ill persons)
- Strict stay at home policy if ill
- Gamifying hygiene rules e.g. to discourage touching face
- Regular handwashing schedule
- Disinfect high touch surfaces regularly and between users
- Outdoor lessons where possible
- Consider opening windows and adjusting conditioning
- Enhance hygiene and screening for illness among food preparation (canteen) staff and their close contacts
- Review after-school care arrangements that lead to mixing of children from multiple classes and ages
Box 3. Household-based Interventions

All Households

- Enhanced hand sanitisation
- Gamifying hygiene rules e.g. to discourage touching face
- Disinfect high touch surfaces regularly
- “Welcome if you are well” signs on front door.
- Increase ventilation rates in the home by opening windows or adjusting air conditioning
- Promote cough and sneeze etiquette

Households with ill members (in addition to measures above)

- Ill household members are given own room if possible and only one person cares for them
- The door to the ill persons room is kept closed*
- Wearing simple surgical/dust masks by both infected persons and other family members caring for the case.
- Consider extra protection or alternative accommodation for household members over 65 years or with underlying illness.

*Reference Wein.16

Box 4. Commercial/entertainment/transport setting Interventions

- Sanitisation of hands at building entrance encouraged
- Tap and pay preferred to limit handling of money.
- Disinfect high touch surfaces regularly
- Avoiding crowding through booking and scheduling, online pre-purchasing, limiting attendance numbers.
- Enhance hygiene and screening for illness among food preparation staff and their close contacts.
- Enhance airflow and adjust air conditioning
- Public transport workers/taxi/ride share – vehicle windows opened where possible, increased air flow, high-touch surfaces disinfected.

Organisational capacity benefits

A pre-emptive phase would assist organisations to build capacity for future implementation of more stringent social distancing interventions including allocating responsibilities, consulting with staff and adapting protocols and practicing implementation. WHO is supportive of pre-emptive interventions to prevent COVID-19 in work places.17

The Costs of Pre-emptive intervention

The suite of low cost pre-emptive interventions, other than a working from home policy, is unlikely to affect work productivity and may provide the community with some re-assurance that all is being done to prevent the epidemic. Some may see it as an over-reach but thus far
communities seem to accept or voluntarily adopt low cost interventions and acceptance may be enhanced through consultation and trust building.\(^{18,19}\)

**Influenza co-benefits**

For regions approaching their influenza season, optimal prevention and control of seasonal influenza, such as vaccination, in the face of potential COVID-19 co-circulation is also crucial, to minimise the double burden on health services. The measures discussed here (enhanced hygiene and social distancing) are also effective against influenza, resulting in potential co-benefits for both pathogens.

**Limitations**

Most of the research on mitigation is based on influenza control and it is clear that SARS-CoV-2 transmission dynamics will be different, however, droplet, contact and airborne precautions and the interventions deployed in China align with recommended influenza transmission controls. The assumptions should be modelled to better understand the costs and benefits. The use of masks outside of health settings is controversial and it is important that masks not be diverted from health care supplies. However, surgical masks are protective of large droplet spread and have approximately half the effectiveness of N95 mask for small droplet transmission, and are suggested to be cost saving in some modelled pandemic influenza scenarios.\(^{20}\) They may have a limited role in the community setting prior to widespread transmission if there are adequate supplies and should be considered for use in households caring for COVID-19 cases at home.\(^{16}\)

**Conclusion**

Given the ongoing global dissemination of COVID-19, as of early March 2020, it would be sensible for most countries and regions to assume they have had an importation of at least one case of COVID-19 and that the disease is spreading locally whether recognised or not. We believe these practices should be implemented in all countries as soon as possible.

**Acknowledgements**

We would like to thank Kirsten Williamson for her thoughtful review of the draft manuscript.

**References**


Subject: Wolf - Why that coronavirus beard might be a bad idea - Maxwell Judges & conflict of interests, Larry Summer's Luncheon with Epstein & the Lolita Express,

Date: 2020/07/15 13:29:20

Priority: Normal

Type: Note
Hello Wolf,
Left the above message on your FB page about an hour ago. Re your MASK comment.
A privacy reminder from Google

Search Results
Web results

Why that coronavirus beard might be a bad idea - Los Angeles ...

Mar 24, 2020 - If having facial hair means you're touching your face more often, an infectious disease expert says, 'That's not good.'

Also saw your interview with Prof. Summers

I didn't hear you ask Prof. Summers any questions about his links to Melanie Walker, Epstein's art adviser who also works at the World Economic Forum?
Your main theme seems to be harping on about herding MASKS, yet I have never seen you in a MASK? Masks are for sick people with communicable diseases, as you should be well aware of, and then only in the proper setting.
Also, surprisingly CNN has not reported to their viewing public about the potential conflict of interest regarding the two Judges, Nathan, and Preska assigned to the Ghislaine Maxwell Case. - Does no one look into the background of Judges before they assign them a case? https://twitter.com/stoshmr/status/1279158661252874242

Judge Nathan's failure to recuse, may be solid grounds for appealing her decision to refuse bail! I trust that her DREAM TEAM lawyers
will be well aware of that, and appeal her decision.

Judge Nathan as you will note from the below links is a close Obama associate, & Democratic and has links to Andrew Cuomo's office of the Attorney General who prosecuted Hon. President Trump's businesses /charities in New York. She may therefore also be politically motivated!
If it is true that Judge Nathan once held a mock trial as described below
that would indicate that she has/had already formed a view about Ghislaine Maxwell before she sat in her case today. I am not a fan of what is alleged that Ms. Maxwell has purportedly done, but I am a great believer in disposal of a fair trial and or procedure.

The judges who have been assigned the Maxwell case seem to have a political/ moral agenda.

Ghislaine Maxwell could’ve flown to France anytime she wanted during the numerous years after the original Epstein court case yet she chose to remain here. There is such a thing as confiscating her Passports. Anyone with a reasonable mind, can see that Ghislaine Maxwell has already been tried in the court of public opinion and will never receive a fair trial in New York State in particular.

Anyway, attaching a few links for you to consider and or investigate for their newsworthiness on your show.

Thanks for noting the points raised. Warm regards, Rufus York, Geneva, Switzerland

P.S. by the way one of President Trump’s favorite Journalists Peter Alexander is struggling for air below whilst asking questions in a White House Briefing, couldn’t understand what he was trying to say, but he was struggling whilst speaking.

Since 2010 until her appointment as a United States District Judge, Nathan worked in the office of the Attorney General of New York as a special counsel to the state's Solicitor General Barbara Dale Underwood (born August 16, 1944).

As Attorney General, Underwood successfully sued Donald Trump and his foundation, Donald J. Trump Foundation, for "a pattern of persistent illegal conduct."
https://en.wikipedia.org/wiki/Barbara_Underwood

On March 31, 2011, President Obama nominated Nathan to a seat on the U.S. District Court for the Southern District of New York to replace Judge Sidney H. Stein, who took senior status in 2010. The United States Senate confirmed Nathan in a 48–44 vote on October 13, 2011. She received her judicial commission on October 17, 2011.
https://www.wikiwand.com/en/Alison_Nathan

Also on the case is (l-r) Alex Rossmillor, Alison Moe and Maureen Comey, James Comey’s daughter
Maureen Comey being among the federal prosecutors on the Ghislaine Maxwell case has raised eyebrows among NYPD detectives assigned to the task force. One detective close to the case told Los Angeles that appointing Comey, an Assistant U.S. Attorney with no experience in human trafficking cases and one with close ties to a bureau that’s come under fire for the handling of the Epstein case in Florida, has an air of “impropriety.” Comey was hired by the Southern District as a clerk in 2014, and became a prosecutor in 2015, an unusually short amount of time to be assigned one of the most high-profile investigations in the country.

Yesterday Dershowitz, who has been accused of sexual misconduct by at least one Epstein victim, sent out a bizarre tweet where he waived “any right of privacy,” if, in fact, “Epstein made secret videos of all the men who had sex in his houses and planes.”

I hope Epstein made videos
There have been suggestions that Epstein made secret videos of all the men who had sex in his houses and planes. I hope he did and they are all revealed, because they will prove I am not among them. I hereby waive any right of privacy in Epstein videos.
— Alan Dershowitz (@AlanDersh) July 5, 2020- I hope Epstein made videos.
From left: James Comey; his daughters Kate and Maurene; and his wife, Patrice

Annie Farmer also spoke at Maxwell's bail hearing, recalling meeting Donald Trump and Ivana Trump in addition to seeing lawyer Alan Dershowitz regularly visiting Epstein's New York home as well as her visit to Les Wexner's house in Ohio and her sister's connection to Epstein and Maxwell.
Bill Clinton is accused of having an affair with Ghislaine Maxwell during trips they took on pedophile Jeffrey Epstein's private jet, an explosive new book claims.

The details of the alleged affair between the former president and the British socialite are detailed in a new book - A Convenient Death: The Mysterious Demise of Jeffrey Epstein. In an excerpt of the book, obtained by the New York Post, sources said Clinton would have sex with Maxwell during overseas trips on Epstein's Lolita Express plane and he would visit her at her Manhattan townhouse.

The former president has denied having the affair with Maxwell.
Hon. Loretta A. Preska ’73 to Oversee Reconciliation Program for Victims of Clergy Sexual Abuse, By Shane Danaher on October 21, 2016
https://protect2.fireeye.com/url?k=d741e096-8b15e9bd-d741d1a9-0cc47a6d17cc-94604cee09a9ef4a&u=https://homemetry.com/house/140+37TH+ST.+New+York+NY

Established for the purpose of providing financial compensation to victims of clergy sexual abuse, the IRCP was inaugurated on October 6 by Archbishop of New York Timothy Cardinal Dolan. “This program will, please God, continue to help bring a measure of peace to those who have suffered abuse by a member of the clergy of the archdiocese,” Archbishop Dolan wrote in a message earlier this month.

Judge Preska, along with former Police Commissioner Raymond W. Kelly and Associate Clinical Professor of Psychiatry at Columbia University Jeanette Cueva, M.D., will oversee the implementation of the IRCP’s mandate.

A New York federal judge on Friday sentenced Hammond, 28, to the maximum 10 years in prison for a 2011 hacking spree that exposed confidential and sometimes personal information about law enforcement officers, private intelligence firms and U.S. government contractors and cost millions of dollars in damages. He had pleaded guilty in May.
In a lengthy statement to the court, Hammond, part of a loose band of politically motivated hackers known as Anonymous, said he knew what he was doing was illegal
but had become frustrated with the ineffectiveness of peaceful demonstrations. "I have tried everything from voting petitions to peaceful protest and have found that those in power do not want the truth to be exposed," Hammond said. "When we speak truth to power, we are ignored at best and brutally suppressed at worst."

Judge Loretta Preska https://en.wikipedia.org/wiki/Loretta_Preska to be Honored with Trailblazer Award
The Trailblazer Award is named for Israel Putnam, major general in the American Revolution, for whom Putnam County is named.
The Gordon Family, honored with the 2013 Historic Family of Philipstown Award, was profiled in the September 13 edition of The Paper.
Born in Albany, Preska attended the College of Saint Rose in that city, earning her Bachelor of Arts degree with a major in chemistry. She credits a well-timed piece of advice from a professor for her decision to pursue law rather than scientific research as her career path. In a talk she gave at Fordham University earlier this year, Preska recalled that the professor simply told her, “You should work with people.” https://protect2.fireeye.com/url?k=a6588553-fa0cac78-a658b46c-0cc47a6d17cc-956882355e871fe4&u=https://highlandscurrent.org/2013/09/21/judge-oretta-preska-to-be-honored-with-trailblazer-award/
Judge Preska is married to Thomas J. Kavaler, with whom she attended law school. Kavaler was the editor-in-chief of the Fordham Law Review and is a partner at Cahill Gordon & Reindel.
Judge Preska has been assigned the case of United States Vs Ghislaine Maxwell: https://www.youtube.com/watch?v=qnxEQYu9z

Photo:- Tom Kavaler and Judge Michael Garcia at the Lawyers Luncheon

Fordham Founder's Award Dinner and Campaign Close Celebration
Cardinal Dolan with Tom Kavaler and the Honorable Loretta Preska
Supporters of Inner-City Scholarship Fund raised $500,000 at the 26th Annual Lawyers Luncheon on November 5. Over 500
attorneys from the New York legal community attended the event at Cipriani 42nd Street. Fox 5 journalist Dari Alexander served as Master of Ceremonies. His Eminence Timothy Cardinal Dolan presented this year’s Thomas More Award to Thomas J. Kavaler, Husband of Judge Loretta Preska https://en.wikipedia.org/wiki/Loretta_Preska and Partner and Executive Committee Member, Cahill Gordon & Reindel LLP. Since 1990, the St. Thomas More Award has been given to a friend of Inner-City who exemplifies the virtues of scholarship, leadership, loyalty and service to the legal profession. https://protect2.fireeye.com/url?k=408573e1-1cd15aca-408542de-0cc47a6d17cc-4b6d079d06570e6b&u=http://www.innercityscholarshipfund.org/pdf/newsletters/icsf_2016.winter.news.pdf
Google List of Jesuits
https://protect2.fireeye.com/url?k=ea96bd4b-b6c29460-ea968c74-0cc47a6d17cc-516ea38e4c75ad63&u=https://www.google.com/search?q=photo%20album%20of%20jesuits&tbm=isch&hl=en&gl=en&tbs=rimg:3ACTSeKgHCcfIVYbegUaqYF&ved=0CBwQuIBahcKEwiA1vzQ9J3qAhAAAAAHQAAAAAQDA&biw=1422&bih=668
Photo Album Jesuits
http://faculty.fairfield.edu/jmac/jp/jplme.htm
The Founder of the Society of Jesus (Jesuit) Ignatius de Loyola himself procured its [the inquisition] erection in Portugal in 1545-6 (The Encyclopaedia Britannica: A Dictionary of Arts, Sciences, Volume 13)

Pope Francis the Jesuit Pope & promoter of the World Lockdown in 2020 with UN Chief António Manuel de Oliveira Guterres.

Remarks by His Holiness The Jesuit Pope Francis and fellow Roman Catholic, United Nations Secretary-General António Guterres - https://www.youtube.com/watch?v=CePSM3QMkEQ
Jesuit Coadjutor, Andrew Mark Cuomo flattening the curve,
https://www.youtube.com/watch?v=m8nCjNk3djc

Andrew Mark Cuomo born December 6, 1957
Roman Catholic
https://protect2.fireeye.com/url?k=bd8799c5-e1d3b0ee-bd87a8fa-0cc47a6d17cc-c0efb95a95d7a755&u=https://www.nndb.com/lists/758/000094476/
During his governorship, Cuomo oversaw the passage of a law legalizing same-sex marriage in New York; creation of the United States Climate Alliance, a group of states committed to fighting climate change by following the terms of the Paris Climate Accords; passage of the strictest gun control law in the U.S.;
His parents were both of Italian descent; his paternal grandparents were from Nocera Inferiore and Tramonti in southern Italy, while his maternal grandparents were from SicilyHis younger

---

**Chris Cuomo**

**Jesuit Coadjutor, Chris Cuomo**

**AKA** Christopher Charles Cuomo

**Born:** 9-Aug-1970  
**Birthplace:** Queens, NY

**Gender:** Male  
**Religion:** Roman Catholic  
**Race or Ethnicity:** White  
**Sexual orientation:** Straight  
**Occupation:** Journalist

**Nationality:** United States  
**Executive summary:** Co-Host, CNN New Day

**Father:** Mario Cuomo (Governor of New York, b. 15-Jun-1932, d. 1-Jan-2015)  
**Mother:** Matilda Raffa  
**Sister:** Margaret I. Cuomo  
**Brother:** Andrew Cuomo (Governor of New York, b. 6-Dec-1957)
Sister: Maria Cuomo (m. Kenneth Cole)
Sister: Madeline Cuomo
Wife: Cristina Greeven (m. 24-Nov-2001, two daughters, one son)
Daughter: Bella
Daughter: Carolina Regina (b. 2011)
Son: Mario (b. 2005)

High School: The Albany Academy
University: BA, Yale University
Law School: JD, Fordham University (1995) (jesuit)
Timothy Cardinal Dolan and Thomas Kavalier
From: Clark Tibbs PhageVax-VHO <cta@ee.net>

'Clark Tibbs PhageVax-VHO' <cta@ee.net>
<br> <Brenton.Temple@governor.ohio.gov>
<br> <Sandra.Ringer@governor.ohio.gov>
<br> <Matthew.Donahue@governor.ohio.gov>
<br> <John.Danish@governor.ohio.gov>
<br> <Bridget.Harrison@governor.ohio.gov>
<br> <Sandra.Ringer@governor.ohio.gov>
<br> <Michael.Murray@governor.ohio.gov>
<br> <Karline.Hray@governor.ohio.gov>
<br> <Carolyn.Kuruc@governor.ohio.gov>
<br> <Lynna.Mihalik@development.ohio.gov>
<br> <Dan.Bowerman@development.ohio.gov>
<br> <ELLEN.SALEHI@ODH.OHIO.GOV>
<br> <ORBIT@ODH.OHIO.GOV>
<br> <Rebecca.Fugitt@ODH.OHIO.GOV>
<br> <financialincentives@development.ohio.gov>
<br> <John.Werkman@development.ohio.gov>
<br> <Rasheda.Hansard@development.ohio.gov>
<br> <Brenton.Temple@governor.ohio.gov>
<br> <Lynna.Mihalik@development.ohio.gov>
<br> <Dan.Bowerman@development.ohio.gov>
<br> <ORBIT@ODH.OHIO.GOV>
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<br> <LETICIA.MEDEROS@mail.house.gov>
<br> <CHRISTIAN.LOVELL@mail.house.gov>
<br> <VANESSA.PATEL@mail.house.gov>
<br> Fauci, Anthony (NIH/NIAD) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYD168F235PDLT) cn=Recipients/cn=826965b24a314ffca7eddc6e8225aa7-anthony.fau
<br> <afauci@niaid.nih.gov>
<br> <Conrad, Patricia (NIH/NIAD) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYD168F235PDLT) cn=Recipients/cn=3793ae43a1744d4f6f8a56f600c0c975b-patricia.co
<br> <conrapda@niaid.nih.gov>
<br> <Armstrong, Kimberly (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYD168F235PDLT) cn=Recipients/cn=5b778c7e17734740b14ffbae3d4ed5f52-Armstrong, Kim
<br> <blyrm@armstrong@hhs.gov>
<br> <Kimberly.Reed@exam.gov>
<br> <Khanna, Gopai (AHRQ/IOD) /o=ExchangeLabs/ou=Exchange Administrative Group (FYD168F235PDLT) cn=Recipients/cn=76ea01c03eb347608851b240d65e1197-Khanna, Gopai
<br> <gopai.khanna@ahrq.hhs.gov>
<br> <Meyers, David (AHRQ/IOD) /o=ExchangeLabs/ou=Exchange Administrative Group (FYD168F235PDLT) cn=Recipients/cn=ef0a99be51c1b409db60cbf9e2b5c77-Meyers, Dav
<br> <David.meyers@ahrq.hhs.gov>

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'T Clark Tibbs PhageVax-VHO' <cta@ee.net>

<clark@phagevax.com>
<br> <clark@phagevax.com>
<br> <clark@gmail.com>
<br> <clark@gmail.com>
<br> <david@gmail.com>
<br> <david@gmail.com>
<br> <david@yahoo.com>
<br> <david@yahoo.com>
<br> <david@brown.edu>
<br> <david@brown.edu>
<br> <david@YALE.EDU>
<br> <david@YALE.EDU>
<br> <kendall@hhmi.org>
<br> <kendall@hhmi.org>
<br> <Carl Merrill' <merrilcarl@msn.com>
<br> 'David Ellis' <david@highside.io>
<br> 'David M. Manuta, Ph.D., FAIC <dmanuta@dmanuta.com>
<br> <Emergency_Casework@brown senate.gov>
<br> <Emily_Benavides@portman senate.gov>
<br> <emily.baumgaertner@latimes.com>
<br> <enquiries@health.gov.au>
JUST FOR USA ... WE WILL NEED ... 700 MILLION DOSES.

It seems that the US Federal Government is funding a few quality vaccine platform-types (vs. the 2019-nCoV), however ... how many doses can be made in time to protect us? ... (we will need 2 doses; 1 week apart) and how fast can these quantities of doses get to the US Citizens?

---------------------

Over this weekend, I will ask our Vaccine-Expert Authors for realistic estimates on how many doses ... and ... how fast ... and get back with you.

Thank you, Clark Tibbs 1-740-366-9013

[PS: Please look at the last document at https://protect2.fierceeye.com/url?k=047a6feb-582e46c0-047a5ed4-0cc47a6d17cc-18cdda0985973c6&u=http://www.phagevax.com/ ... Topic is: Flu Vaccines; speed to market.] (Now Attached)

---

From: Clark Tibbs PhageVax-VHO [mailto:cta@ee.net]
Sent: Friday, January 31, 2020 5:53 PM
To: Brenton.Temple@governor.ohio.gov; Sandra.Ringer@governor.ohio.gov;
   Matthew.Donahue@governor.ohio.gov; John.Danish@governor.ohio.gov; Bridget.Harrison@governor.ohio.gov;
   Sandra.Ringer@governor.ohio.gov; Michael.Murry@governor.ohio.gov; Karine.Hray@governor.ohio.gov;
   Carolyn.Kuruc@governor.ohio.gov; Lydia.Mihalik@development.ohio.gov; Dan.Bowerman@development.ohio.gov;
   ELLEN.SALEH@ODH.OHIO.GOV; ORBIT@ODH.OHIO.GOV; Rebecca.Fugitt@ODH.OHIO.GOV;
   financialincentives@development.ohio.gov; John.Werkman@development.ohio.gov;
   Rasheda.Hansard@development.ohio.gov; Brenton.Temple@governor.ohio.gov;
   Lydia.Mihalik@development.ohio.gov; Dan.Bowerman@development.ohio.gov; ELLEN.SALEH@ODH.OHIO.GOV;
   ORBIT@ODH.OHIO.GOV; Rebecca.Fugitt@ODH.OHIO.GOV; financialincentives@development.ohio.gov;
   John.Werkman@development.ohio.gov; Rasheda.Hansard@development.ohio.gov
Cc: Clark Tibbs PhageVax-VHO; clark@phagevax.com; LETICIA.MEDEROS@mail.house.gov;
   CHRISTIAN.LOVELL@mail.house.gov; VANESSA.PATEL@mail.house.gov

Subject: To US Rep Rosa DeLauro (CT) :: VACCINE OFFER :: T-4 Lambda Phage Head Vaccine Platform
vs. the 2019-nCoV Virus ... Jan 31

To US Rep Rosa DeLauro (CT)  202-275-3661

... via ...

LETICIA.MEDEROS@mail.house.gov  Chief of Staff
CHRISTIAN.LOVELL@mail.house.gov
VANESSA.PATEL@mail.house.gov

My name is Clark Tibbs in Newark, Ohio.

Can you please forward this to the ... Governor of CONNECTICUT ... for prompt funding consideration?
We are going to need all the help we can get.
JUST FOR USA ... WE WILL NEED ... 700 MILLION DOSES.

Clark Tibbs, CEO
CAGE CODE: 4M4V6 www.sam.gov
Phone: 740.366.9013 Fax: 740.366.5230 Cell: [6]

From: Clark Tibbs PhageVax-VHO [mailto:PhageVax@roadrunner.com]
Sent: Friday, January 31, 2020 5:08 PM
To: 'Brenton.Temple@governor.ohio.gov'; 'Sandra.Ringer@governor.ohio.gov'
Cc: 'Clark Tibbs PhageVax-VHO'; 'clark@phagevax.com'; 'clarktibbs2020@gmail.com'
Subject: To Ringer & Temple for To Gov. Mike DeWine :: VACCINE OFFER :: T-4 Lambda Phage Head Vaccine Platform vs. the 2019-nCoV Virus ... Jan 31

TO:
Brenton Temple at (614) 644-0789 or at Brenton.Temple@governor.ohio.gov
Sandy Ringer, Exec. Assistant to the Governor - Sandra.Ringer@governor.ohio.gov - 614-644-0795

My name is Clark Tibbs in Newark, Ohio.
Can you please forward this to the Governor of Ohio, for prompt funding consideration?

Clark Tibbs, CEO
CAGE CODE: 4M4V6 www.sam.gov
Phone: 740.366.9013 Fax: 740.366.5230 Cell: [6]

From: Clark Tibbs PhageVax-VHO [mailto:PhageVax@roadrunner.com]
Sent: Friday, January 31, 2020 4:47 PM
To: 'Matthew.Donahue@governor.ohio.gov'; 'John.Danish@governor.ohio.gov'; 'Bridget.Harrison@governor.ohio.gov'; 'Sandra.Ringer@governor.ohio.gov'; 'Michael.Murry@governor.ohio.gov'; 'Karine.Hray@governor.ohio.gov'; 'Carolyn.Kuruc@governor.ohio.gov'; 'Lydia.Mihalik@development.ohio.gov'; 'Dan.Bowerman@development.ohio.gov'; 'ELLEN.SALEHI@ODH.OHIO.GOV'; 'ORBIR@ODH.OHIO.GOV'; 'Rebecca.Fugitt@ODH.OHIO.GOV'; 'financialincentives@development.ohio.gov'; 'John.Werkman@development.ohio.gov'; 'Rasheda.Hansard@development.ohio.gov', Brenton.Temple@governor.ohio.gov
Subject: To Gov. Mike DeWine :: VACCINE OFFER :: T-4 Lambda Phage Head Vaccine Platform vs. the 2019-nCoV Virus ... Jan 31

To:
Gov. Mike DeWine
... via ...
Atty. Matt Donahue - Chief Legal Counsel - Matthew.Donahue@governor.ohio.gov - 614-644-0825
Atty. John Danish - Chief Deputy Legal Counsel - John.Danish@governor.ohio.gov - 614-644-0836

Bridget Harrison, Assist. Policy Director, Health &Human Services -
Bridget.Harrison@governor.ohio.gov - 614-644-0871
Sandy Ringer, Exec. Assistant to the Governor - Sandra.Ringer@governor.ohio.gov - 614-644-0795
Michael Murry, Deputy Chief of Staff - Michael.Murry@governor.ohio.gov - 614-728-8274
Karine Hray, Director, Business Advocacy, Common Sense Initiative, Lt. Gov. -
Karine.Hray@governor.ohio.gov - 614-644-0852
Carolyn Kuruc, Director, Common Sense Initiative - Carolyn.Kuruc@governor.ohio.gov - 614-995-5728

Hello Mike DeWine, My name is Clark Tibbs in Newark, Ohio. Let's talk this evening and this weekend, please?

Please scan over this attached document and then forward to your Scientists in Infection and Immunity?

This is an Emergency. Do you have Emergency Funding?

We would be interested in their prompt assessment, please?

Regards,

Clark Tibbs, CEO
PhageVax, Inc. https://protect2.fireeye.com/url?k=e0b8a3e4-bcec8acf-e0b892db-0cc47a6d17cc-b592545d18747610&u=http://www.phagevax.com/
CAGE CODE: 4M4V6 www.sam.gov
Phone: 740.366.9013 Fax: 740.366.5230 Cell: |
E-mail: Clark@PhageVax.com -or- PhageVax@roadrunner.com -or- CTA@ee.net
General Offices & HQ: 855 Sharon Valley Road, Suite 101 Newark, Ohio 43055-2860 USA

================================================================================
WHO declares nCoV public health emergency amid virus spread

Lisa Schnirring | News Editor | CIDRAP News | Jan 30, 2020

The main worry is the possible affect on weaker nations.

More »

Data suggest nCoV more infectious than 1918 flu, but what does that mean?

Stephanie Soucheray | News Reporter | CIDRAP News | Jan 30, 2020

The R0 was found to be 2.2, the number of people each patient might infect.

More »

First human-to-human nCoV spread reported in US

Lisa Schnirring | News Editor | CIDRAP News | Jan 30, 2020

The husband of Chicago's first case-patient has contracted the novel coronavirus, marking the 6th US case.

More »

Coronavirus: What it does to the body - BBC News - 1-30-20

- 

AT https://protect2.fireeye.com/url?k=10035755-4c577e7e-1003666a-0ce47a6d17cc-3d1c4d174c8307cf+u=http://virological.org/ ... 

Initial genome release of novel coronavirus

Novel 2019 coronavirus
You have selected 0 posts.

select all

cancel selecting

http://virological.org/user_avatar/virological.org/arambaut/45/425_2.png

arambaut ARTIC Network

2
21h

10th January 2020

This posting is communicated by Edward C. Holmes, University of Sydney on behalf of the consortium led by Professor Yong-Zhen Zhang, Fudan University, Shanghai

The Shanghai Public Health Clinical Center & School of Public Health, in collaboration with the Central Hospital of Wuhan, Huazhong University of Science and Technology, the Wuhan Center for Disease Control and Prevention, the National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control, and the University of Sydney, Sydney, Australia is releasing a coronavirus genome from a case of a respiratory disease from the Wuhan outbreak. The sequence has also been deposited on GenBank (accession MN908947) and will be released as soon as possible.

The sequence can be downloaded here:

WH-Human_1.fasta.gz (8.9 KB – this is a fasta file compressed using gzip. Uncompress using gzip -d WH-Human_1.fasta.gz)

Disclaimer:
Please feel free to download, share, use, and analyze this data. We ask that you communicate with us if you wish to publish results that use these data in a journal. If you have any other questions –then please also contact us directly.

Professor Yong-Zhen Zhang,
Shanghai Public Health Clinical Center & School of Public Health,
Fudan University, Shanghai, China.

zhangyongzhen@shphc.org.cn  See also: Virological.net post

=================================================================================================

=================================================================================================
Look at this ... 'dreadful' ... and globally-important Report: (from 17 Jan to 22 Jan 2020)
Report 2: Estimating the potential total number of novel Coronavirus cases in Wuhan City, China

- Imperial College London today in a new estimate of 2019-nCoV activity in Wuhan said the city
probably now has 4,000 symptomatic cases. The report's 95% confidence interval ranges from 1,000
to 9,700.

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- ... AND TO ...

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ABSTRACT Bacillus anthracis and Yersinia pestis, the causative agents of anthrax and plague, respectively, are two of the deadliest pathogenic bacteria that have been used as biological warfare agents. Although Biothrax is a licensed vaccine against anthrax, no Food and Drug Administration-approved vaccine exists for plague. Here, we report the development of a dual anthrax-plague nanoparticle vaccine employing bacteriophage (phage) T4 as a platform. Using an in vitro assembly system, the 120- by 86-nm heads (capsids) of phage T4 were arrayed with anthrax and plague antigens fused to the small outer capsid protein Soc (9 kDa). The antigens included the anthrax protective antigen (PA) (83 kDa) and the mutated (mut) capsule antigen F1 and the low-calcium-response V antigen of the type 3 secretion system from Y. pestis (F1mutV) (56 kDa). These viral nanoparticles elicited robust anthrax- and plague-specific immune responses and provided complete protection against inhalational anthrax and/or pneumatic plague in three animal challenge models, namely, mice, rats, and rabbits. Protection was demonstrated even when the animals were simultaneously challenged with lethal doses of both anthrax lethal toxin and Y. pestis CO92 bacteria. Unlike the traditional subunit vaccines, the phage T4 vaccine uses a highly stable nanoparticle scaffold, provides multivalency, requires no adjuvant, and elicits broad T-helper 1 and 2 immune responses that are essential for complete clearance of bacteria during infection. Therefore, phage T4 is a unique nanoparticle platform to formulate multivalent vaccines against high-risk pathogens for national preparedness against potential bioterror attacks and emerging infections.

IMPORTANCE Following the deadly anthrax attacks of 2001, the Centers for Disease Control and Prevention (CDC) determined that Bacillus anthracis and Yersinia pestis that cause anthrax and plague, respectively, are two Tier 1 select agents that pose the greatest threat to the national security of the United States. Both cause rapid death, in 3 to 6 days, of exposed individuals. We engineered a virus nanoparticle vaccine using bacteriophage T4 by incorporating key antigens of both B. anthracis and Y. pestis into one formulation. Two doses of this vaccine provided complete protection against both inhalational anthrax and pneumonic plague in animal models. This dual anthrax-plague vaccine is a strong candidate for stockpiling against a potential bioterror attack involving either one or both of these biothreat agents. Further, our results establish the T4 nanoparticle as a novel platform to develop multivalent vaccines against pathogens of high public health significance.
KEYWORDS anthrax vaccine, bacteriophage T4, biodefense, plague vaccine, small outer capsid protein, vaccine delivery, virus nanoparticles

Vaccines are one of the most successful medical interventions of the past millennium (1). Millions of lives have been saved by mass administration of vaccines against deadly pathogens such as smallpox and flu. However, effective vaccines are still lacking for many pathogens, including biothreat agents such as the Gram-positive bacterium Bacillus anthracis that causes anthrax and the Gram-negative bacterium Yersinia pestis that causes plague. According to the Centers for Disease Control and Prevention (CDC), these two organisms are two of the Tier 1 select agents that pose the greatest threat to national security (2). Both are highly virulent resulting in mortality (as high as 100%) of the subjects within 3 to 6 days of infection. The organisms can be weaponized and transmitted through inhalation of aerosolized droplets and can be disseminated relatively easily for the purposes of biological warfare or bioterrorism (3, 4). Designing a vaccine that can protect the public against these threats is therefore a national priority. Additionally, plague is a significant threat to global health. It causes periodic outbreaks around the world. The latest example is the 2017 Madagascar outbreak that resulted in 209 deaths (>70% of the cases were pneumonic plague) (5).

Vaccine development historically relied on the whole pathogen containing either the inactivated (heat- or formalin-killed) organisms or live attenuated (less virulent mutant) organisms (1). Several such vaccines have been developed against anthrax and plague in the past. The Biothrax anthrax vaccine (AVA [anthrax vaccine alum-adsorbed]) is derived from the culture filtrate of the attenuated B. anthracis strain V770-NP1-R (6, 7). This strain secretes the anthrax protective antigen (PA), a primary target for anthrax vaccine design, into the culture medium, but also traces of the other two components of the tripartite anthrax toxin, the lethal factor (LF) and the edema factor (EF) (6–8). This vaccine does have untoward side effects, and therefore, new anthrax vaccines are highly sought. Similarly, plague vaccines were developed using the formalin-killed or live attenuated Yersinia pestis bacteria (9–11). However, these whole-pathogen vaccines produce severe side effects such as reactogenicity at the injection site. Hence, these vaccines have either been discontinued or used only in a limited way to protect at-risk military and laboratory personnel (6, 10–12).

Subunit vaccines containing only the target antigen(s) of a pathogen are safer alternatives to whole-pathogen vaccines (13, 14). Numerous recombinant vaccines against anthrax or plague have been under investigation, but none have yet been licensed (6, 15–18). The recombinant anthrax vaccines are composed primarily of PA (6, 18), whereas the plague vaccines contain two surface antigens of Y. pestis, the capsular protein Cfa1 (or F1) (15.6 kDa) and the low-calcium-response V antigen LcrV (or V) (37.2 kDa) (15–17). A bivalent vaccine consisting of all three antigens fused into a single polypeptide has also been developed (19). However, the subunit vaccines generally are unstable, may not generate sufficient immune responses for complete protection, and require the addition of nonspecific “adjuvants” such as aluminum hydroxide or liposomes to enhance immunogenicity and protective efficacy (13, 20–22).

One of the reasons for poor immunogenicity of subunit vaccines is the lack of the pathogen-associated molecular patterns (PAMPs) observed in whole-pathogen vaccines, which are recognized by the host immune system and trigger innate as well as adaptive immune responses (22, 23). One way to overcome this limitation is to incorporate the target antigen as part of a virus nanoparticle structure (24–27). Phages, such as T4, lambda, and M13, have been used as viral nanoparticle platforms to display antigens (28–30). The antigen molecules so arrayed on the nanoparticle surface would mimic the PAMPs of a pathogenic virus, potentially leading to stimulation of strong immune responses (24, 25).

Here, we report the development of a dual viral nanoparticle vaccine against both anthrax and plague using bacteriophage (phage) T4 (Fig. 1). The 120- by 86-nm-size phage T4 head (capsid) is decorated with anthrax PA (83 kDa) and plague F1mutV.
(56 kDa) fused to the small outer capsid protein (Soc) (9 kDa). F1mutV is a fusion protein of a mutant F1 antigen and V antigen. The mutant F1 produces a soluble monomeric protein, as opposed to the native F1 which polymerizes into heterogeneous aggregates, yet it retains the full immunogenicity of the native protein (17). Since Soc assembles on phage T4 capsid as a trimer at the quasi-three-fold axes (Fig. 1A) (31, 32), the PA and F1mutV antigens attached to Soc might be recognized by the host immune system as repeating structures arranged symmetrically on the nanoparticle (Fig. 1B), similar to PAMPs. Indeed, our studies demonstrated that such nanoparticles generated robust antigen-specific immune responses and provided complete protection against both anthrax and plague in three different animal models, namely, mice, rats, and rabbits. Furthermore, the T4 nanoparticle vaccine, unlike the traditional subunit vaccines, do not require any adjuvant and generated balanced T1, T2- and T3-based antibody responses, which are highly desirable for any vaccine but particularly relevant for clearance of pathogenic plague bacteria (10, 33). Finally, the T4 nanoparticle vaccine provided complete protection against simultaneous challenge by both anthrax lethal toxin (LeTx) and Y. pestis CO92. These results suggest that the phage T4 vaccine might be a good candidate for stockpiling against a potential bioterror attack involving either one or both of these biothreat agents. Further, our results establish the T4 nanoparticle as a novel platform to develop multivalent biodefense vaccines containing additional biothreat antigens, as well as for engineering vaccines against other emerging pathogens of high public health significance.

RESULTS

Preparation of T4 nanoparticles decorated with anthrax and plague antigens. To develop a phage T4 vaccine against both B. anthracis and Y. pestis, we constructed three recombinants by fusing the anthrax and plague antigens to phage RB69 Soc. The three recombinants were F1mutV-Soc-PA (148 kDa), F1mutV-Soc (66 kDa), and Soc-PA (93 kDa). Our previous studies have shown that both the N and C termini of RB69 Soc are exposed on the capsid surface, and both can be used to display recombinant proteins efficiently (34, 35). Phage RB69 is closely related to T4, and its Soc protein binds to phage T4 capsid as well as the T4 Soc protein does (34). As reported previously (34), the binding affinity, copy number per capsid, and capsid stabilization by Soc binding are nearly the same for RB69 Soc as those of T4 Soc. However, we observed that proteins fused to RB69 Soc showed greater solubility than the proteins fused to T4 Soc (17). Since such solubility is a significant factor in vaccine manufacture, we used RB69 Soc instead of T4 Soc for antigen display. The choice of the plague antigen F1mutV and the anthrax antigen PA was based on our previous studies in which these antigens stimulated protective immune responses in animal models (17, 19, 36–38). The His-tagged recombinant proteins were overexpressed in Escherichia coli and purified by immobilized nickel affinity chromatography followed by size exclusion chromatography (see Fig. S1 in the supplemental material). The purified proteins were then
assembled on T4 nanoparticles in three different display formats: (i) display of F1mutV-Soc-PA, (ii) display of F1mutV-Soc and Soc-PA on the same capsid, and (iii) a 1:1 mixture of T4 phage particles separately displayed with F1mutV-Soc or Soc-PA. Of these display formats, the latter produced particles with the highest copy number of antigens per capsid, whereas F1mutV-Soc-PA produced the lowest copy number. Hence, this formulation, a mixture of T4 nanoparticles displaying either F1mutV-Soc or Soc-PA (abbreviated as T4-F1mutV/PA) was selected for immunological studies.

To optimize the copy number for immunization experiments, $2 \times 10^{10}$ particles of purified Soc- (and Hoc-) phage were incubated with F1mutV-Soc or Soc-PA proteins at different ratios of antigen molecules to Soc binding sites (Fig. 1B and 2). Binding increased with increasing ratio, reaching saturation at $\sim 20:1$ (Fig. 2). The copy numbers of antigens displayed per capsid ($B_{\text{max}}$) were 650 for the 66-kDa F1mutV-Soc and 361 for the 93-kDa Soc-PA, and the binding concentrations at which half of the capsid binding sites were occupied ($BC_{50}$) were 348 nM and 1,140 nM, respectively (Fig. 2; see Materials and Methods for details on the determination of $B_{\text{max}}$ and $BC_{50}$). Since there are 870 Soc binding sites per capsid, the percent occupancy values were 75 for F1mutV-Soc and 41 for Soc-PA. These values represent high occupancies, considering that both the 83-kDa PA and the 56-kDa F1mutV would encounter steric constraints to access all the Soc binding sites on the capsid surface, the former more so than the latter, as reflected in the data.

The T4 nanoparticles decorated with anthrax and plague antigens provide near-complete protection to mice against anthrax lethal toxin and pneumonic plague challenges with Y. pestis CO92. BALB/c mice (10 mice per group) were immunized by the intramuscular (i.m.) route with 25 $\mu$g of each of the T4 nanoparticle preparations containing F1mutV-Soc and Soc-PA and boosted on day 21 (Fig. 3A). Mice
immunized with the T4 phage lacking the antigens served as a control group. A series of experiments were performed to determine the immunogenicity and protective efficacy of the T4-delivered antigens. Enzyme-linked immunosorbent assays (ELISAs) showed high levels of both FIV-specific and PA-specific IgG antibodies, up to endpoint titers of $\sim 3 \times 10^5$ (Fig. 3B). Anthrax lethal toxin (LeTx) neutralization assays demonstrated that the T4-PA immunized animals also elicited robust LeTx neutralization titers (the dilution of serum inducing 50% neutralization [$EC_{50}$] of 4,052 ± 281) (Fig. 3C). The control animals were negative for both types of antibodies (Fig. 3B and C).

The protective efficacy of T4-delivered F1mutV/PA was evaluated by two dual-challenge models that we have recently developed: (i) sequential challenge (Fig. 3D) in which the animals were first exposed to one threat agent and the survivors were then exposed to the second threat agent, and (ii) simultaneous challenge (Fig. 3E) in which the animals were exposed to both threat agents at the same time. For sequential challenge, mice (10 mice per group) immunized as described above (Fig. 3A) were injected intraperitoneally (i.p.) with one 100% lethal dose (LD$_{100}$) of LeTx (1:1 mixture of PA and LF [100 μg each]) on day 42. The immunized group was 80% protected against LeTx challenge, whereas 100% of the negative-control mice died within 2 days of challenge (Fig. 3D). Thirty-three days later, the surviving animals were challenged with 400 50% lethal doses (LD$_{50}$) of Y. pestis CO92 by intranasal (i.n.) administration to develop pneumonic plague. The naive mice were used as negative controls. The T4-F1mutV/PA group showed 100% protection (no death), whereas the naive animals showed 100% death within 4 days after Y. pestis CO92 challenge (Fig. 3D).

For simultaneous dual challenge, mice ($n = 8$) immunized by the same scheme (Fig. 3A) were challenged with both LeTx (1 LD$_{100}$, i.p. administration) and Y. pestis CO92 (200 LD$_{50}$, i.n. administration) 23 days after the boost (Fig. 3A). As shown in Fig. 3E, all the control mice died within 2 days of challenge, whereas the T4-delivered F1mutV/PA provided 88% protection (one death out of eight mice). Furthermore, the survivors showed clearing of Y. pestis bacteria by 3 days postchallenge (Fig. 3F). The Y. pestis CO92 strain used in the challenge experiment contained a luciferase (lux) expression cassette for imaging the bacteria in vivo in real time (39). The immunized animals were
negative for bioluminescence, whereas the control mice showed bacterial dissemination throughout the body (Fig. 3F); these data were confirmed by colony count determination at the termination of the experiment or as the animals succumbed to infection (data not shown).

The T4 nanoparticles provide complete protection to rats against both anthrax and plague. The rat is a natural host for *Y. pestis* infection, which occurs through rat fleas. Therefore, rats are one of the most reliable models to assess the protective efficacy of vaccines against plague (40). Likewise, rats are exquisitely sensitive to LeTx (19). To evaluate the immunogenicity and protective efficacy of the T4 bivalent vaccine using this model, Brown Norway rats (*n* = 9) were immunized using the scheme shown in Fig. 4A. The T4-delivered immunogens induced high levels of antigen-specific IgG titers in rats, up to \(-1.25 \times 10^5\) and \(-6.25 \times 10^5\) of F1mutV-specific and PA-specific IgG, respectively (Fig. 4B). The T4-F1mutV/PA group consistently also generated high levels of LeTx neutralizing antibodies (EC\textsubscript{50} of 4.285 ± 0.409) (Fig. 4C). The control animals, as expected, were negative for the antigen-specific total IgG and LeTx neutralizing antibodies (Fig. 4B and C).

The protective efficacy of the T4 bivalent vaccine in rats was also tested by our dual-challenge models (Fig. 4D and E). For sequential challenge, the animals (*n* = 9) were first subjected to Lm challenge with 400 LD\textsubscript{50} of *Y. pestis* CO92. The T4 bivalent vaccine showed 100% protection, whereas all the rats in the control group died within 2 days postchallenge (Fig. 4D). The surviving rats were then challenged with 1 LD\textsubscript{100} of LeTx (7.5 \(\mu\)g each of PA and LF) by intravenous (i.v.) injection on day 70 after *Y. pestis* CO92 challenge. All the rats immunized with T4 dual anthrax-plague vaccines survived (Fig. 4D), but rats in the control group (negative control) died within 2 h of the LeTx challenge. This is consistent with previous studies in that rats are highly sensitive to i.v. administration of LeTx, a challenge regime that results in rapid death (19). In a separate experiment, the protective efficacy of the T4 vaccine was further evaluated by the simultaneous dual-challenge model where the rats (*n* = 6) were immunized as de-
 subscribed above and challenged with both LeTx (1 LD100, i.v.) and Y. pestis CO92 (400 LD50, i.n.) at the same time (Fig. 4E). The T4 dual vaccines once again showed 100% protection, whereas the control animals succumbed to either the LeTx challenge or to Y. pestis infection (Fig. 4E).

The T4 nanoparticle vaccine induces high levels of both T helper-1- and T helper-2-dependent antibody responses. Stimulation of both arms of the immune system, humoral (Th1) and cellular (Th1), is essential for protection against Y. pestis infection (10), and probably beneficial for protection against B. anthracis infection (41). With this in mind, we determined the IgG subclass of the induced antibodies (Fig. 5). In mice, the IgG2a titer represents the Th1 response, whereas the IgG1 titer reflects the Th2 response. Our data showed that the T4-displayed F1mutV/PA group elicited high levels of both IgG1 and IgG2a antibodies against F1mutV or PA, whereas the control animals were negative for both types of antibodies (Fig. 5A and B). The IgG subclass specificity of the antibodies induced in rats exhibited trends similar to those in mice (Fig. 5C and D). The T4 nanoparticle-displayed F1mutV/PA induced high levels of both IgG1 and IgG2a antibodies against both F1mutV and PA immunogens (Fig. 5C and D). However, a bias toward Th1 was even stronger in the case of anti-PA than in the case of anti-F1mutV (Fig. 5C and D). These results, which were consistently observed in two animal models, showed that the T4 nanoparticle-delivered antigens stimulated strong antibody responses derived from both the Th1 cellular system and the Th2 humoral system (17, 42). In contrast, we and others have previously noted that soluble antigens (with Alhydrogel as an adjuvant) showed a clear bias toward the Th2 responses (17, 43). This is also consistent with the clearance of pathogenic Y. pestis lux bacteria in the challenge experiments described above. However, more studies are needed to directly examine the Th1 and Th2 responses and to further explore the mechanisms of T4 nanoparticle vaccine-induced protection.

The T4 nanoparticles confer complete protection to rabbits against inhalational anthrax. The T4 dual anthrax-plague vaccine was further evaluated in a New Zealand White (NZW) rabbit model that is considered to be the best model for inhalation anthrax. The pathology of rabbits challenged with aerosolized Ames spores shows remarkable similarity to that in humans infected with encapsulated toxigenic B. anthracis spores (44, 45). NZW rabbits (10 rabbits per group) were primed on day 0 and boosted on day 14 by the i.m. injection of the T4 bivalent anthrax-plague vaccine formulation (Fig. 6A). Sera were collected on the schedule shown in Fig. 6A and subjected to immunological analyses. The data showed that the T4 nanoparticle vaccines induced
FIG 6 (A) Immunization scheme for rabbit study. Rabbits (10 rabbits in the T4-F1mutV/PA group and 6 rabbits in the control group) were immunized on day 0 and given a boost on day 14. Animals were challenged with 200 LD₅₀ of aerosolized B. anthracis Ames spores 2 weeks after the boost. (B) PA-specific total IgG antibody titers. The titers for bleed on days 0, 12, 20, and 42 are shown. (C) LeTx neutralizing antibody titers. (D) F1V-specific total IgG antibody titers for day 20. Error bars represent standard deviations (SD) of the means. Values that are significantly different by Student’s t test are indicated by bars and asterisks as follows: ***, P < 0.001; ****, P < 0.0001. (E) Survival of the rabbits challenged with 200 LD₅₀ of aerosolized B. anthracis Ames spores. The survival data are from 10 vaccinated rabbits and 6 control rabbits.

high levels of anti-PA IgG antibodies as well as LeTx neutralizing antibodies on day 20 (Fig. 6B and C). The rabbits also induced high levels of anti-F1mutV antibodies, up to an endpoint titer of 1.6 × 10⁹ (Fig. 6D). The control group showed no antibodies to either PA or F1mutV (Fig. 6B to D).

Rabbits were challenged 2 weeks after the boost with 200 LD₅₀ of aerosolized B. anthracis Ames spores. All the naive control rabbits succumbed to the anthrax disease 2 to 4 days postinfection, while the T4 dual-vaccine-immunized rabbits were 100% protected (Fig. 6E). Blood samples for bacteremia were drawn before the challenge on day 27 and on days 29 to 33 (2 to 6 days postexposure) and 42 (15 days postexposure). Bacteremia was not detected in vaccinated animals, whereas all unvaccinated animals became positive for bacteremia before they succumbed to the disease. To determine the bacterial loads of internal organs, postmortem collection of specimens was performed after scheduled euthanasia of surviving animals on study day 42 (T4-F1mutV/PA group) or after animals died due to the anthrax exposure (control group). All vaccinated animals had cleared the agent from the lungs and did not have any bacteria in the brain, liver, or spleen. In contrast, tissue samples collected from control animals were positive for B. anthracis (except for one rabbit whose liver was negative), indicating systemic anthrax infection.

DISCUSSION

The deadly anthrax attacks of 2001 using weaponized spores of B. anthracis illustrated the enormous dangers posed by biothreat agents in creating chaos and terror among the public (3, 4). Stockpiling of a biodefense vaccine that can protect people against multiple biothreat agents would provide an effective countermeasure to mitigate such future attacks. Despite intense efforts for nearly 2 decades, no such vaccine is on the horizon for licensure. We describe here a nanoparticle vaccine delivery platform using phage T4 that can be engineered to create multivalent biodefense vaccines against different pathogens. As a proof of principle, a dual anthrax-plague vaccine is formulated by incorporating three different antigens from two Tier 1 select agents into phage T4 nanoparticles; protective antigen from B. anthracis and the capsular protein F1 and the low-calcium-response V antigen from Y. pestis.
The anthrax and plague antigens were assembled in vitro on the capsid of phage T4 through fusion to the phage outer capsid protein Soc. High-affinity interactions between Soc and the capsid fixed the antigens at symmetric positions of the capsid lattice. Recent studies showed that repeat structures of the viral capsid could be recognized by Toll-like receptor 2 (TLR-2) as a PAMP and could lead to the induction of an innate immune response (46). Therefore, a simple mixture of anthrax and plague antigen particles, with the displayed antigens resembling the repeat structures or molecular patterns seen on a natural viral pathogen, might then be presented to the host immune system.

Strikingly, the T4 nanoparticle vaccine elicited high titers of antigen-specific antibodies against both anthrax and plague antigens. Neither antigenic interference nor enhancement of antibody responses was evident. Furthermore, the dual vaccine was highly efficacious in protecting animals against lethal challenges with anthrax and/or plague agent. This was observed in three different animal models: BALB/c mice, Brown Norway rats, and New Zealand White rabbits. Indeed, complete protection of vaccinated animals was observed even when the animals were simultaneously challenged with LeTx and the highly virulent Y. pestis CO92 bacteria in the rat model or in an inhalational anthrax model where the rabbits were challenged with the aerosolized Ames spores of B. anthracis. These models represent two of the best models available to assess the efficacy of plague and anthrax vaccines, respectively.

It is significant that the dual anthrax-plague vaccine, unlike the traditional subunit vaccines, elicited robust immune responses against both antigens in the absence of an adjuvant. In fact, addition of adjuvants such as Alhydrogel and/or liposomes to the nanoparticles did not enhance the immune responses (data not shown). We speculate that this might be because the viral nanoparticles, mimicking the PAMPS of a natural pathogen, engage with the TLRs and robustly stimulate the innate and adaptive immune systems of the host and do not need an external adjuvant (46). Consistent with this hypothesis, the T4 dual vaccine elicited both T111- and T112-mediated antibody responses against both antigens. This seems to be a signature characteristic of the phage T4 nanoparticle platform, one that is highly desirable for clearance of pathogenic organisms during natural infection. However, further studies are needed to understand the mechanisms.

In conclusion, our studies highlight some unique properties of the T4 phage nanoparticle that are distinct from the traditional subunit vaccines, which could facilitate formulation of multivalent vaccines against high-risk pathogens. Potentially, additional antigens from other bioterror agents and/or from emerging pathogens could be incorporated using the same principle, and these formulations can be customized to address different threats in different geographical regions of the world. Additional advantages of phage T4 platform include the following: highly stable structure, scalability, cost-effectiveness, safety, and lack of preexisting immunity in humans. Together, these factors could accelerate the streamlining of clinical trials, manufacture, and deployment at a much reduced cost, time, and effort. Phage T4, thus, is a good candidate to develop as a “universal” platform for creating and stockpiling multivalent vaccines as part of our national preparedness against potential future bioterror and emerging infections. With some more refinement, this platform may have the most desirable target product profile for licensure.

MATERIALS AND METHODS

Ethics statement. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (47) recommended by the National Institutes of Health. All animal experiments were performed according to the protocols approved by the Institutional Animal Care and Use Committees of the University of Texas Medical Branch, Galveston, TX (Office of Laboratory Animal Welfare assurance number A3314-01), The Catholic University of America, Washington, DC (Office of Laboratory Animal Welfare assurance number A4431-01), and Southern Research Institute, Birmingham, AL (Office of Laboratory Animal Welfare assurance number A3036-01). All of the select agent animal research was conducted in the animal biosafety level 3 (ABSL3) suite, and the principal investigators have registered with the CDC to work with these pathogens.
Plasmids, bacterial, and phage T4. The E. coli expression vector pET28b (EMD Biosciences, Darmstadt, Germany) was used for recombinant plasmid construction. Expression plasmid pET-F1mutV-Soc was constructed previously (17, 48). The pET-Soc-PA plasmid was constructed by replacing the F1mut gene of pET-F1mutV-PA (19) with Soc, which was amplified from pET-F1mutV-Soc by PCR. The amplified Soc fragment was doubly digested with Nhel and HindIII and cloned into pET-F1mutV-PA, linearized with the same enzymes, to replace F1mutV. The resulting pET-Soc-PA contains the Soc gene fused in frame to the N terminus of PA with a short linker (Glu-Ala-Ser-Ala) between the Soc gene and PA. All plasmids were confirmed by sequencing. E. coli strains DH5α was used for cloning. E. coli strain P301 was used to propagate hoc soci− phage T4 as described previously (49–51). The E. coli BL21-CodonPlus (DE3)-RIL cells (Agilent Technologies, Santa Clara, CA) were used for expression of genes encoding target proteins.

Purification of proteins. The E. coli BL21-CodonPlus (DE3)-RIL cells containing either pET-Soc-PA or pET-F1mutV-Soc were induced with 1 mM isopropyl β-D-1-thiogalactopyranoside (IPTG) for 2 to 3 h at 28°C. Recombinant proteins were purified as described previously (17, 48). Briefly, cells were harvested and resuspended in binding buffer (50 mM Tris-HCl [pH 8.0], 300 mM NaCl, and 20 mM imidazole) containing protease inhibitor cocktail (Roche, USA, Indianapolis, IN). After the cells were lysed by 19,610 lb/in2 using a French press (Aminco, Urbana, IL), the soluble fractions of cell lysate containing the His-tagged fusion proteins were isolated by centrifugation. Proteins were purified first by HisTrap column (AKTA-prime; GE Healthcare Bio-Sciences Corp., Piscataway, NJ) followed by size exclusion chromatography on a HiLoad 16/60 Superdex 200 column (AKTA-FPLC; GE Healthcare). The proteins were then quantified and stored at −80°C until use.

Purification of Hoc soci− T4 phage. Hoc soci− T4 phages were purified as described previously (48, 49). Briefly, the propagated T4 phage on E. coli P301 was collected by centrifugation for 45 min at 25,000 × g. The pellet containing T4 phages was resuspended in 40 μl Mg buffer (26 mM NaNO3, 68 mM NaCl, 22 mM K2PO4, 1 mM MgSO4, pH 7.5) containing 10 μg/ml DNAse I and chloroform (0.4 M) and incubated at 37°C for 30 min. The lysate was subjected to low-speed centrifugation (6,000 × g for 10 min) and high-speed centrifugation (35,000 × g for 45 min), and the final phage pellet was resuspended in 200 μl of Tris-Mg buffer (10 mM Tris-HCl [pH 7.5], 50 mM NaCl, and 5 mM MgCl2) and purified by CsCl density gradient centrifugation.

In vitro binding of antigens to phage T4. In vitro binding of Soc fusion proteins to Hoc soci− T4 phage was conducted as previously described (17, 48). The same batch of purified phages was used for all the animal immunization experiments (below). The proteins and phages used were highly pure, after going through multiple rounds of purification steps as described above. As previously reported (17), the endotoxin levels in three different batches of purified proteins ranged from 0.05 to 0.8 endotoxin unit (EU) per mg protein, which is recommended endotoxin levels. 10 and 20 EU/ml in gene vectors and subunit vaccines, respectively (52). Moreover, the T4 nanoparticle vaccine used for immunizations had undergone additional purification during the in vitro binding reaction where the displayed particles were washed twice with excess phosphate-buffered saline (PBS) to remove the unbound antigen and any other minor contaminants. Briefly, F1mutV-Soc or Soc-PA proteins were incubated with purified Hoc soci− Soc− T4 phage at 4°C for 45 min. The phage particles containing the bound proteins were centrifuged at 34,000 × g for 45 min. After two washes with excess PBS buffer (pH 7.4) to remove unbound proteins, the final phage pellets containing the bound antigens were resuspended in PBS buffer (pH 7.4) and analyzed by SDS–PAGE using Novex 4–20% Tris-Glycine Mini Gels (Thermo Fisher Scientific, Waltham, MA).

The copy number of displayed antigen per capsid was calculated by quantifying the density of Coomassie blue-stained Soc fusion bands and the internal control band, T4 gp23, using the Bio-Rad ChemiDoc MP Imaging System. Each lane was individually quantified to minimize any staining differences. Since the copy number of the major capsid protein gp23 (molecular weight [MW] of 49 kDa) was established to be 930 per capsid and that of the tail sheath protein gp18 (MW of 72 kDa) was established to be 138 per phage and since we used 2 × 1010 particles in 200-μl reaction mixture, we could compute the copy number of bound antigen per capsid. However, keeping in mind differences in the staining densities of proteins and quantification of pixel densities, we estimated experimental variation to be within twofold. Further, the data shown are consistent with the copy numbers determined in previous studies using phage T4 Soc-PA (35) and samples prepared for many immunization experiments performed as part of this study. For Fig. 2, the copy number is shown on the y axis at each of the ratios used.

The concentration of the free antigen (x axis) was determined by subtracting the capsid-bound antigen from the total antigen added to the reaction mixture. Saturation binding curves (Fig. 2B and D) were then generated from these data. The Bmax and BC50 values were determined by nonlinear regression analysis using GraphPad Prism 7 software (San Diego, CA). BC50, a measure of binding affinity, is defined as the molar concentration of Soc fusion protein (ligand) at which half the available capsid binding sites are occupied by the ligand. Bmax is defined as the maximum number of binding sites occupied by the displayed Soc fusion protein per capsid particle as determined from the saturation binding curve.

Mouse immunizations and challenges. Six- to eight-week-old female BALB/c mice (17 to 20 g) purchased from The Jackson Laboratory (Bar Harbor, ME) were randomly assigned to groups and allowed to acclimate for 7 days. Antigens were displayed on T4 as described above. A total of 50 μg antigen (25 μg of each F1mutV and PA) was injected on days 0 and 21 via the i.m. route. Control mice received the same amount of T4 but without any antigen. Blood samples were collected from each animal by the retro-orbital route on day 0 (prebleed) and day 35 for immunological analyses. Mice were sequentially or simultaneously challenged with LeTx and Y. pestis CO92 as described previously (19). Briefly, in sequential challenge, mice were ip. challenged first with 1 LD50 of LeTx, followed by i.n. challenge with 400 LD50 (1 LD50 = 100 CFU in BALB/c mice) of Y. pestis CO92 33 days after LeTx challenge. In a separate
simultaneous challenge experiments, mice were immunized as described above and i.p. challenged with 1 LD_{50} of LeTx, followed by i.n. challenge with 200 LD_{50} Y. pestis CO92 on the same day. All animals were anesthetized by inhalation of 2% to 4% isoflurane (to effect) before challenge. Animals were monitored twice daily for mortality and other clinical symptoms.

*Rat immunizations and challenges*. Female Brown Norway rats (50 to 75 g) were purchased from Charles River Laboratories (New Jersey) and randomly grouped. After 7 days acclimation, rats were immunized by intramuscular (i.m.) route with T4-displayed antigens prepared as described above. Twenty-five micrograms of each antigen was used for immunizations as indicated in the figures. The animals were bled on day 35 by the saphenous vein, and sera were obtained for immunological analyses. Rats were sequentially challenged on day 42 with 400 LD_{50} Y. pestis CO92 (i.n.) followed by 1 LD_{50} LeTx (7.5 μg of each of the toxin components (LF and PA) challenge (i.v.). In a separate simultaneous challenge experiment, rats (six rats per group) were immunized as described above and challenged simultaneously with 1 LD_{50} of LeTx and 400 LD_{50} Y. pestis CO92 3 weeks after boost. All rats were anesthetized by inhalation of 2% to 4% isoflurane (to effect) before challenge. Rats were monitored twice a day for morbidity and mortality.

**Rabbit immunization and challenge.** The rabbit study was conducted by the Southern Research Institute (study number 13538.01:15; Birmingham, AL). A total of 16 New Zealand White rabbits were randomly divided into two groups. Group 1 was vaccinated with T4-displayed antigen (50 μg) (10 rabbits, equal numbers of males and females), while group 2 received the same amount of T4 but without any antigen (6 rabbits; equal numbers of males and females). Rabbits were immunized on days 0 and 14. Sera were collected on days 0 (preimmune), 12, 20, and 42 for immunological analyses. For the challenge experiments, the animals were loaded in the head-out plethysmograph, and a custom designed nose-only inhalation challenge mask was placed over the snout of each rabbit so that the mouth and naris were covered. At the start of the challenge period, the nebulizer and liquid impinger were actuated. Animals received the aerosol challenge until a cumulative inhaled volume of 20 liters had been reached. The exposure volume was 11.7 to 22.8 min. Animals were challenged with 200 LD_{50} of aerosolized 8. anthracis Ames spores on day 28 and monitored for morbidity and mortality until day 42. The remaining animals were then euthanized by an intravenous administration of a barbiturate overdose, and tissues (brain, liver, lung, and spleen) were collected for 8. anthracis detection on the same day. Blood samples (approximately 0.2 ml) were also collected on days 27, 29, 33, and 42 for microbiological analysis (bacteremia).

**Determination of IgG and IgG subtype antibodies.** Antibody titers were determined by ELISA as described previously (17, 42). Briefly, each well of a 96-well plate was coated with 100 ng of F1mutV or PA diluted in coating buffer (0.05 M sodium carbonate-sodium bicarbonate [pH 9.6]) overnight at 4°C. The plates were then blocked with 3% bovine serum albumin (BSA) in PBS (pH 7.4) for 1 h at 37°C. After 1 h of incubation at 37°C with serially diluted serum samples, plates were washed with PBS-T (PBS with 0.1% Tween 20 [pH 7.4]). For total IgG, horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG (KPL, Gaithersburg, MD), rabbit anti-rat IgG (Invitrogen), or goat anti-rabbit IgG (KPL, Gaithersburg, MD) was used as the secondary antibody. For mouse or rat IgG subtypes, HRP-conjugated goat anti-mouse or HRP-conjugated mouse anti-rat IgG1 or IgG2a secondary antibodies (Abcam, Cambridge, MA) were used. Samples were initially diluted 1:200; serial fivefold dilutions were performed as necessary to ensure that values reached the endpoint. For rabbit anti-PA IgG titers, plates were coated with PA, and affinity-purified rabbit anti-PA polyclonal antibody was used to generate a standard curve, from which the sample anti-PA IgG concentrations (in nanograms per milliliter) were determined. 3,3',5,5'-Tetramethyldibenzyne (TMB) microwell peroxidase substrate kit (KPL, Gaithersburg, MD) was used for staining.

**Anthrax LeTx neutralization assay.** Anthrax lethal-toxin-neutralizing assay was performed as described previously (53). Briefly, PA and LF were diluted to the final concentration of 200 ng/ml with Dulbecco’s modified Eagle’s medium (DMEM). Serially diluted serum samples were added to the toxin mixture, incubated for 1 h at 37°C, and then transferred to RAW264.7 macrophage cells grown to confluence in 96-well plates and incubated for 5 h. The viability of cells was assessed by incubation with MTT (3-(4,5-dimethylthiazol-2-y1)-2,5-diphenyltetrazolium bromide) (Sigma, St. Louis, MO) at a final concentration of 0.5 mg/ml for 30 min. The medium was aspirated, the insoluble pigment (formazan) produced by living cells was dissolved by adding a solution containing 0.5% SDS, 25 mM HCl and 90% isopropanol, and the optical density (570 nm) was measured to assess viability. The effective serum concentration inducing 50% neutralization (EC_{50}) was calculated with Graphpad Prism-7 software (San Diego, CA).

**Live-animal imaging.** *In vivo* imaging was performed as described previously (39). Briefly, 3 days after challenge with Y. pestis CO92-luciferase strain, the animals were imaged by using an IVIS 200 bioluminescence and fluorescence whole-body imaging workstation (Caliper Corp., Alameda, CA) in the ABSL-3 at the University of Texas Medical Branch (UTMB) facility after lightly anesthetizing the animals with isoflurane.

**Statistical analyses.** Results are expressed as means ± standard deviations (SD). Statistical comparisons between groups were evaluated by Student’s t test. The animal mortality data were analyzed by the Kaplan-Meier survival estimate. A P value of <0.05 was considered statistically significant.

**SUPPLEMENTAL MATERIAL**

Supplemental material for this article may be found at https://doi.org/10.1128/mBio.01926-18.

FIG S1, TIF file, 2 MB.
ACKNOWLEDGMENTS
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Earlier and Faster Production of Influenza Vaccine
For Pandemic Mitigation

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Introduction

As noted in the recent Centers for Disease Control and Prevention community planning guidance, the only intervention that can reasonably be expected to control an influenza pandemic is vaccination of a large fraction of the population with a strain-matched vaccine. Planners and modelers commonly assume that such a vaccine intervention would be similar to recent vaccination interventions for seasonal influenza, employing egg-based vaccine production technology. Thus analyses assume that pandemic influenza vaccine will not be available until four to six months after the onset of the pandemic, and that vaccine could not be produced faster than 4 million doses per week (corresponding to 100 million doses in 6 months). Under this view, several recent studies have analyzed how various non-vaccine interventions might be able to control an influenza pandemic until vaccine can be delivered. Other studies do not incorporate vaccination production and delivery because of the assumption that it would be too late.

Alternative approaches to egg-based vaccine production would grow virus in bioreactors using mammalian cell cultures, insect cell cultures (e.g. NovaVax, Inc. and Protein Sciences, Inc.), or bacteria (e.g. PhageVax, Inc.). These technology developments might reduce the lag time between identification of the influenza strain and initial vaccine production capability, and might also allow higher US production rates. This analysis considers the potential of these new technologies to mitigate a pandemic.

The effectiveness of a vaccine intervention to control an influenza pandemic will depend on 1) when the vaccine will first become available, 2) how many people can be treated per week once vaccination starts, 3) how effective the vaccine is, and 4) how many days following inoculation are required for immunity to build up. In addition, the impact of a vaccine intervention on the pandemic will depend on other interventions that are used in conjunction. This analysis compares the impact of vaccine distribution starting four months earlier than the seasonal influenza experience, comparing the impact of a range of vaccine production rates. It also compares the case of a two-dose course with a one-dose requirement. Most significantly, it examines the impact of early vaccine intervention used in conjunction with antiviral medication.

If a vaccine can be produced four months earlier relative to egg-based seasonal influenza vaccine production, at a production rate sufficient to vaccinate 95% of the
population within a one-month period, the impact on the pandemic would be enormous. In
the absence of any other intervention, such a vaccine would reduce the mortality rate by a
factor of five (from 614 deaths per 100,000 persons to 121 deaths per 100,000). Furthermore,
if the existing strategic national stockpile (SNS) of 20 million courses of antiviral
medication is used in conjunction with the vaccine intervention (for therapeutic treatment
of diagnosed cases and prophylactic treatment of household members of diagnosed cases),
the additional use of the early, rapidly produced vaccine would reduce the mortality from
550 per 100,000 to only 3 per 100,000, well below the mortality rate of seasonal influenza.

Scenario Assessment with the EpiSimS Simulation

The disease spread simulation engine EpiSimS\textsuperscript{5} was used to simulate the course
of influenza pandemics, with various assumptions about vaccine production rate. Details of
the modeling assumptions and methodology were described in a previous article\textsuperscript{6}. The
EpiSimS simulations were run with a synthetic population constructed to statistically
match the 2000 population demographics of southern California at the census tract level.
The synthetic population contains 19 million individuals living in 6 million households,
with an additional 938,000 locations representing actual schools, businesses, shops, or
restaurant addresses. The age distribution, family size distribution, household income
distribution and employment status of the synthetic population match the US census data
at census tract level, in six southern California counties. On day 0 of the simulation, the
population is seeded with 100 infected individuals, so that by day 3, 0.00035\% of the
population is symptomatic.

A basecase scenario was constructed for this analysis, to emulate the planning
scenario used by DHHS\textsuperscript{7,8}. This basecase scenario has vaccine as the only intervention,
consistent with seasonal influenza vaccine production using egg-based technology. The
vaccine begins to be distributed on day 150. The vaccine requires two doses, so 0.67\% of the
population can be treated per week beginning on day 150. The second dose is administered
4 weeks after the first, and 80\% effectiveness is attained 2 weeks after the second dose.

The prevalence (fraction of the population that is symptomatic) reaches 0.1\% on day
33±1. The peak in the number symptomatic cases is reached 30 days later (day 63, on
average) when 9.92\% of the population is symptomatic. The pandemic essentially runs its
complete course before the egg-based vaccine begins to be distributed, and the pandemic
trajectory the same as if there were no vaccine at all. For the whole pandemic in the
basecase scenario, the clinical attack rate (i.e. the fraction of the population that ever
became symptomatic) is 30.6\%, and the mortality rate (i.e., the fraction of the population
that dies) is 614 deaths per 100,000 population.

Assessment of Early Vaccine at Various Production Rates

For consistency with seasonal influenza experience, the early vaccine scenarios
assume that the vaccine requires a single dose, that it provides complete immunity in 80\%
of recipients, and that this immunity is developed 14 days after inoculation. We further
assume that of the 20\% of inoculated persons that don’t develop immunity, if they do
become infected, they would be only one fifth as infectious as their unvaccinated
counterparts. We also assume that every unvaccinated individual has an equal chance of receiving the next available dose—i.e. this analysis did not examine strategies where the early vaccine is given preferentially to at-risk demographic categories or to healthcare workers, or to students.

Whereas the basecase scenario begins delivery of vaccine on day 150, a set of early vaccine scenarios begin vaccination on day 33, which is the day on which 0.1% of the population is symptomatic. This represents a four month advance on when vaccine can start production, relative to egg-based technology. Four early vaccine scenarios then produce and deliver 4, 8, 12 or 75 million doses per week, nationwide. These production rates would enable inoculation of 0, 1.33%, 2.66%, 4%, or 25% of the US population per week, respectively. Note that 75 million doses per week might be produced by 300 local production facilities, each producing 1 million doses per month. Table 1 shows the peak symptomatic fraction of the population, the clinical attack rate, and the mortality, for each vaccine production/delivery rate that result from EpiSimS simulation of these early vaccination scenarios. The percentage of the population that is currently symptomatic is shown against time for each vaccination scenario in Fig. 1.

<table>
<thead>
<tr>
<th>Assumed US vaccine production rate, doses per week</th>
<th>Percentage of population vaccinated per week</th>
<th>Symptomatic percentage of population at pandemic peak</th>
<th>Clinical Attack Rate</th>
<th>Mortality, deaths per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>9.92%</td>
<td>30.6%</td>
<td>614</td>
</tr>
<tr>
<td>4 million</td>
<td>1.3%</td>
<td>9.51%</td>
<td>29.2%</td>
<td>573</td>
</tr>
<tr>
<td>8 million</td>
<td>2.7%</td>
<td>9.03%</td>
<td>27.6%</td>
<td>532</td>
</tr>
<tr>
<td>12 million</td>
<td>4.0%</td>
<td>8.45%</td>
<td>25.8%</td>
<td>486</td>
</tr>
<tr>
<td>75 million</td>
<td>25%</td>
<td>4.48%</td>
<td>11.4%</td>
<td>121</td>
</tr>
</tbody>
</table>

Table 1. Summary of simulation results for various early vaccine production rates.

At distribution rates typical of seasonal influenza vaccine, even this four month advancement in production time only produces a 7% reduction in mortality. However, if vaccination distribution can be initiated one month after 0.1% of the population is symptomatic, and can be delivered to 95% of the population within one month of initial distribution, then the mortality rate of pandemic influenza can be reduced more than five-fold.
Fig. 1. The current percentage of the population that is symptomatic during an influenza pandemic, using a vaccine intervention beginning on day 33 and continuing at several vaccine production rates.

Assessment of Early Vaccine Combined with SNS Antiviral Medication

At the end of 2006, the US Strategic National Stockpile (SNS) held 20 million courses of antiviral medications (Tamiflu and Relenza), enough to treat 6.7% of the population. Presumably, administration of these antivirals would begin as soon as an influenza pandemic is recognized. The assumed antiviral treatment strategy is that all diagnosed cases would receive a therapeutic course of treatment (five doses), and that 95% of household members of diagnosed persons would receive a prophylactic course (10 doses), beginning between 12 and 24 hours after the diagnosis of the household index case. As with vaccination, there will likely be a small fraction of the population that will refuse medication.

Three scenarios were constructed for EpiSimS simulation to assess the effectiveness of combined early vaccine and antiviral interventions. The first scenario uses antivirals as the only intervention. The second has a combined intervention using antivirals and early vaccine at a moderate production rate sufficient to vaccinate 4% of the population per week. The third has a combined intervention using antivirals and early vaccine at a high production rate, sufficient to vaccinate 25% of the population per week. In both combined scenarios, vaccination production and distribution begins on day 34.
In the antiviral-only scenario, the strategy of treating diagnosed cases and their household members slows the disease spread but does not control the pandemic. The pandemic growth rate is found to be reduced to about 9% per day while the antiviral stockpile lasts, compared to about 17% per day with no intervention. A prevalence of 0.1% of the population being symptomatic is attained on day 51. The SNS antiviral stockpile is exhausted on day 81. At the time the SNS antiviral stockpile is exhausted, 1.34% of the population is symptomatic. The pandemic then explodes, reaching a peak symptomatic fraction of 8.1% on day 105. Even with the SNS antivirals, the pandemic still essentially runs its complete course before the egg-based vaccine would have any impact. For the whole pandemic in the SNS antiviral intervention scenario, the clinical attack rate (i.e. the fraction of the population that ever became symptomatic) obtained by EpiSimS simulation is 28.5%, and the mortality rate (i.e., the fraction of the population that dies) is 541 deaths per 100,000 population.

In the combined intervention scenarios, vaccine distribution begins on day 34, and is delivered thereafter at a rate of 4% (moderate production rate) or 25% (high production rate) of the population per week. Due to the assumed two week period to develop immunity, the vaccination intervention does not begin to provide any protection until day 48. The results are tabulated in Table 2. At a moderate vaccine delivery rate of 4% of the population per week beginning on day 34, the antiviral stockpile lasts an additional 7 days, not running out until day 88 instead of day 81. The clinical attack rate is reduced to 13.2%, and the mortality rate drops to 191 deaths per 100,000.

For the scenario combining the SNS antiviral intervention with the early vaccine at high production rate, the pandemic is controlled to such an extent that the antivirals never run out. Where the SNS holds sufficient courses of antivirals to treat 6.7% of the population, the combined use of early high-production-rate vaccine reduces the need for antivirals to only 1.31% of the population. The clinical attack rate drops to 0.48%, and the mortality rate drops to 2.7 deaths per 100,000 persons, well below the mortality rate associated with seasonal influenza.

<table>
<thead>
<tr>
<th>Assumed US vaccine production rate, doses per week</th>
<th>Percentage of population vaccinated per week</th>
<th>Symptomatic percentage of population at pandemic peak</th>
<th>Clinical Attack Rate</th>
<th>Mortality, deaths per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>8.1%</td>
<td>28.5%</td>
<td>541</td>
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<td>12 million</td>
<td>4%</td>
<td>2.65%</td>
<td>13.2%</td>
<td>191</td>
</tr>
<tr>
<td>75 million</td>
<td>25%</td>
<td>0.16%</td>
<td>0.48%</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Table 2. Summary of simulation results for combined antiviral and early vaccine intervention scenarios.

The time trajectories of the current symptomatic percentage of the population are shown in Fig. 2, for the basecase scenario, the SNS antiviral intervention scenario, and the combined antiviral & early vaccine intervention scenarios.
Comparison of One versus Two Vaccine Dose Requirement

Two scenarios were constructed to compare the cases in which either one or two vaccine doses are needed to produce 80% effectiveness. In both scenarios, the vaccine is produced at 8 million doses per week, and the distribution begins on day 34. For the one-dose case, an 80% immune response is attained 14 days after inoculation. For the two-dose case, the 80% immune response is attained 42 days after the first inoculation (14 days after the second inoculation). Since the dose production rate is the same in both cases, the one-dose case will enable 2.6% of the population to be treated per week, while the two-dose case will only enable 1.3% of the population to be treated per week.

The EpiSimS simulation of the two-dose early vaccine scenario, where 1.3% of the population is treated per week beginning on day 34, finds essentially no reduction in the pandemic
relative to the basecase scenario. The clinical attack rate is 30.6%, which is the same found for the basecase. The mortality rate is reduced from 614 to 609 per 100,000 population.

For the one-dose scenario, where 2.6% of the population is treated per week beginning on day 34, the EpiSimS simulation find a slight impact relative to egg-based or no vaccine production. The clinical attack rate is reduced to 27.6%, and the mortality rate is reduced to 532 deaths per 100,000 population. This scenario is illustrated in Fig. 1 as the 8 million doses per week case.

**Conclusion**

Several vaccine production platforms (based on mammalian cells, caterpillar cells, or bacterial cultures) show potential to enable the US to produce influenza vaccine four months earlier, and at **15 to 20 times faster** than the egg-based platform used for seasonal influenza vaccine production. With a good vaccine (a single dose providing 80% efficacy within 14 days of inoculation) becoming available for distribution within one month of isolation of the pandemic strain, detailed disease spread simulation finds that at a production rate of 75 million doses of vaccine per week in the US, the mortality rate can be reduced from **614 per 100,000 to 121 per 100,000**.

A more telling assessment of the impact of early, high-production vaccine takes into consideration the probable use of the SNS antiviral stockpile. The use of the current antiviral stockpile alone would delay the pandemic, but when the antivirals run out, the pandemic will explode. A scenario which combines the SNS antiviral stockpile with early, high-production vaccine, is assessed to be very effective, **reducing the mortality rate to only 2.7 deaths per 100,000 population**, which is well below the mortality rate for seasonal influenza in the US of **12 deaths per 100,000 people per flu season**.

**Acknowledgements**

The authors would like to thank Clark Tibbs of PhageVax, Inc. for discussions on developments in vaccine production platforms, and Deborah Kubicek for constructing the population data files used to set up the EpiSimS southern California synthetic population.

**References**

China Reports Huge Jump In New Coronavirus Infections, Deaths; Stocks Tumble

Profile picture for user Tyler Durden
by Tyler Durden

Wed, 02/12/2020 - 19:00

Summary:

- China's Hubei province admits a massive spike in virus cases and deaths (14,840 additional cases and 242 additional deaths)
- The Sun reports first case confirmed in London, bringing UK total to 9
- China Grand Prix cancelled
- Couple onboard 'Diamond Princess' tell CNBC situation is "frankly terrifying"
- AFP publishes report exposing worsening shortages of food and supplies in Wuhan
- Cruise ship rejected by four countries allowed to dock in Cambodia
- Rumors of 10k in Wuhan not included in official count of cases
- NYT follows WSJ in exploring problems with Chinese testing kits
- Global Times says US should restart travel to China
- US officials complain about China still denying American help
• First ship-to-shore infection occurs in Japan from 'Diamond Princess'
• State Department lets non-essential personnel and their families leave Hong Kong because of outbreak

***

Update (1855ET): Hubei just released its latest round of coronavirus outbreak figures, and in a clear confirmation of the 'conspiracy theory' that China had altered the way it was reporting Covid-19 deaths and cases - clearly in order to suggest that things were improving and you should go back to work, while ideally buying stocks, the province at the epicenter of the Coronavirus pandemic just came clean and the numbers are stunning.

The number of cases exploded by 14,840, resulting in a total of 48,206 cases, including 13,332 clinically diagnosed cases:

[Graph of Number of New Cases in China]

What happened? Recall that on Monday we published "This Is How China Is Rigging The Number Of Coronavirus Infections" in which we explained that China on Feb 7 moved the goalposts by changing the definition of the term "infection" and that "going forward patients who tested positive for the virus but have no symptoms will no longer be regarded as confirmed."

Well, it appears that a few days later, China changed its mind and has reverted to the original definition of "infection" while also including
"clinical diagnosis" to determine if a new infection had take place. This is how Hubei explained the change:

With the deepening of understanding of new coronavirus pneumonia and the accumulation of experience in diagnosis and treatment, in view of the characteristics of the epidemic in Hubei Province, the General Office of the National Health and Health Commission and the Office of the State Administration of Traditional Chinese Medicine issued the "Diagnosis and Treatment Plan for New Coronavirus Infected Pneumonia (Trial (Version) "adds" clinical diagnosis "to the case diagnosis classification in Hubei Province, so that patients can receive standardized treatment according to confirmed cases as early as possible to further improve the success rate of treatment.

According to the plan, Hubei Province has recently conducted investigations on suspected cases and revised the diagnosis results, and newly diagnosed patients were diagnosed according to the new diagnosis classification. In order to be consistent with the classification of case diagnosis issued by other provinces across the country, starting today, Hubei Province will include the number of clinically diagnosed cases into the number of confirmed cases for publication.

Of course, the real reason for the original change as noted above was to give the impression that China was succeeding in containing the infection, which helped boost stocks - both in China and globally - sharply higher, and in the case of the S&P, to new all time highs.

And while China can now claim it wants a more comprehensive definition of "infection" because it is suddenly so concerned about all those people it ordered to go back to work on Monday (with new cases now emerging in people's workplaces forcing an immediate quarantine of all workers and co-workers), it somehow also changed the definition of "death", because at the same time as the explosion in new cases, which clearly indicates that the pandemic is now clearly out of control, the number of reported deaths in Hubei alone spiked by 242 to 1,310 (we are still waiting for the official number of deaths across all of China which will likely add quite a few more cases to the Hubei total).
In kneejerk reaction to the shocking surge in both new cases and deaths, Dow futures immediately plunged...

And yuan is tumbling...
Who could have seen that coming? The stock market wanted so badly to believe the Chinese data... bonds and commodities knew better.

***

Update (1515ET): What are they hiding? Well, isn't it obvious?

Yesterday, Dr. Tedros revealed at a WHO press conference that China had finally agreed to allow a team of international experts to study the outbreak on the mainland. This ended weeks of Beijing steadfastly refusing any international aid as more than a thousand people died in Hubei's overwhelmed hospitals.

Now, US health officials are complaining that Beijing is still blocking them from visiting China by refusing to allow Americans to join the WHO team traveling to China. US officials affirmed Wednesday afternoon in New York that they still hadn't been given a reason for the refusal, and we strongly doubt one will be offered. After all, the Politburo certainly isn't in the habit of explaining its decisions.

In the US, the CDC warned during a press conference too early to know if warm spring weather will slow or stop the coronavirus outbreak, as it usually is enough to bring the annual North American flu season to an end.

Contradicting President Trump, Nancy Messonnier, director of the CDC’s National Center for Immunization and Respiratory Diseases, said Wednesday that she hopes “it will go down as the weather warms up, but it’s premature to assume that.”
The CDC also revealed earlier that some of the test kits it had distributed to state health officials might be defective, amid broader scrutiny of the tests that have so often failed to detect the virus in infected patients.

On Monday, Trump once again said from the White House that "heat" would kill the virus. President Trump promised China any help it needs weeks ago, and the CDC has repeatedly offered to send doctors and nurses, but China has repeatedly refused.

In other news, Treasury Secretary Steven Mnuchin said during a Wednesday interview that the virus outbreak would likely slow implementation of the US-China trade deal, the latest warning about the viability of the pact. We still need three to four more weeks of data from the outbreak to really begin to understand what the impact will be, Mnuchin added.

After a senior regime economist assured the Chinese public that the hit to economic growth as a result of the virus would be minimal, President Xi and the Communist Party's senior leaders have ordered local officials to accelerate the reopening of China's economy, including ordering local factories and offices back to work.

Earlier, President Xi and the leadership announced a slate of monetary and fiscal policy measures to support the Chinese economy, including tax cuts and yet more monetary easing.

But as markets found some degree of comfort in today's news out of China (despite looming doubts about Beijing's ability to contain the
outbreak and whether the numbers released by the regime are legitimate), the 'Diamond Princess', a cruise ship quarantined at a port in Yokohama, has become the site of the first confirmed ship-to-shore transmission, as a Japanese government official who boarded the ship to survey the situation has been diagnosed with the virus, according to the New York Times. That brings the number of coronavirus cases stemming from the ship to 176.

In Hong Kong, the US State Department is allowing all nonemergency consulate employees and their families to leave because of the coronavirus outbreak.

Not long after China's top officials pledged to stabilize the Chinese economy and restore the world's confidence in the Middle Kingdom, WSJ reports that a survey of economists found 83% believe the outbreak will hurt Q1 growth in the US, where only 13 cases have been identified.

"The negative demand shock from coronavirus is significant," said Constance Hunter, chief economist at KPMG. China's GDP will be impacted significantly and this will show up in everything from commodity prices to demand for global goods and services," she said.

Not to worry, though. We're sure that the patriotic socialist values of the Chinese people (or perhaps some badly goalseeked economic data) will come through in a pinch to save the Chinese economy from a house of cards style liquidity crisis.

***

Update (1325ET): As Twitter digests reports of the first confirmed case in London, adding to Wednesday's torrent of coronavirus outbreak-related news, WHO Director General Dr. Tedros Adhanom Ghebreyesus, is speaking from Lausanne, delivering the WHO's latest update on the outbreak, briefings that have become a daily occurrence.

Sounding uncharacteristically pessimistic, Dr. Tedros warned that the outbreak could still go in any direction, suggesting that Beijing's heroic efforts aren't really the "model for emerging nations", as he once described it.

In other news, Global Times editor Hu Xijin, a longtime mouthpiece for the Communist regime on Twitter, also took the next step in Beijing's carefully crafted narrative (which CNBC's Eunice Yoon unravels in a
string of tweets included below): He demanded that Western airlines reopen travel to China.

This comes as a senior economist for the regime said Wednesday that China can still hit its growth targets for 2020, and that the outbreak would likely be only a temporary bump.

Hu Xijin 胡錦濤 @HuXijin_GT

New infection cases outside of Hubei have dropped for 8 consecutive days. In Beijing with more than 21 million population, the daily new case of infection is around 10 recently. It is now time for the US and other countries to actively consider resuming flights to China.

306
1:16 PM - Feb 12, 2020
Twitter Ads info and privacy
408 people are talking about this

As evidence, Hu cites a drop in new cases outside Hubei, ignoring all the other frightening stats that his own regime has voluntarily shared with the press.

***

Update (1310ET): After a relatively slow day for coronavirus news, the Murdoch-owned UK tabloid the Sun reported Wednesday afternoon that the first coronavirus case has been confirmed in London.
The infected individual is a Chinese national. The paper said officials will now be scrambling to trace his steps and find and test everybody whom he came in contact with.

The news comes as 12 Sussex schools have been placed on infection alert as some teachers and students have been asked to quarantine themselves.

The paper is citing a source as city hall.

BBC reports all 83 people who were being held in quarantine at Arrowe Park Hospital in Wirral have tested negative.

This case in London is the UK’s ninth.

The news hits just as the WHO's is beginning its latest press update at its headquarters in Switzerland.

Click on the "WATCH LIVE:" link in the Twitter box immediately below to watch the 53-minute archived PBS NewsHour broadcast from WHO headquarters:
WATCH LIVE: World Health Organization update on the novel coronavirus -- Feb. 12, 2020 https://twitter.com/i/broadcasts/1RDx1QjVAjKL ...

13
1:15 PM - Feb 12, 2020

Twitter Ads info and privacy

20 people are talking about this

***

Update (0955ET): Evaluation Only. Created with Aspose.HTML. Copyright 2013-2020 Aspose Pty Ltd.coronavirus outbreak from Beijing, just perfectly summed up the current state of things in China, as the regime projects a message of optimism to appease markets and investors...while many remain skeptical of China's numbers.

Eunice Yoon✓@onlyyoontv

#China reports lowest # new #COVID19 cases since late-Jan. Health off'ls say drop in new confirmed cases from 3,887 on Feb 4 to 2,015 Feb 11 “positive changes". Drop seems to support prediction by gov’t epidemiologist Zhong Nanshan outbreak to peak late-Feb, maybe over by April.

412
9:16 AM - Feb 12, 2020

Twitter Ads info and privacy
Upbeat remarks coincide with slight change in attitude of government priorities. #China now describes local requirements on factories as “inappropriate”, “inconsistent” for “orderly” reopening. Gov’t economist says China can hit goal to double GDP by 2020 with 5.7% annual growth.

State TV reports President Xi chaired cabinet meeting on #virus prevention. #China to implement prudent yet flexible monetary policy; roll out targeted tax, fee cuts; boost investment projects; lower loan rates to firms; push factories to resume work; vows to avoid mass layoffs.

Leaders reveal their concerns about econ damage. Online people happy about drop in cases, hope outbreak to peak soon. Others skeptical about
numbers, want more evidence virus squashed. (My read: so it could take
more time for people to shop, see movies, go back to normal life.)

9:46 AM - Feb 12, 2020
Twitter Ads info and privacy
31 people are talking about this

Late last night, Reuters reported on remarks from an influential
economist at a top regime-controlled think tank. Cai Fang, the vice head
of the Chinese Academy of Social Sciences, insisted in a column
published in the People's Daily, the Communist Party's main newspaper,
that the impact of the virus-inspired lockdown would be a "one off", and
that China's economy will quickly recover and meet the government's
growth goals for the year.

Everybody knows China's economic data are ruthlessly goalseeked, so
we suspect that these remarks will prove a self-fulfilling prophecy.
And don't forget - as Reuters reminds us - this year is critical for the Communist Party to fulfill its goal of doubling GDP in the ten years to 2020. They're just about on track, but a pullback now could ruin the whole enterprise and make them look weak. Which is why we suspect the data will be as doctored as it can reasonably be without it being immediately dismissed as unreliable.

***

Update (0824ET): At this point, some of the world's most prestigious media organizations, including WSJ and NYT, have reported that health
officials are probably undercounting the number of coronavirus cases in Wuhan.

After WSJ spotlighted the issue in a story published online last night recounting how officials turned away seriously ill patients who failed to pass swabtests, the NYT followed up this morning with a piece about Beijing's efforts to speed up testing.

Dr. Zhang Xiaochun, who works in a hospital in Wuhan, was in dismay. Her patient had been running a fever for nine days, and a CT scan showed signs of pneumonia — symptoms of the new coronavirus sweeping across the central Chinese city.

But a test to confirm the diagnosis would take at least two days. To Dr. Zhang, that meant a delay in isolating her patient — and getting potentially lifesaving treatment.

This past week, Dr. Zhang started a social media campaign with an urgent call to simplify screening for the new coronavirus. It was an unusually public effort that quickly found support among public health experts and the government as China grapples with one of the deadliest epidemics in its recent history.

"The purpose is to isolate and treat quickly," Dr. Zhang said in a telephone interview. "It amounts to extraordinary measures taken in extraordinary times."

To fix the issue, Chinese health officials are trying to increase the supply of nucleic acid coronavirus tests, which they believe to be more reliable than swap tests, which often don't go deep enough into a patient's chest to find evidence of the virus.

A major bottleneck has been a shortage of nucleic acid testing kits used to confirm the presence of the coronavirus. So Dr. Zhang proposed that doctors could first use CT scans to detect pneumonia and quickly isolate and treat patients who have it.

CT scans are convenient and can produce immediate results, Dr. Zhang said. Experts say people infected with the coronavirus would be likely to have lesions in both lungs.

Following a week of Chinese police rounding up anyone suspected to be infected and locking them away in an official quarantine, the rumors are that there are 10,000 cases in Wuhan who have been clinically diagnosed via CAT scans of their chest (as we explained earlier, swab
tests being used in viral tests are notoriously unreliable), but haven't been included in the official statistics, as twitter user @fxmacro reminds us.

FxMacro@fxmacro

Numbers have peaked but don't be surprised to see an uptick over the next week because there are 10k clinically diagnosed via cat scans but not counted as confirmed in hubei ... with another 10k still awaiting testing the rest of China is well on its way to recovery

Even the WHO has warned that we're only seeing "the tip of the iceberg."

It's definitely something worth thinking about.

The number of cases and deaths hasn't changed since Tuesday night in the US, with the number of confirmed cases around the world topping 45,000, with 44,653 of those in mainland China, according to the SCMP.
How many are infected?

Coronavirus

<table>
<thead>
<tr>
<th>Total</th>
<th>Cases</th>
<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mainland China</td>
<td>42,638</td>
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<td></td>
<td>Japan</td>
<td>163</td>
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<td></td>
<td>Hong Kong</td>
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<td>Singapore</td>
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<td>South Korea</td>
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<td>Taiwan</td>
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<td>Vietnam</td>
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<td></td>
<td>Germany</td>
<td>14</td>
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</tbody>
</table>

Source: China's NHIC, state media, other authorities

We leave you with this clip shared by reporter Jennifer Zeng of hazmat-suit-wearing workers loading bodies into a van...horrifying scenes that have become common in Wuhan.

Click on the image immediately below in the Twitter box to watch the 37-second Twitter video:

Jennifer Zeng@jenniferatntd

Child screaming while shooting:”Mom ! So many bodies in the van! So many!” Mom says:”Yes, I saw it.” One of the many scenes in #China during #CoronavirusOutbreak #coronavirus #COVID19 “妈妈，车里面好多尸体！”

#武汉肺炎 #新冠肺炎 #新型冠状病毒
Stock markets across the globe are back on the front foot Wednesday morning after officials in Hubei reported a lower number of confirmed cases, and a lower number of deaths, in their morning update, inspiring optimism that the "People's War" - as President Xi put it - against Covid-19 can be won.
Interestingly enough, while the market felt satisfied that Chinese health authorities are finally getting a handle on the virus now that Beijing and Shanghai have joined the ranks of cities suffering 'partial lockdowns', most of the major newsflow concerning the outbreak shifted to Britain, where a 'super spreader' who picked up the virus in Singapore has apparently wreaked havoc on the country's national health system, having infected at least two medical personnel.

Officials at Worthing Hospital in West Sussex confirmed late Tuesday that a member of their hospital staff was among the eight confirmed cases of Covid-19 in the UK announced earlier this week. The Worthing staff member is different from a locum doctor working in Brighton who is also among the eight confirmed cases.

Yesterday, it was reported that two prisoners at HMP Bulkingdon - including one who was recently extradited from Thailand - are being tested for the virus and being held in isolation. They are both reported to be suffering flu-like symptoms.

As of Tuesday evening, a total of 1,358 people have been tested for coronavirus in the UK, of which 1,350 were confirmed negative and eight positive, the Department of Health said. But as the WSJ reminded us last night, virus tests are often inaccurate and can even rule out patients who are obviously suffering from symptoms of viral pneumonia.

The health-care worker at Worthing went on to treat "a small number" of patients over two days before he was pulled into a quarantine.
As Worthing hospital posted signs calling for patients to immediately report any mysterious flu-like symptoms, the seventh Brighton and Hove schools issued warnings to parents about the coronavirus outbreak on the south coast, prompting some to keep their children home. Two families with children at Carden Primary School have been told to isolate in place.

The Guardian also reported some details about the British man and alleged druggie who was expatriated back from Thailand and may have carried the virus with him.

The 31-year-old man's name is Mark Rumble, was flown back to the UK on Jan. 27. He was arrested in Pattaya, Thailand, last November

In other news, CNBC conducted an interview with a couple stuck aboard the Diamond Princess, two of more than two dozen Americans stuck on board the ship. The couple said the experience of watching people get carted off the ship day to day has been "frankly terrifying", and they questioned why authorities have been evacuating healthy people in recent days.

"They say [Feb. 19] - if we're healthy on that date we can go. They say we're all safest here quarantining in place. If that's true, then why are they offloading buses of people who they don't want to get sick? We've had 100 new cases since the quarantine started. This is not making sense."

Will they ever go on another cruise? "It'll be a while."

Click on the image immediately below in the Twitter box to watch the 2-minute and 20-second Twitter video:

Squawk Box✔@SquawkCNBC

"Those numbers that we hear from the captain over the loudspeaker are terrifying," says Gay Courter, a quarantined passenger on the Diamond Princess cruise ship. "This whole thing has failed and they are using triage to prevent deaths of the most elderly." #coronavirus
The couple added that they had found a hospital in Fla. that would take them under quarantine conditions, and aren't sure why they need to stay here on a cruise ship moored in Japan if they haven't tested positive for the virus.

Since being quarantined eight days ago, 136 passengers and crew aboard the 'Diamond Princess' have been found to have contracted the virus, making it the center of the largest outbreak outside mainland China.

In Wuhan, intensifying supply shortages of food, medicine, fuel and other critical supplies are beginning to weigh on the local population, who have been trapped in place for more than two weeks, according to an Epoch Times reporter.

曾鋐 Jennifer Zeng@jenniferatntd

Supermarket in #wuhan running out of supplies, people lining up to buy, some starting to steal, one of the many scenes in #China during
# CoronavirusOutbreak # COVID19

https://twitter.com/hk_epochtimes/status/1227488352347283457 ...

香港大紀元@HK_EpochTimes

彈盡糧絕！#武漢 買菜排長龍 有人開始偷菜#武漢肺炎

(新冠肺炎) 疫情持續擴散，中國各地封城、封路，運輸中斷，疫情嚴重的湖北等地生活物資匱乏，武漢居民買菜排成長龍，有人甚至開始偷農民地裏的菜。

全文：https://buff.ly/31SBWoJ #coronavirus #wuhan
A brave team of AFP reporters who have been documenting the effort to combat the virus on the frontlines of the outbreak published a sweeping report on Tuesday exposing how truly isolated Wuhan had become.

Racing fans received some disappointing news last night when it was reported that the Chinese Grand Prix is expected to be postponed because of the outbreak. The Formula-1 race was scheduled to be held in Shanghai on April 19.

In other news, Indonesia has rejected experts suspicions that health officials might be hiding instances of viral infection. In Russia, two Chinese who were found to be infected and quarantined in Siberia last month have recovered, and been released. Both had 'mild' forms of the virus. Russia has closed its border with China and North Korea because of the outbreak and suspended

Last night, we reported that the death toll from the virus had climbed above 1,000 as Hubei reported another 94 deaths.

Finally, we leave readers with a sliver of good news: A cruise ship with no coronavirus patients that had been denied by four countries, and was in danger of running out of food and fuel in the next day or two, has been allowed to dock in Cambodia.
UK Government Document Warns Coronavirus Could Infect 80 Per Cent, Kill Half A Million Brits

Worst case scenario leaked.

Paul Joseph Watson | Infowars.com - February 26, 2020
A leaked UK government document warns that under a worst case scenario, 80 per cent of Brits could be infected with the coronavirus and half a million would die.

The document, which was leaked to the Sun newspaper, outlines “the reasonable worst case” outcome in which four fifths of the country to succumb to the virus.

“The current planning assumption is that 2-3 per cent of symptomatic cases will result in a fatality,” states the document, meaning that 500,000 would die.

A spokesman for the Department of Health and Social Care emphasized that such numbers were a worst case scenario and “this does not mean we expect it to happen.”

Earlier today, more than 300 staff members of American oil company Chevron were evacuated from a building in London’s Canary Wharf after an employee returning from an infected country reported flu symptoms.
There are currently only 13 confirmed cases of coronavirus in England, although the World Health Organization just warned countries outside of China that they were “simply not ready” for the spread of the virus.

“It can get ready very fast, but the big shift has to be in the mindset,” said Dr Bruce Aylward, the WHO’s China envoy.

For the first time, more new cases have been reported in countries outside of China than inside, with 411 inside China and 427 outside.

The WHO’s Tedros Adhanom Ghebreyesus said the sudden rise in coronavirus cases in Italy, Iran and South Korea was “deeply concerning.”

As we highlighted yesterday, despite the rapid spread of the virus in Italy, EU officials have refused to consider closing the borders.
Marks, Peter (FDA/CBER) <peter.marks@fda.hhs.gov>;
Adams, Jerome (HHS/OASH) <jerome.adams@hhs.gov>;
Lester Don Holt Jr <lester.holt@nbculni.com>;
Mikhail Sergeyevich Gorbachev <info@gcint.org>;
Alexander, Peter (NBCUniversal) <peter.alexander@nbculni.com>;
Mitchell, Andrea (NBC NEWS) <Andrea.Mitchell@nbculni.com>;
Fauci, Anthony (NIH/NAID) <afauci@niaid.nih.gov>;
Andrew Mark Cuomo <Melissa.DeRosa@governor.ny.gov>;
David Malpass <DMalpass@iic.org>;
Earhardt, Ainsley <Ainsley.Earhardt@foxnews.com>;
Kilmeade, Brian <Brian.Kilmeade@foxnews.com>;
Dana Perino <dana.perino@foxnews.com>;
Mike Emanuel <mike.emanuel@foxnews.com>;
Greg Palkot <greg.palkot@foxnews.com>;
Steve Doocy <Steve.Doocy@foxnews.com>;
Randal Howard Paul <press.paul.senate.gov>;
Stephen K Bannon <pschweizer@breitbart.com>;
John Gieve Roberts Jr <rebecca.lowson@supremecourt.uk>;
Okamoto Geoffrey <geoffrey.okamoto@imf.org>;
Kristalina Georgieva <Kristalina.Georgieva@imf.org>;
David Malpass <DMalpass@iic.org>;
Hahn, Stephen (FDA) <stephen.hahn@fda.hhs.gov>;
Jay Robert Inslee <jrobert.inslee@gov.wa.gov>;
Alison Morris <alison.morris@nbculni.com>;
Dana Ruth Schwartz <dana.rusher@turner.com>;
Hillary Diane Rodham Clinton <philippe.reines@bgsdc.com>;
Lester Don Holt Jr <lester.holt@nbculni.com>;
Mitchell, Andrea (NBC NEWS) <Andrea.Mitchell@nbculni.com>;
Victoria I Nuñand aka Kagan <vnuland@brookings.edu>;
Fiona Hill <fiona.hill@brookings.edu>;
Eric Frederick Trump <etump@trumporg.com>;
Donald John Trump Summer White House <blembcke@maralagoclub.com>;
Briana Williams <briana.williams@nbculni.com>;
Rupert Murdoch <rupert.murdoch@fox.com>;
Chase Carey <chase.carey@fox.com>;
Jared Harris <jared.harris@politic.com>.
Subject: Fwd: Lester:-Ad majorem Dei Pfizer? The Jesuit Order's Pfizer Vaccine - "We intend to openly rule the world, and without concealment, decide the fate of empires" (UK Orders Large Quantity of Pfizer mRNA Vaccine)

Date: 2020/07/28 19:48:11
Priority: Normal
Type: Note

-------- Forwarded Message --------
Lester, was watching your nightly here:- NBC Nightly News Broadcast (Full) - July 23rd, 2020 | NBC Nightly News very interesting as per usual, but, you're wrong about taking for granted that us peasants out here are bound to know someone that has had the corona virus, it seems to only be the rich and famous that get it, but then recover real fast...
https://www.youtube.com/watch?v=1DAXRyFgURQ

Here's some links for you to consider for your next show perhaps to enlighten the dumb masses.

Thanks Lester, Warm Regards, Rufus York, Geneva, Switzerland (close to WHO HQ)
DON'T TRUST RED CROSS IN THE PANDEMIC
https://www.youtube.com/watch?v=A6FT_whaq

Red Cross Misstates How Donors' Dollars Are Spent
While the Red Cross is known for disaster services, its main business is actually collecting and selling blood. Last year, the charity took in $2 billion from the blood operation.
https://www.npr.org/2014/12/04/368453320/red-cross-misstates-how-donors-dollars-are-spent?t=1595865658725
Red Cross CEO Tried to Kill Government Investigation
Despite public vows of transparency, CEO Gail McGovern lobbied a congressman to spike an inquiry by the Government Accountability Office.
Gail J. McGovern - https://protect2.fireeye.com/url?k=0e11bdab-52459480-0e118c94-0cc47a6d17cc-d9e9f8367ebeb072&u=https://www.nnbd.com/people/458/000168951/
Member of the Board Hartford Financial https://protect2.fireeye.com/url?k=cfa68ec0-93f2a7eb-cfa6bfff-0cc47a6d17cc-9ea2a12d3752ec23&u=https://www.nnbd.com/people/458/000168951/
“Gail McGovern is Red Cross president and CEO and is paid $600,000 a year — this is considered to be in the mid-range for a large nonprofit in the range of $3.4 billion a year. 2018 McGovern is currently a member of the board of trustees of Johns Hopkins University https://pages.jh.edu/news_info/news/univ03/jul03/trustees.html -
Ugur Sahin, founder of BioNTech, [https://protect2.fireeye.com/url?k=87109b11-db44b23a-8710aa2e-0cc47a6d17cc-71a05a69a1068d9d&u=https://biontech.de/our-dna/leadership](https://protect2.fireeye.com/url?k=87109b11-db44b23a-8710aa2e-0cc47a6d17cc-71a05a69a1068d9d&u=https://biontech.de/our-dna/leadership)

Prof Sahin, said, that an mRNA vaccine could be ready by the autumn.

[https://www.ft.com/content/36ddd384-6abf-11ea-a3c9-1fc6fedcca75](https://www.ft.com/content/36ddd384-6abf-11ea-a3c9-1fc6fedcca75)

**UK Orders Large Quantity of Pfizer mRNA Vaccine JUL 20, 2020 | GRANT M. GALLAGHER**


> It's a very unique way of making a vaccine and, so far, no (such) vaccine has been licenced for infectious disease.'

Prof. Isabelle Bekeredjian-Ding, Paul Ehrlich Institut, Germany

The race for a vaccine against the novel coronavirus, or SARS-CoV-2, is on, with 54 different vaccines under development, two of which are already being tested in humans, according to the World Health Organization.

And among the different candidates is a new player on the scene – mRNA vaccines.
One mRNA vaccine developed by US company Moderna began its first human trials on 16 March, whereas another under development by German company CureVac has been offered €80 million in investment by the European Commission.

Ugur Sahin, MD, CEO of BioNTech, said in a press release.

https://en.wikipedia.org/wiki/CureVacand as well as
BIONTECH https://protect2.fireeye.com/url?p=3c168ed2-6042a7f9-3c16bfed-0cc47a6d17cc-
450ef693850d26c2&u=https://biontech.de/our-dna/leadership -

**Pfizer and BioNTech Dose First Participants in the U.S. as Part of Global COVID-19 mRNA Vaccine Development Program**

detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mr
na_vaccine_development_program

**THE DESTRUCTION BY THE PANDEMIC AND WHAT IT'S DOING TO THE POOR AMERICAN MASSES & World Wide, (it is the end of time, AS YOU KNOW IT! )**

https://www.youtube.com/watch?v=zBDd9GFR65k

**Ad majorem Dei Pfizer**
https://www.youtube.com/watch?v=YFhqXbcUpig

**Meet our Team:**

---

**Bill Carapezzi**
Executive Vice President, Global Business Services and Transformation - Bill holds a Bachelor of Science degree in Accounting from Jesuit Fairfield University,
https://en.wikipedia.org/wiki/Fairfield_University
https://www.pfizer.com/people/leadership/executives/bill_carapezzi
Frank D’Amelio

is the Chief Financial Officer and Executive Vice President, Global Supply, Born and raised in New Jersey, Frank earned his MBA in Finance from Catholic St. John’s University [https://en.wikipedia.org/wiki/St._John%27s_University_(New_York_City)] and his bachelor’s degree in Accounting from Jesuit St. Peter’s University.
[https://en.wikipedia.org/wiki/Saint_Peter%27s_University]

https://www.pfizer.com/people/leadership/executives/frank_damelio

Rady Johnson, Rady Johnson is Executive Vice President and Pfizer’s Chief Compliance, Quality and Risk Officer. He is a graduate of the the Jesuit Georgetown University Law Center.
[https://en.wikipedia.org/wiki/Georgetown_University_Law_Center]
[https://www.pfizer.com/people/leadership/executives/rady_johnson]

Imagine if you can... a disease so deadly, you don't even know you have it, until you're tested. They Want to Kill Six Billion of Us - Here's How They'll Do It
[https://www.youtube.com/watch?v=K66EDRFvEuu]

the perfidious Jesuit, Auto de Fe &the Grand Inquisitor for the devil

"We intend to openly rule the world, and without concealment, decide the fate of empires"
[https://core.ac.uk/reader/213080618]

https://protec2.fireeye.com/url?k=56f9dd76-0aadf45d-56f9ec49-0cc47a6d17ec-b568915adb6e9e6e&u=https://www.nndb.com/people/220/000044088/
Augustus Welby Pugin
AKA Augustus Welby Northmore Pugin
Born: 1-Mar-1812
Birthplace: Bloomsbury, London, England
Died: 14-Sep-1852
Location of death: Ramsgate, Kent, England
Cause of death: Exhaustion
Occupation: Architect
Nationality: England

Executive summary: Built the Houses of Parliament

The most prominent British architect of the 19th Century,
Converted to Catholicism
https://protect2.fireeye.com/url?k=d8c50b17-8491223c-d8c53a28-0cc47a6d17cc-0adfc66c49354df6&u=https://www.nndb.com/event/930/000084678/
The Founder of the Society of Jesus (Jesuit) Ignatius de Loyola himself procured its [the inquisition] erection in Portugal in 1545-6 (The Encyclopaedia Britannica: A Dictionary of Arts, Sciences, Volume 13)

Pope Francis the Jesuit Pope & promoter of the World Lockdown in 2020 with UN Chief António Manuel de Oliveira Guterres.

Remarks by His Holiness The Jesuit Pope Francis and fellow Roman Catholic, United Nations Secretary-General António Guterres - https://www.youtube.com/watch?v=CePSM3QmKEQ
Jesuit Coadjutor, Andrew Mark Cuomo flattening the curve, https://www.youtube.com/watch?v=m8nCjNk3djc

Andrew Mark Cuomo born December 6, 1957)
Roman Catholic
https://protect2.fireeye.com/url?k=6e6b7fba-323f5691-6e6b4e85-0ce47a6d17cc-badb8c2a25a2a6e5&u=https://www.mndb.com/lists/758/000094476/
Executive Summary:- Corona Virus Hoaxer
During his governorship, Cuomo oversaw the passage of a law legalizing same-sex marriage in New York; creation of the United States Climate Alliance, a group of states committed to fighting climate change by following the terms of the Paris Climate Accords; passage of the strictest gun control law in the U.S.;
His parents were both of Italian descent; his paternal grandparents were from Nocera Inferiore and Tramonti in southern Italy, while his maternal grandparents were from SicilyHis younger brother, Chris Cuomo, is a CNN journalist.
Chris Cuomo

Jesuit Coadjutor, Chris Cuomo

AKA Christopher Charles Cuomo

Born: 9-Aug-1970
Birthplace: Queens, NY

Gender: Male
Religion: Roman Catholic
Race or Ethnicity: White
Sexual orientation: Straight
Occupation: Journalist

Nationality: United States
Executive summary: Co-Host, CNN New Day (Corona Virus Hoaxer)

Father: Mario Cuomo (Governor of New York, b. 15-Jun-1932, d. 1-Jan-2015)
Mother: Matilda Raffa
Sister: Margaret I. Cuomo
Brother: Andrew Cuomo (Governor of New York, b. 6-Dec-1957)
Sister: Maria Cuomo (m. Kenneth Cole)
Sister: Madeline Cuomo
Wife: Cristina Greeven (m. 24-Nov-2001, two daughters, one son)
Daughter: Bella
Daughter: Carolina Regina (b. 2011)
Son: Mario (b. 2005)
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**Delivered Date:** 2020/07/28 19:48:11
Marc Lipsitch (@mlipsitch)

14/02/2020, 17:53

Evaluation Only. Created with Aspose.HTML. Copyright 2013–2020 Aspose Pty Ltd. ("dispersion in R0") which could mean that many locations outside Wuhan could "get lucky" and escape major onward transmission. hopkinsidd.github.io/nCoV-Sandbox/D...
Subject: 2-7-20 ... nCoV 82% are Mild, 15% Severe, and 3% Critical ..... Why isn't this Lysin vs. STREP & STAPH FDA approved? CI O2 for SALE

Date: 2020/02/07 21:59:16
Priority: Normal
Type: Note

See this attachment:
A 'strep' infection complicated the nCoV victim in the Philippines, thus his death. Why isn't this Lysin FDA approved?

- Also see: Chlorine Dioxide (CI O2) ... for SALE ! ... from 2014 Call 740-502-9010 to Order. For Export, as well.

2019-nCoV near-real-time Monitor-Chart ... from Johns Hopkins ... 34,824 Cases, a few minutes ago.
https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda759474f0d4e4e4f89ee86a3a3e84

Below is from:

WHO warns of PPE shortage; nCoV pace slows slightly in China ... Feb 07, 2020
The World Health Organization (WHO) today warned of severe disruptions in the personal protective equipment (PPE) supply, with increased demand—including some inappropriate use—leading to inflated prices and shortages for healthcare workers who need the equipment most.

In other developments, the number of novel coronavirus (2019-nCoV) illnesses from China fell slightly for a second day in a row, with 3,143 new cases reported.

**PPE supplies squeezed by soaring demand, price mark-ups**

At a media telebriefing today, Tedros Adhanom Ghebreyesus, PhD, the WHO's director general, said the group has been working with PPE stakeholders to assess the supply and ensure that equipment flows to where it's needed most.

From the WHO's assessment, demand for PPE is up to **100 times higher** than normal and prices are up to **20 times higher**, exacerbated by widespread inappropriate use outside of patient care. There are now depleted stockpiles and a 4- to 6-month backlog. "Global stocks are now insufficient to meet the needs of WHO and its partners," he said, adding that responders need 7% to 10% of market capacity to protect China's frontline healthcare workers.

The WHO said it discourages stockpiling in areas where transmission is low, and Tedros called on all countries and companies to work with WHO to ensure fair and rational use of supplies and balance the market. "We all have a part to play in keeping each other safe," he said.

WHO officials said the problem doesn't relate to surgical masks worn by the public, but rather PPE materials used in medical care, such as N95 masks.

**Mike Ryan, MD**, who heads the WHO's health emergencies program, said there are many stakeholders across the PPE network, including raw-materials providers, manufacturers, wholesalers, distributors, and retailers. "This is not an easy problem to solve," he said, adding that the public and private sector need to cooperate closely so that health workers who need it aren't without PPE.

Ryan said disruption isn't a sign that the private sector failed, "but there are normal market forces that need to be managed." Health officials are hoping to define a minimal amount of supply that needs to be protected so the **right materials** get to the **right people** at the **right time**, he added.

**China’s case count**

Earlier today, China reported 3,143 new cases, the second decline in as many days, bringing the outbreak total to **31,161 cases**, according to the latest update from the country's National Health Commission (NHC).

There were 73 more deaths, 69 of them from Hubei province, raising the fatality count to 636.
Officials reported 962 serious cases, putting that total at 4,821. So far, 1,540 patients have recovered and been discharged from the hospital.

At today's briefing, Tedros said it's too soon to say if China's outbreak has peaked, noting that epidemiological curves can zigzag.

Also at the briefing, Maria Van Kerkhove, PhD, the WHO’s technical lead for MERS-CoV, said that from data the WHO has seen on 17,000 of China's cases, 82% are mild, 15% severe, and 3% critical.

She noted that so far, only one amplifying event in a healthcare setting—a hallmark of Middle East respiratory coronavirus (MERS-CoV)—has been reported in China's outbreak.

In other developments in China:

- Health officials have ramped up control measures in Wuhan, steering some sick people into quarantine areas such as stadiums and hotels and ordering door-to-door fever checks of all households, the New York Times reported today.

- The country's state news agency Xinhua today had a few more details about the identification of pangolins as a possible intermediate carrier of the virus, first noted yesterday in a brief announcement from South China Agriculture University. The news report said the genome of the animal virus is 99% similar to the virus isolated from people. So far other scientists have not evaluated the findings. In some parts of the world, pangolin meat is a delicacy and the scales are used in traditional medicine.

**Hospital study details nosocomial infections, rapid spread**

Chlorine Dioxide (ClO2) ... for SALE ! Call 740-502-9010 to Order. (See Attachment.) Clinicians from Wuhan today reported their observations from the largest case series so far on patients hospitalized with 2019-nCoV pneumonia. Their report covers 138 patients who were hospitalized from Jan 1 to Jan 28 at Zhongnan Hospital in Wuhan and appears today in the Journal of the American Medical Association (JAMA).

Hospital-associated transmission was suspected for 41% of patients, which the authors said reflects rapid human-to-human spread.

The healthcare-related cases included 40 healthcare workers and 17 patients.

Of the infected health workers, 31 worked on general wards, 7 in the emergency department, and 2 in the intensive care unit (ICU). Ten of the health workers and 4 patients are thought to have been infected by 1 patient who had abdominal symptoms and was admitted to the surgical department

Among the 138 patients, fever, fatigue, and dry cough were the most common symptoms. The median age was 56 years and just over half (54%) were men.
Chest computed tomography showed bilateral patchy shadows or ground-glass opacity in all patients. The lab findings were similar to those for patients infected with SARS (severe acute respiratory syndrome) and MERS-CoV.

The team found that 26% of patients required ICU admission and 4.3% died. Those admitted to the ICU were older and had more underlying health conditions. However, the proportions of men and women were equal, which differed from an earlier study that showed a tilt toward males. The authors said the higher proportion of men in the earlier studies likely reflected the number of patients who worked at the seafood market, most of whom were male.

US announces support for response

The US State Department today announced that the government is prepared to spend up to $100 million in existing funds to help China and other countries, directly and through multilateral organizations, according to a department statement.

Earlier this week, the WHO unveiled a response strategy for battling the outbreak over the next 3 months, which came with a request for $675 million to fund the plan.

The State Department added that it has helped transport nearly 17.8 tons of donated medical supplies to China, including PPE, respirators, and other materials.

"The United States is and will remain the world's most generous donor. We encourage the rest of the world to match our commitment. Working together, we can have a profound impact to contain this growing threat," the department said.

See also:

Feb 7 WHO daily situation report    Feb 7 NHC statement
Feb 7 Xinhua report    Feb 7 JAMA study    Feb 7 US State Department press release
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Novel Bacteriophage Lysin with Broad Lytic Activity Protects against Mixed Infection by *Streptococcus pyogenes* and Methicillin-Resistant *Staphylococcus aureus*

Daniel B. Gilmer, Jonathan E. Schmitz, Chad W. Euler, Vincent A. Fischetti
Laboratory of Bacterial Pathogenesis and Immunology, The Rockefeller University, New York, New York, USA

Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pyogenes* (group A streptococci [GrAS]) cause serious and sometimes fatal human diseases. They are among the many Gram-positive pathogens for which resistance to leading antibiotics has emerged. As a result, alternative therapies need to be developed to combat these pathogens. We have identified a novel bacteriophage lysin (PlySs2), derived from a *Streptococcus suis* phage, with broad lytic activity against MRSA, vancomycin-intermediate *S. aureus* (VISA), *Streptococcus suis*, *Listeria*, *Staphylococcus simulans*, *Staphylococcus epidermidis*, *Streptococcus equi*, *Streptococcus agalactiae* (group B streptococci [GBS]), *S. pyogenes*, *Streptococcus sanguinis*, group G streptococci (GGs), group E streptococci (GES), and *Streptococcus pneumoniae*. PlySs2 has an N-terminal cysteine-histidine aminopeptidase (CHAP) catalytic domain and a C-terminal SH3b binding domain. It is stable at 50°C for 30 min, 37°C for >24 h, 4°C for 15 days, and −80°C for >7 months; it maintained full activity after 10 freeze-thaw cycles. PlySs2 at 128 μg/ml *in vitro* reduced MRSA and *S. pyogenes* growth by 5 logs and 3 logs within 1 h, respectively, and exhibited a MIC of 16 μg/ml for MRSA. A single, 2-mg dose of PlySs2 protected 92% (22/24) of the mice in a bacteremia model of mixed MRSA and *S. pyogenes* infection. Serially increasing exposure of MRSA and *S. pyogenes* to PlySs2 or mupirocin resulted in no observed resistance to PlySs2 and resistance to mupirocin. To date, no other lysin has shown such notable broad lytic activity, stability, and efficacy against multiple, leading, human bacterial pathogens; as such, PlySs2 has all the characteristics to be an effective therapeutic.

Gram-positive pathogens such as *Streptococcus pyogenes* (group A streptococci [GrAS]), *Staphylococcus aureus*, *Streptococcus agalactiae* (group B streptococci [GBS]), and *Listeria monocytogenes* are responsible for millions of serious and sometimes fatal infections worldwide. Additionally, resistance to conventional antibiotics has been on the rise, resulting in increased infection rates, morbidity, mortality, and treatment costs. Consequently, new therapeutic methods need to be developed to reduce the antibiotic pressure on these pathogens.

*S. pyogenes* annually infects over 750 million people (1), resulting in 25% mortality among the ∼650,000 cases that progress to severe infection (1). This pathogen is responsible for a broad range of infections, such as pharyngitis, impetigo, scarlet fever, erysipelas, cellulitis, toxic shock syndrome, and necrotizing fasciitis; it can lead to serious sequelae, such as rheumatic fever and acute glomerulonephritis (2–4). *S. aureus* is capable of producing severe, secondary infections in immunocompromised individuals, as well as causing disease in otherwise-healthy people. Besides skin and soft tissue infections (SSTIs), *S. aureus* can cause sepsis, pneumonia, necrotizing fasciitis, pyomyositis, endocarditis, toxic shock syndrome, and scalded skin syndrome (5, 6). Unfortunately, many *S. aureus* strains, such as methicillin-resistant *S. aureus* (MRSA) and (less often) vancomycin-resistant *S. aureus* (VRSA), have acquired resistance to one or more antibiotics used as standard therapy. MRSA strains account for more than 50% of hospital isolates causing pneumonia and septicemia (7), particularly in intensive care units, resulting in 30 to 40% mortality (8, 9). While health care-associated MRSA strains usually infect susceptible patients, community-associated MRSA (CA-MRSA) strains can infect healthy individuals (10–13). CA-MRSA strains are often more virulent and are capable of causing more severe diseases (14, 15).

A novel antimicrobial strategy to control resistant bacterial pathogens involves the use of lytic enzymes (also known as endolysins, or lysins) whose genes are carried by bacteriophages (or phages) (reviewed in references 16 and 17). At the end of phage replication and assembly inside a host bacterium, the progeny phage must escape. To accomplish this, phage produce lysins—peptidoglycan hydrolases that degrade the bacterial cell wall—that result in hypotonic lysis of the bacterium and release of phage progeny. When applied exogenously, these enzymes are likewise able to access the peptidoglycan layer in the Gram-positive cell envelope (due to its lack of an outer membrane) and produce the same lytic effect. While no lysin has yet been FDA approved, these enzymes could be used to treat antibiotic-resistant bacteria. Unlike antibiotics, an important feature of phage lysins is their rapid, lethal effect on bacteria (18–20). Lysins are notable for the potencies and specificities they demonstrate, generally toward the species that the phage carrying the lysin gene infects or closely related.
organisms (17–19, 21, 22). As such, they presumably exert a less dramatic effect on the normal flora than conventional antibiotics.

Several lysins have been developed against MRSA (21, 23, 24) and S. pyogenes (25); to date, however, no lysin has shown high lytic activity against multiple species of different bacterial pathogens. While developing a lysin with activity against the zoonotic pathogen *Streptococcus suis*, we discovered an enzyme (PlySs2) with activity against a wide range of Gram-positive pathogens and in *vivo* efficacy against MRSA and *S. pyogenes*. In this report, we describe the initial characterization of the first broadly acting lysin that could be used against multiple Gram-positive pathogens.

**MATERIALS AND METHODS**

**Bacterial strains.** All strains were stored at −80°C (see Table S1 in the supplemental material). *Staphylococcus*, *Streptococcus*, *Listeria*, *Enterococcus*, *Pseudomonas*, and *Bacillus* strains were cultivated in brain heart infusion (BHI) broth, unless the medium was replaced with Mueller–Hinton (MH) medium for MIC determinations, as described below. *Listeria* strains were cultivated in de Man, Rogosa, and Sharpe (MRS) broth (Sigma). *Escherichia coli* was grown in Luria–Bertani (LB) broth. All media were acquired from Becton, Dickinson, and Company (Sparks, MD), unless otherwise stated. Bacteria were propagated at 37°C and shaken at 200 rpm, if necessary.

**Genomic sequence analysis and cloning of PlySs2.** The sequenced genomes of 8 *S. suis* isolates in GenBank were manually inspected for the presence of integrated prophage regions. If a prophage was suspected, the theoretical translations of each open reading frame (ORF) in that region were subjected to BLASTP and Pfam analyses to locate potential lysin–encoding genes.

A candidate lysin gene (PlySs2 from *S. suis* strain 89/1591) was PCR cloned from genomic DNA with the following primers: AATTGCGAC TCAATACAGGTAGAAGACC (forward) and CTTAAGCTTCCCTTTAC AAAATCTAATCCAGC (reverse). The underlined nucleotides represent engineered restriction sites (NheI and HindIII), which were cut with the corresponding enzymes (NEB, Ipswich, MA) to clone PlySs2 into the pBAD24 expression plasmid (pBAD24) carrying genes for ampicillin selection and arabinose induction. The pBAD24–PlySs2 vector was transformed into *E. coli* TOP10 cells (Invitrogen).

**Recombinant expression and purification of PlySs2.** The aforementioned clone was grown as a patch on LB agar supplemented with 0.2% arabinose, permeabilized by a 10-min exposure to chloroform vapor, and overlaid with soft agar containing heat-killed *S. suis* bacteria. A streptococcal clearing zone around the *E. coli* patch confirmed active recombinant expression of PlySs2 (26).

For PlySs2 purification, the above clone was propagated in LB broth (37°C, 220 rpm aeration) with 100 μg/ml ampicillin. Recombinant expression was induced at an optical density of 0.6 (OD600) of −0.8 by addition of arabinose (0.2%, final concentration). Following overnight incubation, the cells were pelleted and resuspended in 15 mM phosphate buffer (PB; pH 8.0; buffer A) supplemented with protease inhibitor cocktail tablets (Roche). Cells were lysed with an Emulsiflex-C5 homogenizer. After debris removal via ultracentrifugation (35,000 × g, 1 h), the supernatant was adjusted to pH 7.4 with the addition of 4 volumes of buffer A.

The sample was passed through a HiTrap fast flow DEAE anion-exchange column (General Electric), and the flowthrough (which contained the desired PlySs2) was subjected to ammonium sulfate precipitation at 225 g/liter (40% saturation). The precipitated protein was resolubilized in 40 ml of 15 mM PB, pH 6.7 (buffer B) for every liter of initial *E. coli* culture. This solution was dialyzed extensively against buffer B. Finally, the dialysate was passed through a HiTrap fast flow carboxymethyl (CM) cation-exchange column (General Electric). The CM column was washed in buffer B plus 17 mM NaCl, which resulted in gradual, pure elution of PlySs2.

The presence of PlySs2 was confirmed based on lytic activity (clearing zones on agar plates containing embedded, autoclaved *Pseudomonas aeruginosa* (26)) and verified by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis with Coomassie stain. All fractions containing PlySs2 were pooled and stored at −80°C. For *in vivo* tests, purified PlySs2 was dialyzed (into 15 mM NaCl, 5 mM PB; pH 7.4), frozen to −80°C, lyophilized overnight, and resuspended in approximately 1/10 of the initial volume before lyophilization. A bicinchoninic acid (BCA) assay (Sigma) was used to determine the protein concentration.

**PlySs2 specificity.** The OD600 of log-phase bacterial cultures was adjusted with buffer A to −1.0 in 96-well microtiter plates (Falcon). PlySs2, at 32 μg/ml, or buffer B control vehicle was added to each sample well. In each run, *S. suis* 7997 was included as a positive control. Spectrophotometric readings (OD600) of each well were taken by using a Spectramax Plus 384 apparatus (Molecular Devices) every minute over 60 min at room temperature. Lysis activity was gauged by the degree of turbidity reduction (based on the OD600) following enzyme addition.

**Bacterialidal assay.** Log-phase bacteria were resuspended in buffer A to an OD600 of 0.1 (0.5 McFarland; −107 CFU/ml), and aliquots were added to wells of a polystyrene microtiter plate (Costar). Actual inoculum titers for each experiment were derived from plating serial dilutions of each inoculum. For each organism, buffer B control vehicle or PlySs2 was added at 128 μg/ml to wells in triplicate. Plates were sealed and incubated at 37°C with agitation every 5 min for 1 h. After incubation, cells were serially diluted in 10-fold increments and plated on BHI agar. Death was calculated as follows: −log (number of cells surviving under test condition) / (number of cells surviving under control condition).

**MIC analysis.** The protocol described by Wiegand et al. (27) was followed to determine MICs, with adjustments as detailed below. Briefly, a final suspension of −5 × 108 cells/ml in MHB (or BHI for *S. pyogenes*) plus sterile-filtered lysin or control vehicle was distributed within a 96-well microtiter plate in triplicate (27). Cells were challenged with 0.5 to 1,024 μg/ml PlySs2 in triplicate. MICs were determined by detection of cell pellet formation in the bottom of rounded wells of polystyrene plates; they were corroborated colorimetrically with alamarBlue (Invitrogen), following the manufacturer’s protocol.

**In vitro resistance studies.** According to an established protocol for the *in vitro* development of mupirocin resistance (28, 29), *S. aureus* CA-MRSA MW2, *S. aureus* MSSA 8325, and *S. pyogenes* MGAS 5005 was grown in the presence of PlySs2 in liquid culture. Initially, bacterial cells at 5 × 108 CFU/ml were grown overnight in the presence of 1/32 × the MIC of PlySs2 against each strain (37°C; BHI broth for *S. pyogenes* with cap secured during gentle shaking; MHB for *S. aureus* with 220 rpm aeration). The cells were pelleted and subdivided into two aliquots.

One aliquot was diluted 10-fold into fresh MHB medium with double the concentration of PlySs2; a portion of the other was spread onto the surface of MHA containing the PlySs2 MIC for that species. The MIC of 4 resultant colonies was recalculated to determine if a resistant clone had emerged (defined as a 4-fold increase in the MIC). The above procedure was repeated over an 8-day period, and the concentration of PlySs2 in the liquid culture was serially doubled from 1/32 × to 4 × the original MIC. This process was also conducted with mupirocin for each MRSA strain, to serve as an antibiotic resistance positive control.

**In vitro characterization of PlySs2.** The optimal biochemical conditions for PlySs2 enzymatic activity against log-phase pathogenic *S. suis* 7997 were screened using the same spectrophotometric analysis for evaluating PlySs2 specificity, as described above. The pH dependence of the enzyme was first addressed using two buffer sets with overlapping pH ranges: citrate/phosphate (pH 4.6 to 8.0) and bis-Tris propane (pH 7.0 to 9.7). Concentrations of NaCl, EDTA, and diithiothreitol (DTT) were also varied.

**PlySs2 stability.** The thermal stability of PlySs2 was studied by preexposing the enzyme to temperature conditions for defined scales of time: various high temperatures for 30 min, 37°C for 4°C days, and −80°C for months. The activity of each aliquot against *S. suis* 7997 was determined spectrophotometrically as described above. PlySs2 activity
was also tested after consecutive freeze-thaw cycles between −80°C and room temperature.

**In vivo murine model.** The Rockefeller University’s Institutional Animal Care and Use Committee approved all in vivo protocols. A systemic infection model described by Daniel et al. (21) was used to test the *in vivo* efficacy of PtySs2 against multiple Gram-positive bacteria. Briefly, 4- to 5-week-old female FVB/NJ mice (weight range, 15 to 20 g) were obtained from The Jackson Laboratory (Bar Harbor, ME). After a period of acclimation, mice were injected intraperitonally (i.p.) with 0.5 ml of mid-log-phase (OD$_{600}$ 0.5) bacteria diluted with 5% hog gastric mucin (Sigma) in saline. Bacterial suspensions contained $\sim 5 \times 10^{6}$ CFU/ml of MR2, $\sim 1 \times 10^{7}$ of S. pyogenes MGAS 50005, or a simultaneous combination of both bacteria at the above concentrations for the mixed infection experiments. Actual bacterial inoculation titers were calculated by serial dilution and plating to Columbia blood agar plates for each experiment.

Mice became bacteremic within 1 to 3 h and contained MRSA and/or *S. pyogenes* within multiple organs, including spleen, liver, kidney, and heart/blood (reference 21 and unpublished observations). Three hours postinfection, the animals were divided into 4 to 5 treatment groups per infection type and were administered i.p. 0.5 ml of either 20 mM phosphate buffer, 2 mg/ml of the streptococcal-specific lysin PtyC (25), 2 mg/ml of the staphylococcal-specific lysin ClyS (21), 2 to 4 mg/ml PtySs2, or a combination of 2 mg/ml PtyC and 2 mg/ml ClyS. A PtySs2 stock of 4 mg/ml was used for *S. pyogenes*-infected mice to increase survival over an initial 70% survival rate with treatment of 2 mg/ml of PtySs2 (data not shown). While this dosage was possible with PtySs2, it was above our obtainable PtyC or ClyS stock concentrations at the time.

The survival rate for each experimental group was monitored every 12 h for the first 24 h and then every 24 h for up to 10 days postinfection. The data were statistically analyzed using by Kaplan-Meier survival curves with standard errors, 95% confidence intervals, and significance levels (log rank/Mantel-Cox test) calculated using the Prism computer program (GraphPad Software, La Jolla, CA).

**RESULTS**

**Identification of PtySs2.** PtySs2 was identified in a prophase region of a serotype 2 strain of *S. suis* 89/1591 (the ORF was originally annotated in GenBank as SH3 type 5 domain protein; ZP_03625529 [S. Lucas, A. Copeland, A. Lapidus, et al., unpublished data]). The putative lysin sequence corresponding to PtySs2 has the greatest homology among *S. suis* sequences to a surface antigen, but this sequence has only 35% identity over 53% coverage, with an E value of <10$^{-7}$. On *S. suis* overlay plates, clearing zones formed around an *E. coli* strain transformed with an expression plasmid for PtySs2 (pBAD24_PtySs2), confirming the successful cloning and soluble expression of the lysin (26). Computational sequence alignment indicated that PtySs2 encodes a predicted N-terminal CHAP catalytic domain (cysteine-histidine amidohydrolase/peptidase; PF05257) and a C-terminal SH3 type 5 binding domain (PF08460) (see Fig. S1 in the supplemental material). CHAP domains are catalytically diverse and can possess either alanine-amidase activity (18) or cross-bridge endopeptidase activity (21). Based on its primary sequence, the PtySs2 CHAP domain is divergent from other database CHAP domains (all pairwise E values were <10$^{-15}$), including those in characterized streptococcal (25) and staphylococcal (21) phage lysins (data not shown, but see Fig. S2 in the supplemental material).

**Purification and yield of PtySs2.** With a predicted pI of 9.01, PtySs2 flowed directly through a DEAE column at pH 7.4 (see Fig. S3, lane 4, in the supplemental material), and (following an ammonium sulfate-precipitation step) eluted cleanly both in the shoulder of the flowthrough peak of a CM column and in the 17 mM NaCl wash (see Materials and Methods for details). The preparation yielded ~60 mg of protein per liter of *E. coli* culture, with >99% purity (see Fig. S3, lane 6). All experiments were performed with this preparation. Concentrating PtySs2 to 20 mg/ml had no deleterious effect on solubility or activity.

**Broad lytic activity.** Purified PtySs2 was tested against a wide range of bacterial species and strains to determine the range of lytic activity. Starting at an OD$_{600}$ of $\sim$1.0, all tested strains of *S. aureus*, including strains resistant to methicillin, vancomycin, daptomycin, mupirocin, and lysterin, were reduced to an OD$_{600}$ ratio $\leq$0.3 after lysis by PtySs2 over 30 min of exposure (Fig. 1). Readings were also taken after 60 min (see Fig. S4 in the supplemental material). The OD$_{600}$ ratios of other staphylococci, including *Staphylococcus simulans* and *Staphylococcus epidermidis*, were reduced to $\sim$0.2.

With streptococci, PtySs2 lysed most tested M serotypes of *S. pyogenes*, including M1, M3, M4, M6, M18, M49, and an M-negative variant, as well as uncapsulated and highly encapsulated strains, decreasing their OD$_{600}$ ratio to $\leq$0.4. PtySs2 also exhibited strong lytic activity against *S. suis*, *Streptococcus equi zooepidemicus*, *Streptococcus equi*, *S. agalactiae* type II (encapsulated), and *S. agalactiae* 090R. The pathogenic *Streptococcus sanguinis* and group G and E streptococci were moderately sensitive to PtySs2. For *Streptococcus mutans*, group C streptococci, *Streptococcus oralis*, *Streptococcus rattius*, and *Streptococcus sobrinus*, the OD$_{600}$ ratio was only reduced to between 0.7 and 0.9. PtySs2 did not reduce the OD$_{600}$ ratio below 0.5 for any *Streptococcus pneumoniae* strains. *Streptococcus gordoni* was the only commensal against which PtySs2 exhibited activity (Fig. 1).

PtySs2 showed some activity against genera outside *Staphylococcus* and *Streptococcus*. While two strains of *Listeria* sp. were sensitive to PtySs2, other strains were not. In the *Enterococcus* genus, which is associated with high levels of antibiotic resistance, *E. faecalis* was sensitive to PtySs2 (although less so than staphylococci or streptococci), but *E. faecium* was not. No activity was seen against any of the different species of *Bacillus*, strains of lactobacilli, or Gram-negative organisms.

**Efficacy of PtySs2 against Gram-positive pathogens.** PtySs2 was tested for the log fold killing of several species and strains of susceptible organisms that were tested based on the OD$_{600}$ decrease (see above). At 128 µg/ml PtySs2 and with a 60-min exposure, the VISA strain was only reduced by 2 logs. However, PtySs2 reduced the viability of *L. monocytogenes*, *S. agalactiae*, *S. aureus*, and *S. pyogenes* from 3 to >6 logs (Fig. 2).

When the MIC of PtySs2 was tested against these strains, most of the values qualitatively correlated directly to the lytic and killing activities. MICs ranged from 8 to 256 µg/ml for all strains, except the VISA strain, which was not inhibited at >1,024 µg/ml (Table 1).

**Resistance to PtySs2.** By using a published, standardized method for calculating resistance, both staphylococcal and streptococcal strains were analyzed for the development of resistance against PtySs2 by serial exposure to incrementally doubling concentrations of the lysin. Under these testing conditions, none of the *S. aureus* or *S. pyogenes* strains exposed to PtySs2 over 8 days developed resistance (defined as a 4-fold increase from the original MIC) (Fig. 3). Following the same procedure, both *S. aureus* strains MW2 and 8325 developed resistance to the antibiotic mupirocin (Fig. 3).

**Biochemical characterization and stability.** PtySs2 activity was tested within a range of pH values to determine its optimum
physiological buffering conditions. The lysin was most active in citrate/phosphate buffer at pH 8.0 (see Fig. S5A in the supplemental material) and in bis-Tris propane buffer at pH 9.7 (see Fig. S5B). PlySs2 could be optimally active at higher pH levels, but those levels would not be physiologically relevant. In the acidic range, there was strong activity at pH 6.0. Unlike certain other lysins, salt did not augment PlySs2 activity (see Fig. S6 in the supplemental material). Conversely, DTT did not inhibit PlySs2 func-

FIG 1 PlySs2 displayed activity against various species. Multiple strains of staphylococci (including MRSA, MSSA, and VISA), streptococci, enterococci, Listeria, bacilli, and lactobacilli were tested for susceptibility to PlySs2 activity. Escherichia and Pseudomonas were tested as Gram-negative controls. Log-phase cultures were exposed to 32 μg/ml PlySs2 for 30 min in PB (for 60-min readings) (see also Fig. S4 in the supplemental material). The final OD_{600} of the treated samples was divided by the final OD_{600} of the untreated samples to generate the normalized values. Complete lysis registered a ratio of ~0.02. ST, serotype.

FIG 2 PlySs2 was bactericidal across multiple species of bacteria. Log-phase bacteria were treated in 96-well plates with 128 μg/ml PlySs2 in buffer A for 60 min, then serially diluted and plated onto BHI agar for CFU enumeration. The log kill was calculated by comparing the difference between vehicle-treated and PlySs2-treated CFU results.
TABLE 1 MIC of PlySs2 for various Gram-positive species

<table>
<thead>
<tr>
<th>Species</th>
<th>Strain</th>
<th>MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Visual</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>HER 1184</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>HER 1083</td>
<td>8</td>
</tr>
<tr>
<td>S. aureus</td>
<td>MSSA 8325</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>MRS A MW2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Lyra</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>VISA III</td>
<td>32</td>
</tr>
<tr>
<td>GrAS</td>
<td>SF370</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>MGAS 5005</td>
<td>128</td>
</tr>
<tr>
<td>GBS</td>
<td>090R</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>Type II</td>
<td>512</td>
</tr>
<tr>
<td>E. coli</td>
<td>TOP10</td>
<td>&gt;1,024</td>
</tr>
</tbody>
</table>

All MICs were evaluated visually for bacterial growth with alamarBlue vital dye (colorimetrically) at concentrations from 0.5 to 1,024 µg/ml of PlySs2 for each strain of each species listed. There was a low MIC for MRSA MW2, as expected, and a higher MIC for GrAS strain MGAS 5005. The MIC of PlySs2 for the negative control, E. coli, was above the limits of the assay. For a reference, ClyS, LysK, and CHAPs lysins have registered MICs against S. aureus strains from 50 to 80 µg/ml.

**DISCUSSION**

A novel S. suis lysin, PlySs2, has demonstrated broad lytic activity against multiple Gram-positive pathogens, including S. pyogenes and S. aureus, in vitro. All previously characterized lysins, by contrast, have demonstrated activity against a narrow spectrum of species. Likewise, no lysin has been used to clear a bacteremic infection in vivo by more than one pathogenic organism; mixed infections, to our knowledge, have not been previously tested.

A noted strength of many lysins is their target specificity. Antibiotics may kill commensal organisms along with target pathogens, potentially leading to adverse sequelae (e.g., diarrhea or more serious Clostridium difficile complications). In contrast, lysins might be used to treat a single pathogen without disrupting the normal bacterial flora (17), although this specificity could admittedly be a limitation in treating multiple pathogens. Our

**FIG 3** MRSA, MSSA, and GrAS did not acquire resistance to PlySs2 in vitro. MRSA strain MW2, MSSA strain 8325, and GrAS strain MGAS 5005 were exposed to 1/32× to 4× the MIC of PlySs2 and mupirocin (S. aureus strains) over 8 days. The daily MICs of PlySs2 were compared to the starting MIC of PlySs2 for each strain of bacteria to ascertain resistance. None developed resistance to PlySs2. Both MW2 and 8325 developed resistance to the positive control, mupirocin.

June 2013 Volume 57 Number 6 aascsm.org 2747
FIG 4 PlySs2 protected mice from death caused by mixed MRSA and GsAS infection. FVB/NJ mice were injected i.p. with 5% mucin containing the pathogen of interest. Three hours postinfection, mice received one i.p. injection of either 20 mM phosphate buffer (control) or lysin treatment. (A) Survival data for the MRSA infection. Mice were infected with \( \sim 5 \times 10^5 \) CFU of MRSA strain MW2 and treated with either 1 mg of ClyS, 1 mg of PlyC, or 1 mg of PlySs2. (B) Survival data for the GsAS infection. Mice were infected with \( \sim 1 \times 10^5 \) GsAS strain MGAS 5005 and treated with either 1 mg of ClyS, 1 mg of PlyC, or 2 mg of PlySs2. (C) Survival data for the mixed MRSA and GsAS infection. Mice were infected with a combination of both bacteria from the above inoculums at the same concentrations. Mice were treated with either 1 mg of ClyS, 1 mg of PlyC, a combination of 1 mg of ClyS plus 1 mg of PlyC, or 2 mg of PlySs2. In all tests (A to C), mice were monitored for survival over 10 days. The results from 4 independent experiments were combined, and the data are plotted as a Kaplan-Meier survival curve; bars indicate standard errors. All the PlySs2 treatment groups (A to C) showed statistically significant differences \( (P < 0.0001) \) compared to the nonspecific single lysin or buffer controls, based on the log rank (Mantel-Cox) test.

Results show it is possible that a single lysin like PlySs2 could be used to treat multiple Gram-positive pathogens, leaving many Gram-positive and all Gram-negative commensals unaffected. Furthermore, this study also demonstrated that a combination of lysins (PlyC and ClyS) with different specificities could be used effectively to treat mixed infections (Fig. 4C).

PlySs2 exhibits activity against members of two distinct phylogenetic orders: Bacillales (Staphylococcus, Listeria, etc.) and Lactobacillales (Streptococcus, Enterococcus, etc.). The peptidoglycan structures of these two orders are quite similar except for their cross-bridges, which vary widely in composition and length (30). Phage lysins have not previously displayed activity on different families or genera (and rarely on different species) (21). Furthermore, other lysins usually retain greater activity against the species infected by the phage from which the lysin was cloned, whereas PlySs2 demonstrated more activity against S. aureus than against S. suis.

All tested strains of S. aureus were highly susceptible to lysis by PlySs2 (Fig. 1), including strains resistant to methicillin, vancomycin, daptomycin, mupirocin, and lysozyme. Its lytic activity against VISA and Newman strains was somewhat less than its lytic activity against other staphylococcal strains. The reduced activity against the VISA strains could be the result of the thicker cell wall in these organisms (31), which would increase the time necessary to result in lysis. The strong activity of PlySs2 against S. simulans and S. epidermidis supports its use in treatment of a wide array of other staphylococcal infections.

Many streptococci were susceptible to in vitro PlySs2 lysis. PlySs2 exhibited potent lytic activity against its native species, S. suis, as well as S. equi, S. equi zoonoticus, and S. pyogenes. Of note, there was no difference in PlySs2 activity against encapsulated or highly encapsulated variants of S. pyogenes. PlySs2 also demonstrated comparable activity against strains of GB5 with or without a virulence-enhancing capsule (S. agalactiae type II and S. agalactiae 090R, respectively). Moderate activity was observed against group C, E, and G streptococci, suggesting in vivo experiments will be necessary to determine if PlySs2 can be used to treat infections by these organisms. It is unlikely that PlySs2 could be used therapeutically for S. mutans, S. oralis, S. rattus, and S. sobrinus infections, or for some strains of S. pneumoniae, because of its low activity against these pathogens. PlySs2 did not lyse any commensal lactobacilli. PlySs2 showed significant activity against other genera, killing some strains of Listeria and E. faecalis, but not E. faecium or strains of bacilli. The ability of PlySs2 to lyse a wide range of pathogens, without lysing many commensals, suggests that certain pathogens persist by sharing a binding receptor for this lysin.

We found that the bactericidal assays quantitatively confirmed PlySs2's ability to effectively kill strains that vary in drug resistance and encapsulation, with correlations between the lytic, bacterial, and MIC assays. Thus, even though they were not tested, it is likely that pathogens that were found to be more sensitive to PlySs2 lysis than S. pyogenes MGAS 5005 in vitro may also be sensitive to PlySs2 in vivo. The MIC of PlySs2 against several S.
aureus strains was less than or equal to the MICs of other staphylococcal lysins, including ClyS, LysK, and CHAP \(_3\) (21, 29, 32, 33).

The binding domain of PlySs2 may contribute to its unique activity profile. Phage lysin binding domains have been shown to determine lysin specificity (34). As such, an SH3b (bacterial homolog of SH3) domain of a Bacillus cereus endopeptidase has been shown to bind the free amino group of the N-terminal alanine in the stem peptide of the peptidoglycan (35). Because of its ubiquity in peptidoglycans, this amide could also be the substrate for the PlySs2 SH3b domain. Accordingly, experiments are in progress to determine the binding and cleavage substrates for PlySs2.

An important finding in this study was our ability to clear mixed MRSA and S. pyogenes bacteremic infections from 92% of mice with a single dose of PlySs2. This survival rate was better than the 80% survival of mice treated with the combination of ClyS and PlyC (Fig. 4C). In a mixed infection, use of either PlyC or ClyS alone eliminated only one of the infecting pathogens, resulting in death by the other; this death occurred within the same time frame and rate as the corresponding singly infected, nontreated controls, i.e., MRSA-infected animals died within 24 h and S. pyogenes-infected animals died within 3 days. These results strongly support the idea that PlySs2 cures the animals of their infection by simultaneously killing both pathogens.

Recent studies have indicated that secondary infections caused by colonizing MRSA, S. pyogenes, or S. pneumoniae account for up to 90% of deaths from influenza pandemics (36–39). Mupirocin and polynorin are the only anti-infectives approved to reduce colonizing pathogenic bacteria on mucous membranes, but S. aureus can develop resistance to each (40). Lysins with specific activities against either staphylococci, streptococci, or pneumococci have each been shown to decolonize these pathogens in animal models of oral and nasal mucosal colonization (18, 19, 21, 22, 24, 41); however, a mixture of the three enzymes would need to be used to remove these pathogens. PlySs2 alone could be used to decolonize susceptible populations of staphylococci, streptococci, and perhaps certain pneumococcal isolates during flu season to reduce the possibility of a secondary infection.

The inability of pathogenic targets (MRSA and S. pyogenes) to establish resistance to PlySs2 (under conditions leading to mupirocin resistance) is consistent with findings for other lysins, such as PlyG (41). Antibiotic resistance may occur when bacteria either inactivate the drug or alter the target site. An extracellular lysin protease has yet to be identified, and it is less likely that a PlySs2-susceptible pathogen could easily alter the PlySs2 peptidoglycan target. To date, the only known resistance to a lysin-like molecule involves the insertion of a serine residue into an S. aureus penicillin cross-bridge to establish resistance to lysostaphin (a nonphage endopeptidase from S. simulans). However, it is unlikely that PlySs2 is a canonical cross-bridge endopeptidase, because of its activity against disparate bacterial species with diverse cross-bridge structures (42), including lysostaphin-resistant staphylococci.

PlySs2 is more tractable and stable than previously reported lysins (21, 25, 26). Its preparation is straightforward, yielding very pure, high yields of product in just a few steps. It remains soluble in concentrations exceeding 20 mg/ml (data not shown) and can be subjected to high or low temperatures for prolonged periods with little effect on its activity, even when repeatedly freeze-thawed. These features support PlySs2 as a suitable lysin for further development.

PlySs2 represents a novel breakthrough in the field of bacteriophage lysin technology. It is now possible to envision other lysins with broad therapeutic activities that retain specificity to a subset of mostly pathogenic Gram-positive organisms. For PlySs2, this novel capability possibly lies in the divergent PlySs2 CHAP domain and unique SH3 binding domain. PlySs2 occupies a vital space along the spectrum between strict lysin specificity and unselective antibiotic activity. Ideally, a therapeutic agent should have activity against major pathogens without affecting commensals; this report of PlySs2 is the first to indicate that a lysin could serve that function.

In summary, while pursuing a novel treatment for S. suis infection, we discovered a lysin with broad lytic activity against strains of MRSA, VISA, S. suis, Listeria, S. simulans, S. equi zooepidemicus, S. equi, S. agalactiae, S. pyogenes, S. sanguinis, S. gordoni, group G streptococci, group F streptococci, E. faecalis, and S. pneumoniae. PlySs2 was relatively simple to produce, tractable, and very stable. We demonstrated here the ability of PlySs2 to protect mice with mixed infection by MRSA and S. pyogenes. Neither of these pathogens was observed to develop resistance to PlySs2 in vitro. PlySs2 could therefore become a vital addition to the armamentarium against multidrug-resistant S. aureus, S. pyogenes, and various other Gram-positive pathogens.

ACKNOWLEDGMENTS

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Daniel Gilmer is a Gilliam fellow of the Howard Hughes Medical Institute. This work was supported by U.S. PHS grant AI11822 to V. A. Fischetti.

V. A. Fischetti has equity in ContraFect Corp., a company that has licensed the rights to PlySs2.

REFERENCES

9. Laupland KB, Ross T, Gregson DB. 2008. Staphylococcus aureus blood-


A 2\textsuperscript{nd} Nurse in Dallas, TX has been infected. The PPE-Protocol should include ClO2.

Some full PPE Sets made in N. England cost US$40 each, for example.

ClO2 PRICING & TERMS: \( \frac{1}{2} \) down at Order and remaining \( \frac{1}{2} \) paid at Delivery in USA.

\textbf{8-TIMES DIOXIGUARD\textsuperscript{TM} Liquid} CHLORINE DIOXIDE (ClO2) CONCENTRATE for use as a disinfectant against various bacteria and viruses, including Ebola (and other filovirus-types) in W. Africa. We shall employ good faith and best efforts to assist PIH.

\textbf{DIOXIGUARD\textsuperscript{TM} Liquid} for PPE disinfection, instrument & hospital application as well as general topical use, is a fast acting disinfectant, and kills all bacteria, \textit{viruses} and fungi within \textbf{one minute}, in vitro, including mycobacteria, amoeba, and spores.

\textbf{NOTE:} \textbf{8 Times} Concentration of ClO2: [to save on shipping and container costs.]

Price per “Usable” Gallon of ClO2 (after dilution on-site) ..... $6.59

Therefore, \textbf{8 Times} Concentration of ClO2 in each 5-Gallon Stackable Plastic Container.

..... $263.60 + Cost of 5-Gallon Shipping Container (below) = $15.00 ... \textbf{Total: $278.60}

Standard LTL (Limited Truck Load) Common Carrier charges will vary to your “supply-aggregation locations” in the USA. The ClO2 is made in Melville, Long Island, NY.

The ClO2 can be diluted at locations in W. Africa with \textbf{7-parts} water to \textbf{1-part} of ClO2.

The ClO2 can be transported (on standard plastic or wooden pallets) in these 5-Gallon Plastic Stackable Containers (shown below):

\begin{quote}
PLEASE NOTE THAT THIS PRODUCT SHOULD BE SOLD IN FULL PALLET QUANTITIES ACCORDING TO THE FOLLOWING PALLET STACKING ARRANGEMENTS:
\end{quote}

\textbf{3 Qty Containers stacked vertical (max) on each pallet} \times \textbf{9 Qty Containers per Layer} = \textbf{27 Qty Containers per Pallet}. .... \textbf{Total Price per Pallet} ....... $7,522.20

These 27 Qty Containers will make \textbf{1,080 Qty Useable Gallons} of ClO2
Other On-site Uses for 8x Chlorine Dioxide (ClO2)

ClO2 can be “fogged” in Aircraft Cabins.

The ClO2 solution is nontoxic or irritating and can be placed on the body.

**Dilution from the “Usable” Gallon of ClO2**
To produce acceptable drinking (potable) water would need a dilution of approx. 50 times.
To disinfect a wound requires approx. 20 times dilution. For fungal infections, 10 times.

Stability of solution is 2 years, if kept near room temperature. At 40 deg C, 104 deg F, bacterial kill time will slowly reduce.

Most microorganisms are killed within one minute, including spores and virus.

An 8oz. Useable Sample of ClO2 disinfecting solution can be supplied for your testing.

**Below is a Description on the 5-Gallon Shipping Containers:**

BELOW IS FROM:

5 Gallon Rectangular Winpak®
The follow up to our popular round Winpak® tight head pail offers these advantages: Safe, snug fit aboard pallet. Increases stacking and shipping performance. No wasted pallet space. Maximizes shipping and storage savings. Ample label/screen decoration area. Constructed of high molecular, high density polyethylene, the Rectangular Winpak® features an integral 70mm opening, and an 18mm pouring vent with its own accompanying screwcap. The unit is also equipped with the popular Winpak® style swing handle on the top face to facilitate easy lifting and handling. Meets UN Packaging Type 3H1Y18100 and applicable FDA regulations.
More ClO2 Technical Information
http://frontierpharm.com/pages/white-papers
http://frontierpharm.com/pages/the-science-of-dioxicare

Frontier™ can supply 1-part Chlorine Dioxide ClO2 for spray onto soiled
Personal Protective Equipment (PPE) during and after the shifts.

ClO2 Product Shipments could be aggregated at DoD (or other) US-based Airfields and airlifted
to W. Africa. We can ship to any location in the USA, as well.

Frontier’s Howard Alliger Patents: # 4,084,747, # 4,330,531

Other ClO2 Products (provided and priced separately):

Frontier’s DIOXIDERM™ ClO2 Disinfectant Gel could be applied to a “sweat band” to form a
protective barrier that may reduce Ebola virus dripping into the eyes, nose & mouth of the Health
Care Workers (HCWs). This same product could be used before and after use of standard protective
gloves.

Frontier’s DIOXIDERM™ Disinfectant Gel (Skin Protectant), makes novel use of ClO2 and
is available as a "skin cream" in a two-part system. The amount to be applied is mixed just
before use automatically, and the chlorine dioxide is released slowly. Lesion response is rapid,
especially when treating diseases such as pox lesions or acne. Dual dispensers simplify the
application. Similarly, a new dual toothpaste and mouthwash, DIOXIBRITE™ and
DIOXIRINSE™ are available which kill all bacteria in vitro and deodorize the oral cavity.

At high ClO2 ppm, the method of rapid bacterial and viral kill appears to be the softening and
destroying of the cell wall or viral capsid. Human cells do not have similar cell walls and are
apparently unaffected. Our skin and bodies are likely protected from the general oxidative effects
of ClO2 by the many reducing agents in our cells and blood, such as catalase, glutathione,
superoxide dismutase, vitamins E, C, A, B complex, uric acid, zinc and selenium. This is
probably the same internal protective mechanism that prevents damage from oxygen and free
radicals. Bacteria and viruses do not contain most of these reducing compounds. Because ClO2
is a strong oxidizing agent and also itself a free radical, it quickly neutralizes reactive molecules,
such as cytokines and oxygen free-radicals such as NO•, O2−, H2O2, HClO, and OH• that are
produced in the body by macrophages. These oxygen compounds are released in response to
stress or infection and cause inflammation and pain. Other potential irritants found in wounds are
similarly oxidized or reduced, such as leukotrienes, TNF, and interleukin. This neutralizing
property of ClO2, combined with its ability to completely disinfect, makes DIOXIDERM™ and
DIOXIGUARD™ ideal wound medications. Unlike iodine compounds, or chlorhexidine, healing
is not impeded. Veterinarians have been treating deep wounds and abscesses on tigers and
elephants as well as dogs and cats with outstanding success. DIOXIDERM™ GEL had similar
striking results on human (otherwise non-healing) diabetic ulcers. If our body could manage to
manufacture chlorine dioxide, as it does hypochlorite, hydrogen peroxide and superoxide, it would probably do so.

NON-TOXICITY

Many evaluations have shown ClO2 compounds to be non-toxic. Five decades of use have not indicated any adverse effects on health. The main areas of use has been disinfecting water supplies, the elimination of unwanted tastes and odors, and bleaching in the pulp and paper and textile industries. Toxicology tests include ingestion of ClO2 in drinking water, additions to tissue culture, injections into the blood, seed disinfection, insect egg disinfection, injections under the skin of animals and into the brains of mice, burns administered to over 1500 rats, and injections into the stalks of plants.

ClO2 shows fast disinfection and non-toxicity that are properties not normally found side-by-side in the same compound. For example, formaldehyde and peracetic acid are strong and often used sterilants, but they are also toxic and irritating. Chlorhexidine and iodine compounds inhibit wound healing. Because both speed of pathogen-deactivation and non-toxicity are combined in the Frontier™ ClO2 Liquids and Gels, the immediate use of same to control Filovirus (Ebola and the like) are opened for important Oral and Topical (Skin Barrier) and Surface Disinfection/Decontamination for spray onto soiled Personal Protective Equipment (PPE) during and after the 8 hour to 12 hour shifts and on and in latrine surfaces, bed frames and chairs and other reusable clinic equipment in W. Africa and beyond.
Subject: USG-WHO MCM Cooperation Call

Date: 2020/05/20 17:50:37

Start Date: 2020/05/29 08:00:00

End Date: 2020/05/29 09:00:00

Priority: Normal

Type: Appointment

Location: WebEx/Zoom

Kerr, Lawrence (HHS/OGA); Weinberger, Collin (OS/OGA); Moudy, Robin (OS/OGA); Chandrasekera, Ruvani (OS/OGA); Ferrey, Seth (OS/OGA); Aasen, Adam (HHS/OGA); Snyder, Anne (HHS/OGA); Wood, Rachel (HHS/OGA); Olson, Leandra (HHS/OGA); Schmeissner, Peter (HHS/OGA); LaHood, Natalie (OS/OGA); Smith, Steven T (Geneva); 'SmithSR1@state.gov'; Marks, Peter (FDA/CBER); Woodcock, Janet (FDA/CDER); Abdoo, Mark (FDA/OC); Disbrow, Gary (OS/ASPR/BARDA); Houchens, Christopher (OS/ASPR/BARDA); Johnson, Robert (OS/ASPR/BARDA); 'swaminathans@who.int'; 'ryann@who.int'; 'simonsons@who.int'; 'simaom@who.int'; 'aywardb@who.int'; Messonnier, Nancy (CDC/DDID/NCIRD/OD); Helfand, Rita (CDC/DDID/NCEZID/OD); Hyde, Terri (CDC/DDPHYSICS/CGH/GID); Cohn, Amanda (CDC/DDID/NCIRD/OD); Montgomery, Joel M. (CDC/DDID/NCEZID/DHCFP); Brooks, John T. (CDC/DDID/NCHHSTP/DHPSE); Mair, Michael (FDA/OC); 'matthew.j.hepburn.clv@mail.mil'; Mcqueen, COL Anthony (HHS/IOS); Smith, Michael (MIL); 'sadam@fnih.org'; Lane, Cliff (NIH/NIAID) [E]; Gruber, Marion (FDA/CBER); Krause, Philip (FDA/CBER); Thomas, Ashley (FDA/CDER); 'borgesa@who.int'; Bugin, Kevin (FDA/CDER); Cho, David S (CBER) (FDA/CBER); Szemore, Christine (NIH/FIC) [E]; Wholley, David (FNHI) [T]; Melencio, Cheryl (FNHI) [T]; Donis, Ruben (OS/ASPR/BARDA); Blatner, Greta (OS/ASPR/BARDA); Ayala, Ana (OS/OGA); Tracy Carson; 'ANNEI, Claudia'; 'MCLIESH, Wendy Maree'; Fernandez, Jose (OS/OGA); Burr, Mara (HHS/OGA); Bleimund, Emily (OS/OGA); Tromberg, Bruce (NIH/NIBIB) [E]; Heemskerk, Jill (NIH/NIBIB) [E]; Elia Nudell; Lamoureille, Gabrielle (HHS/OGA)

Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 8 to 9 am ET/1400-1500 Geneva.

We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
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Office of Global Affairs
U.S. Department of Health and Human Services

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MCLEISH, Wendy Maree <mcleshrw@who.int>
Fernandez, Jose (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (/FYDIBHOFC3PDOL) /cn=Recipients/cn=21d0317aabb9f4d1bb2779f8bb95826543-Fernandez, Jose.Fernandez@hhs.gov>
Burr, Mara (HHS/OS/OGA) <Mara.Burr@hhs.gov>
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<borges@who.int>
Bugin, Kevin (FDA/CBER) <Kevin.Bugin@fda.hhs.gov>
Cho, David S (CBER) (FDA/CBER) <David.Cho@fda.hhs.gov>
Sizemore, Christine (NIH/NIAID) [E] <christine.sizemore@nih.gov>
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Melencio, Cheryl (FNHI) [T] <cmelencio@fnih.org>
Donis, Ruben (OS/ASPR/BARDA) <Ruben.Donis@hhs.gov>
Blatner, Greta (OS/ASPR/BARDA) <Greta.Blatner@hhs.gov>
Heemskerk, Jill (NIH/NIBIB) [E] <jill.heemskerk@nih.gov>
en199 (D) georgetown.edu
Lamourelle, Gabrielle (HHS/OS/OGA) <Gabrielle.Lamourelle@hhs.gov>

Sent Date: 2020/05/20 17:50:37

To: Donis, Ruben (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (/FYDIBHOFC3PDOL) /cn=Recipients/cn=af0d4cf720b3a999e2addcbe03ee32ff-Donis, Ruben.Donis@hhs.gov>
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Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 9 to 10am ET/ 1500- 1600 Geneva.

Attached is the final agenda for the first call on Friday, May 29.

Conference Line Information:
Domestic [0][0]
International [6][6]
Participant Passcode [6][6]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

AL- 5/29/20
Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
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Ferrey, Seth (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group
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Montgomery, Joel M. (CDC/DDID/NCEZID/DHCPP) <ztaq9@cdc.gov>;
Cohn, Amanda (CDC/DDID/NCEZID/OD) <???>;
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Hyde, Terri (CDC/DDID/DHIS/CGH/GID) <tkth4@cdc.gov>;
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Woodcock, Janet (FDA/CBER) <Janet.Woodcock@fda.hhs.gov>;
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LaHood, Natalie (OS/OGA) <Natalie.Lahood@hhs.gov>;
Ölsson, Leandra (HHS/OAGA) <Leandra.Ölsson@hhs.gov>;

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Subject: Canceled: USG-WHO MCM Cooperation Call

Importance: High
Priority: Urgent
Type: OLE.CLASS.(00061055-0000-0000-C000-000000000046)

6/11/2020: Meeting canceled

-AL
Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 8 to 9 am ET/ 1400- 1500 Geneva.

We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
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Office of Global Affairs
U.S. Department of Health and Human Services

Recipient: JohnsHopkinsProducts@georgetown.edu; Heemskerk, Jill (NIH/NIBIB) [E]; Blatner, Gretta (OS/ASPR/BARDA); Donis, Ruben (OS/ASPR/BARDA); Melencio, Cheryl (FNIH) [T]; Wohley, David (FNIH) [T]; Sizemore, Christine (NIH/NIAID) [E]; Cho, David S (CBER) (FDA/CBER); Bugin, Kevin (FDA/CDER); Thomas, Ashley (FDA/CDER); Philip.Krause@fda.hhs.gov

SMTP; Bleimund, Emily (OS/OGA) <Emily.Bleimund@hhs.gov>; Burr, Mara (HHS/OS/OGA) <Mara.Burr@hhs.gov>; Tracy Carson <CarsonTL@state.gov>; Ayala, Ana (OS/OGA) <Ana.Ayala@hhs.gov>; Lane, Cliff (NIH/NIAID) [E] <clane@niaid.nih.gov>; Smith, Michael (NIAID) <michael.w.smith93@mail.nih.gov>; Mcqueen, COL Anthony (HHS/ITOS) <Anthony.Mcqueen@hhs.gov>; Mair, Michael (FDA/OC) <Michael.Mair@fda.hhs.gov>
Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 9-10 am ET/ 1500-1600 Geneva.

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If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
塩口洋務動画規則 unheard 妻夫役者委員会関係者会

keywords: 动画、规则、妻夫役者委員会、関係者会

Snyder, Anne (HHS/OS/OGA)}；

keywords: Snyder, Anne (HHS/OS/OGA)
| Yarielka Arrieta | b(6)agmail.com |

**Subject:** USG-WHO MCM Cooperation Call  
**Date:** 2020/05/20 17:50:37  
**Start Date:** 2020/05/29 08:00:00  
**End Date:** 2020/05/29 09:00:00  
**Priority:** Normal  
**Type:** Appointment  
**Location:** WebEx/Zoom  

Kerr, Lawrence (HHS/OS/OGA); Weinberger, Collin (OS/OGA); Moudy, Robin (OS/OGA); Chandrasekara, Ruvani (OS/OGA); Ferrey, Seth (OS/OGA); Aasen, Adam (HHS/OS/OGA); Snyder, Anne (HHS/OS/OGA); Wood, Rachel (HHS/OS/OGA); Olson, Leandra (HHS/OS/OGA); Schmeissner, Peter (HHS/OGA); LeHood, Natalie (OS/OGA); Smith, Steven T (Geneva); 'SmithSR1@state.gov'; Marks, Peter (FDA/CBER); Woodcock, Janet (FDA/CDER); Abdoo, Mark (FDA/OC); Disbrow, Gary (OS/APSR/BARDA); Houchens, Christopher (OS/APSR/BARDA); Johnson, Robert (OS/APSR/BARDA); Swaminathans@who.int'; 'ryanm@who.int'; 'simonsons@who.int'; 'simao@who.int'; 'alywardb@who.int'; Messonnier, Nancy (CDC/DDID/NCIRD/OD); Helfand, Rita (CDC/DDID/NCIRD/OD); Hyde, Terri (CDC/DDPHS1S/GCH/GID); Cohn, Amanda (CDC/DDID/NCIRD/OD); Montgomery, Joel M. (CDC/DDID/NCIRD/OD); Brooks, John T. (CDC/DDID/NCHSTP/DHPSE); Blair, Michael (FDA/OC); 'matthew.j.hepburn.clv@mail.mil'; Mcqueeny, COL Anthony (HHS/IOS); Smith, Michael (MIL); 'sadam@fhih.org'; Lane, Cliff (NIH/NIAID) [E]; Gruber, Marion (FDA/CBER); Krause, Philip (FDA/CBER); Thomas, Ashley (FDA/CDER); 'borgesa@who.int'; Bugin, Kevin (FDA/CBER); Cho, David S (CBER) (FDA/CBER); Sizemore, Christine (NIH/FIC) [E]; Wholley, David (FNIH) [T]; Melenchic, Cheryl (FNIH) [T]; Donis, Ruben (OS/APSR/BARDA); Blatiner, Greta (OS/APSR/BARDA); Ayala, Ana (OS/OGA); Tracy Carson: 'ANNEI, Claudia'; 'MCLIESEH, Wendy Maree'; Fernandez, Jose (OS/OGA); Burr, Mara (HHS/OS/OGA); Bleimund, Emily (OS/OGA); Tromberg, Bruce (NIH/NIBIB) [E]; Heemskerk, Jill (NIH/NIBIB) [E]; Ella Nudell, Lamoureille, Gabrielle (HHS/OS/OGA); Yarielka Arrieta

Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 8 to 9 am ET/ 1400-1500 Geneva.

We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD  
Director  
Office of Pandemic and Emerging Threats  
Office of Global Affairs  
U.S. Department of Health and Human Services
Sent Date: 2020/05/20 17:50:37

To: Donis, Ruben (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOCHF23SPDLT)/cn=Recipients/cn=af00d720c429f8e2accbe06ee32ff-Donis, Rube
Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 9 to 10am ET/ 1500-1600 Geneva.

Attached is the final agenda for the first call on Friday, May 29.

Conference Line Information:
Domestic [D(6)]
International [D(6)]
Participant Passcode [D(6)]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.
AL-5/29/20
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<th>Role</th>
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<td><a href="mailto:Lawrence.Kerr@hhs.gov">Lawrence.Kerr@hhs.gov</a></td>
<td>Exchange Administrative Group (FYDIBOH23SPDLT)</td>
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Subject: Canceled: USG-WHO MCM Cooperation Call

Importance: High

Priority: Urgent
6/11/2020: Meeting canceled

-AL

Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 8 to 9 am ET/ 1400- 1500 Geneva.

We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Subject: USG-WHO Dialogue on COVID-19 MCMs

Type: OLE.CLASS: {0006:1055-0000-0000-C000-000000000046}

Please join the USG-WHO Dialogue on COVID-19 MCMs. This week's call will be on Friday, July 10 from 9 - 9:45 am ET/ 1500 - 1545 Geneva.
If you have any questions, please contact Arnela.Lopez@hhs.gov and Ruvani.Chandrasekera@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Please join the USG-WHO MCM Dialogue Call. This will be a biweekly call on Fridays from 8 to 9 am ET/1400-1500 Geneva.

We will share the final agenda and the WebEx or Zoom information.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Kerr, Lawrence (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e7497472bb758f8fd6e262c86-Kerr, Lawre <Lawrence.Kerr@hhs.gov>

Kerr, Lawrence (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e7497472bb758f8fd6e262c86-Kerr, Lawre <Lawrence.Kerr@hhs.gov> ; Weinberger, Collin (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=641554f7c84340758827af5889d926-Weinberger, <Collin.Weinberger@hhs.gov> ; Moudy, Robin (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d421d3e0f6474bc3b57983cf5870d69-Moudy, Robi <Robin.Moudy@hhs.gov> ; Chandrasekera, Ruvani (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=678d9f8e02d477ab5d6516bd3659a34-Chandraseke <Ruvani.Chandrasekera@hhs.gov> ; Ferrey, Seth (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2d976148be6c4ea5a25eeb0fd101809-Ferrey, Set <Seth.Ferrey@hhs.gov> ; Assen, Adam (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9df94b81b7594e08cf4a157bd583d5d-Assen, Adam <Adam.Assen@hhs.gov> ; Snyder, Anne (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7410775a42a54f0bb71436b93c600cb9-Snyder, Ann <Anne.Snyder@hhs.gov> ; Olson, Leandra (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dec295d944ee4b57b464d7d5041bb916-olson, lean <Leandra.Olson@hhs.gov> ; Schmeissner, Peter (HHS/O/GA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca385a113c964742b9e94d7ef94614-Schmeissner <Peter.Schmeissner@hhs.gov> ; LaHood, Natalie (OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7d5e131f94ab3b0b1e0b6f23285f11-Lahood, Nat <Natalie.Lahood@hhs.gov> ; Smith, Steven T (Geneva) <SmithST1@state.gov> ; <SmithSR1@state.gov> ; Marks, Peter (FDA/CBER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=df56588b970c43c8a2b8b31406746c-peter.marks <Peter.Marks@fda.hhs.gov> ; Woodcock, Janet (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5f925e9a0f9147b186d40072d474d13d-woodc <Janet.Woodcock@fda.hhs.gov> ; Abdoo, Mark (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8893b91b39b9f378ac6b5d5123cd1-mark.abdoo. <Mark.Abdoo@fda.hhs.gov> ; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4d0bb45f6fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov> ; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04f22b7c91bb5618937975-houchens, C <Christopher.Houchens@hhs.gov> ; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0651e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov> ; <swaminathan@who.int> ; <ryamn@who.int> ; <simonsons@who.int> ;
Sent Date: 2020/05/20 17:50:37

Donis, Ruben (OS/ASPR/BARDA) <Ruben.Donis@hsds.gov>

EX melencio.NIH

SMTP Szemore, Christine (NIH/NAID) [E] <christine.szemore@nih.gov>

To: Ashley, Thomas @fda.hhs.gov

Gruber, Marion (FDA/CBER)

Hyde, Terri (CDC/DDPHSIS/CGH/GID)
Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 9 to 10am ET/ 1500- 1600 Geneva.

Attached is the final agenda for the first call on Friday, May 29.

Conference Line Information:
Domestic: [0(6)]
International: [0(6)]
Participant Passcode: [0(6)]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.
AL- 5/29/20

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
6/11/2020: Meeting canceled

-AL

Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 8 to 9 am ET/ 1400-1500 Geneva.

We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Please join the USG-WHO Dialogue on COVID-19 MCMs. This week’s call will be on Friday, July 10 from 9 - 9:45 am ET/ 1500 - 1545 Geneva.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ruvani.Chandrasekera@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services

Recipient: Gabrielle.Lamoureille@hhs.gov, Lamoureille, Gabrielle (HHS/OS/OGA) <Gabrielle.Lamoureille@hhs.gov>
en419 < >;
SMTP;
Kerr, Lawrence (HHS/OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e74974272b758f6fde626c286-Kerr, Lawre <Lawrence.Kerr@hhs.gov>;
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<Olson, Leandra (HHS/OS/OGA)>

END

Recipient: EX

<SmithSR1@state.gov>
Please join the USG-WHO MCM Dialogue Call on July 24. This will be a biweekly call on Fridays from 8 to 9 am DC/Atlanta, 1400-1500 Geneva.

Please find attached the slides, agenda, and notes from the previous meetings. We will update the WebEx or Zoom information tonight.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
From: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>

Kerr, Lawrence (HHS/OS/OGA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ce9de2e7497472bb75f8f6d6af62c85-Kerr, Lawre <Lawrence.Kerr@hhs.gov>
Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>
Moudy, Robin (OS/OGA) <Robin.Moudy@hhs.gov>
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Olson, Leandra (HHS/OS/OGA) <Leandra.Olson@hhs.gov>
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Motsonier, Nancy (CDC/DDID/NCIRD/OD) <nar5@cdc.gov>
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Hyde, Terri (CDC/DDPHSIS/CGH/GID) <tdhh4@cdc.gov>
Colin, Amanda (CDC/DDID/NCIRD/OD) <anc0@cdc.gov>
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Mair, Michael (FDA/OC) <Michael.Mair@fda.hhs.gov>
<matthewjhepburn.clv@mail.mil>
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Ayala, Ana (OS/OGA) <Ana.Ayala@hhs.gov>
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| Attendees: | Kerr, Lawrence (HHS/OS/OGA); Weinberger, Collin (OS/OGA); Moudy, Robin (OS/OGA); Chandrasekera, Ruvani (OS/OGA); Ferrey, Seth (OS/OGA); Aasen, Adam (HHS/OS/OGA); Snyder, Anne (HHS/OS/OGA); Wood, Rachel (HHS/OS/OGA); Olson, Leandra (HHS/OS/OGA); Schmeissner, Peter (HHS/OGA); LeHoed, Natalie (OS/OGA); Smith, Steven T (Geneva); 'SmithSR1@state.gov'; Marks, Peter (FDA/CBER); Woodcock, Janet (FDA/CDER); Abdoo, Mark (FDA/OC); Disbrow, Gary (OS/ASPR/BARDA); Houchens, Christopher (OS/ASPR/BARDA); Johnson, Robert (OS/ASPR/BARDA); 'swaminathans@who.int'; 'ryam@who.int'; 'simonsone@who.int'; 'simaem@who.int'; 'aylwrdh@who.int'; Messonnaier, Nancy (CDC/DDID/NCIRD/OD); Helfand, Rita (CDC/DDID/NCEZID/OD); Hyde, Terri (CDC/DDPHIS/C/CGH/GID); Cohn, Amanda (CDC/DDID/NCIRD/OD); Montgomery, Joel M. (CDC/DDID/NCEZID/DHCPP); Brooks, John T. (CDC/DDID/NCHHSTP/DHPE); Mair, Michael (FDA/OC); 'matthew.j.heatburn.civ@mail.mil'; Mcqueen, COL Anthony (HHS/OS); Smith, Michael (MIL); 'sadam@fnih.gov'; Lane, Cliff (NIH/NIAID) [E]; Gruber, Marion (FDA/CBER); Krause, Philip (FDA/CBER); Thomas, Ashley (FDA/CBER); 'borgeasa@who.int'; Bugir, Kevin (FDA/CDER); Cho, David S (CBER) (FDA/CBER); Szimore, Christine (NIH/FIC) [E]; Wholley, David (FINH) [T]; Melencio, Cheryl (FINH) [T]; Donis, Ruben (OS/ASPR/BARDA); Blatner, Greta (OS/ASPR/BARDA); Ayala, Ana (OS/OGA); Tracy Carson; ‘NANNEI, Claudia’; ‘MCLIESSH, Wendy Maree’; Fernandez, Jose (OS/OGA); Burr, Mara (HHS/OS/OGA); Bleimund, Emily (OS/OGA); Tromberg, Bruce (NIH/NIBIB) [E]; Heemskeyc, Jill (NIH/NIBIB) [E]; Elia Nudell; Lamourelle, Gabrielle (HHS/OS/OGA); Yariella Arrieta |

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We will share the final agenda and the WebEx or Zoom information.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Please join the USG-WHO MCM Cooperation Call. This will be a biweekly call on Fridays from 9 to 10am ET/ 1500-1600 Geneva.

Attached is the final agenda for the first call on Friday, May 29.

Conference Line Information:
Domestic[866-930-1460]
International[516-227-0042]
Participant Passcode[50225295]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.
AL- 5/29/20

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Subject: Canceled: USG-WHO MCM Cooperation Call

Importance: High

Priority: Urgent

Type: OLE.CLASS.(0006:0155-0000-0000-C000-000000000046)

6/11/2020: Meeting canceled
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We will share the final agenda and the WebEx or Zoom information later this week.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Subject: USG-WHO Dialogue on COVID-19 MCMs

Type: OLE.CLASS.(00061055-0000-0000-C000-00000000046)

Please join the USG-WHO Dialogue on COVID-19 MCMs. This week’s call will be on Friday, July 10 from 9 - 9:45 am ET/ 1500 - 1545 Geneva.

Domestic:(6)
International: (6)
Participant Passcode: (6)

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ruvani.Chandrakeker@hhs.gov.

Larry Kerr, PhD
Director
Subject: USG-WHO MCM Dialogue Call- WebEx Information Embedded
Type: OLE.CLASS.: (00061:055-0000-0000-C000-000000000046)
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Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
Subject: Canceled: USG-WHO MCM Dialogue Call

Importance: High

Priority: Urgent

Type: OLE.CLASS.(00061055-0000-0000-C000-000000000046)

Please join the USG-WHO MCM Dialogue Call. This will be a biweekly call on Fridays from 8 to 9 am ET/1400-1500 Geneva.
We will share the final agenda and the WebEx or Zoom information.

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
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U.S. Department of Health and Human Services
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Wholley, David (FNHI) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=afc96d003f9d4a1831a2d77566ed34e-david.wholl <dwholley@fnih.org>; Melencio, Cheryl (FNHI) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=543edf1790647e6f8d05d209f589fe8c1-cheryl.mele <cmelencio@fnih.org>; Donis, Ruben (OS/ASPR/BARDA) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a00dfc722db42978c2a00e6ee32f-Donis, Rube <Ruben.Donis@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6f91536e1bfb-Blatner, Gr <Gretta.Blatner@hhs.gov>; Heemskeker, Jill (NIH/NIBIB) [E]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5274a3eb4d4c4cc79951f2233b05c18-jill.heemsk <heemskjek@email.nih.gov>; en19 [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user40bea7fa-<en19@georgetown.edu>; Lamoureille, Gabrielle (HHS/OS/OGA) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2d3c3ba1840847b3af08ea0c4d0d137c1-Lamoureille, <Gabrielle.Lamoureille@hhs.gov>; Yarielka Arrieta [f:b(8)]_ gamers@gmail.com>; Hinton, Denise (FDA/OC) [T]: o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a90be508b91e4a19b4839a1ce4f4b75f-denise.hint <Denise.Hinton@fda.hhs.gov>

Subject: Canceled: USG-WHO MCM Dialogue Call

Date: 2020/05/20 17:50:37

Start Date: 2020/05/29 08:00:00

End Date: 2020/05/29 09:00:00

Importance: High

Priority: Urgent

Type: Appointment

Location: WebEx/ Zoom

Attendees:

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Conference Line Information:
Domestic: [b][6]
International: [b][5]
Participant Passcode: [b][6]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.
6/11/2020: Meeting canceled

-AL

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If you have any questions, please contact Arnela.Lopez@hhs.gov and Ana.Ayala@hhs.gov.
Subject: USG-WHO Dialogue on COVID-19 MCMs
Type: OLE.CLASS.(00061055-0000-0000-0000-000000000046)

Please join the USG-WHO Dialogue on COVID-19 MCMs. This week’s call will be on Friday, July 10 from 9 - 9:45 am ET/ 1500 - 1545 Geneva.

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International: [ ]
Participant Passcode: [ ]

If you have any questions, please contact Arnela.Lopez@hhs.gov and Ruvani.Chandrakerka@hhs.gov.

Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Please join the USG-WHO MCM Dialogue Call. This will be a biweekly call on Fridays from 8 to 9 am ET/1400-1500 Geneva.

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Larry Kerr, PhD
敬啓

吾屬之職務係伴隨著群眾生命之安全與健康。因此，我們致力於確保行政機關內之資訊安全。根據《資訊安全國家標準》之規定，任何非必要之資料交換均應避免。

此致

敬禮

[寄件人名]

P.S.

資料來源於[機構名稱]

TO:

Kerr, Lawrence (HHS/OS/OGA) / Exchange Labs / Exchange Administrative Group

Messonnier, Nancy (CDC/DDID/NCIRD/OD) / Exchange Labs / Exchange Administrative Group
Please join the USG-WHO MCM Dialogue Call on July 24. This will be a biweekly call on Fridays from 8 to 9 am DC/Atlanta, 1400-1500 Geneva.

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Larry Kerr, PhD
Director
Office of Pandemic and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
USG-WHO DIALOGUE ON COVID-19 MCMs

FRIDAY, 24 JULY 2020

14:00 – 15:00 (Geneva) | 8:00 – 9:00 (DC/Atlanta)

1. Welcome and roll call
   Ms. Ana Ayala, JD, LLM, Senior Global Health Officer, Pandemic and Emerging Threats, HHS/OGA

2. U.S. COVID-19 vaccine allocation/prioritization planning
   Dr. Kathleen Dooling, MD, MPH, Co-Lead, Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Work Group, Centers for Disease Control and Prevention (CDC)

3. Discussion
   All

4. Closing remarks and next steps
   Ms. Ana Ayala, JD, LLM, Senior Global Health Officer, Pandemic and Emerging Threats, HHS/OGA
Considerations for COVID-19 Vaccine Prioritization

Kathleen Dooling, MD MPH
Sarah Mbaeyi, MD MPH
Identifying priority groups for COVID-19 vaccination
An essential roadmap for vaccine program planning and implementation

- Although the goal is to offer vaccine to the entire U.S. population, identifying priority groups for COVID-19 vaccination is essential to support vaccine planning
  - Necessary to begin planning prior to vaccine approval to avoid delays

- Vaccine prioritization is challenging due to incomplete information on COVID-19 epidemiology and vaccines, including characteristics, timing, and number of doses

- Identifying priority groups: essential to start now with the information available to date, with continuous reassessment as data become available
Importance of identifying COVID-19 vaccine priority groups for implementation planning

- Strengthen vaccine distribution networks to reach target group
- Develop state and local microplans for vaccine implementation
- Create communications strategies to promote vaccination in priority groups
- Plan evaluations to rapidly monitor vaccine safety, effectiveness, and coverage
Lessons learned from pandemic influenza vaccination
Framework for COVID-19 prioritization and implementation planning
Pandemic influenza vaccine prioritization planning
Principles of pandemic vaccine planning to be adapted for COVID-19 vaccination

- 2005: ACIP and National Vaccine Advisory Committee outlined initial vaccine prioritization strategy
- 2007: Public and stakeholder engagement to identify priority groups during a pandemic
- 2008: Development of guidance for allocating and targeting influenza vaccine during a pandemic
- 2009: H1N1 influenza pandemic and vaccine implementation
H1N1 influenza pandemic

- Novel influenza A virus (H1N1) emerged in April 2009, leading to a global pandemic

- H1N1 vaccine became available in October 2009 during second wave of disease

- ACIP recommended priority groups for initial vaccination:
  - Persons at increased risk for severe disease
  - Healthcare personnel
H1N1 vaccine supply and demand

Estimated number of H1N1 cases and vaccine doses distributed – October 2009 to March 2010

Lessons learned from H1N1 vaccine prioritization

- Overly optimistic vaccine supply projections
- Restrictive enforcement of priority groups can lead to vaccine surpluses
- Challenges in expanding vaccination outside of the priority groups to the general public
- Importance of population values
- Need for state and local flexibility in implementation
- H1N1 experience: valuable lessons learned, though complexity of COVID-19 pandemic will lead to new challenges
Guidance for allocating and targeting pandemic influenza vaccine

- Updated in 2018 based on lessons learned from H1N1 pandemic
- Occupational and high risk populations grouped into tiers for prioritization
- Provides framework for adaptation to COVID-19 vaccine prioritization

Tiered approach to defining priority groups for vaccination

- Prioritization framework: roadmap for vaccine program planning
- Tiered priority groups to be adapted for COVID-19 based on:
  - Burden of disease and severity in risk groups
  - Impacts on society and critical infrastructure
  - Characteristics of vaccines
  - Number and timing of doses available
ACIP COVID-19 Vaccine Work Group

Considerations for identifying COVID-19 vaccine priority groups
Role of ACIP in identifying COVID-19 vaccine priority groups

- ACIP provides advice to the CDC director and HHS secretary on use of vaccines in the U.S. civilian population in a transparent, evidence-based process.

- To help inform ACIP deliberations around use of COVID-19 vaccines, the work group is reviewing:
  - Epidemiology of COVID-19
  - Characteristics of vaccine candidates under development
  - Evidence-based vaccine recommendation, ethics, and equity frameworks

https://www.cdc.gov/vaccines/acip/committee/charter.html
Work Group Considerations: Objectives of the COVID-19 Vaccine Program

- Ensure safety and effectiveness of COVID-19 vaccines
- Reduce transmission, morbidity, and mortality in the population
- Help minimize disruption to society and economy, including maintaining healthcare capacity
- Ensure equity in vaccine allocation and distribution
## Identifying vaccine priority groups: Current challenges and preliminary Work Group assumptions

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Work Group assumptions for prioritization</th>
</tr>
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<tbody>
<tr>
<td>Evolving understanding of COVID-19 epidemiology and immunology</td>
<td>• Prioritization should occur based on the information available to date and be continually refined based on data</td>
</tr>
<tr>
<td></td>
<td>• A substantial proportion of the U.S. population, regardless of age, location, or occupation, remains susceptible to COVID-19.</td>
</tr>
<tr>
<td>Current absence of data on safety and efficacy of COVID-19 vaccines</td>
<td>• Vaccines will not be administered until safety and efficacy have been demonstrated.</td>
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<td>• Concerns for reduced efficacy in certain populations (e.g., older adults, immunocompromised individuals) should not preclude their inclusion as priority groups while data are pending.</td>
</tr>
<tr>
<td>Unknown timing and number of vaccine doses</td>
<td>• Number of initial doses may not be sufficient to vaccinate everyone in the priority groups, necessitating sub-prioritization.</td>
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<tr>
<td></td>
<td>• Vaccine doses will become available in incremental quantities over several months.</td>
</tr>
</tbody>
</table>
### Work Group Considerations: Process for identifying proposed priority groups for COVID-19 vaccination

<table>
<thead>
<tr>
<th>Pandemic influenza framework for vaccine allocation</th>
<th>Principles of the Evidence to Recommendations (EtR) Framework</th>
<th>Ethics and equity principles</th>
</tr>
</thead>
<tbody>
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<td>- Burden of disease and severity</td>
<td>- Burden and severity of disease</td>
<td>- Minimize death and serious disease</td>
</tr>
<tr>
<td>- Pandemic severity and impacts on society</td>
<td>- Benefits and possible harms</td>
<td>- Preserve functioning of society</td>
</tr>
<tr>
<td>- Vaccine supply</td>
<td>- Values of the target population</td>
<td>- Reduce disproportionate burden on those with existing disparities</td>
</tr>
<tr>
<td></td>
<td>- Acceptability to stakeholders</td>
<td>Consideration should be give to:</td>
</tr>
<tr>
<td></td>
<td>- Feasibility of implementation</td>
<td>- Maximize benefits/minimize harms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Transparent, fair process</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Just, fair stewardship of vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Removing barriers to vaccination</td>
</tr>
</tbody>
</table>

Criteria for prioritization:

Work Group Considerations: Process for identifying proposed priority groups for COVID-19 vaccination

Proposed prioritization scheme:
• General approach for prioritization to help with operational planning for vaccine implementation
• Iterative process with priority groups to be refined as more information becomes available

Work Group considerations: Highest priority given to healthcare/essential workers and high-risk populations, followed by general population

Proposed priority group includes (to be further refined):
- Healthcare personnel
- Essential workers
- Adults aged ≥65 years
- Long term care facility residents
- Persons with high-risk medical conditions

* Based on 2019 U.S. population of 328 million and information from Department of Defense, Department of Homeland Security, Department of Health and Human Services, and U.S. Census Bureau
Work Group considerations: Among target groups, subset of critical healthcare and other workers should receive initial doses

Highest priority target group includes:
- Highest risk medical, national security, and other essential workers
- Rationale: protect healthcare infrastructure and other critical societal functions

* Based on 2019 U.S. population of 328 million and information from Department of Defense, Department of Homeland Security, Department of Health and Human Services, and U.S. Census Bureau.
Additional data to inform prioritization

- Remaining information gaps in certain population subgroups:
  - Risk of disease and severe outcomes
  - Vaccine safety and efficacy
  - Transmission dynamics and level of population immunity

- Additional data to inform prioritization will be helpful, though may need to make decisions in the setting of unknowns for vaccine implementation planning
ACIP COVID-19 Vaccine Work Group: Proposed Guiding Principles

- **Safety is paramount.** Vaccine safety standards will not be compromised in efforts to accelerate COVID-19 vaccine development.

- **Inclusive clinical trials.** Study participants should reflect groups at risk for COVID-19 to ensure safety and efficacy data are generalizable.

- **Efficient Distribution.** During a pandemic, efficient, expeditious and equitable distribution and administration of approved vaccine is critical.

- **Flexibility.** Within national guidelines, state and local jurisdictions should have flexibility to administer vaccine based on local epidemiology and demand.
“...a committee that will develop an overarching framework to assist policymakers in the U.S. and global health communities in planning for equitable allocation of vaccines against COVID-19”

To inform the decisions by health authorities, including the Advisory Committee on Immunization Practices (ACIP):

- What criteria should be used in setting priorities for equitable allocation of vaccine?
- How should the criteria be applied in determining the first tier of vaccine recipients?
- How can countries ensure equity in allocation of COVID-19 vaccines?
- For the US, how can communities of color be assured access to vaccination?
- What steps should be taken to mitigate vaccine hesitancy, especially among high-priority populations?
Summary

- Identifying priority groups for initial COVID-19 vaccination prior to approval of a vaccine is critical for implementation planning.

- Lessons learned from the H1N1 influenza pandemic highlight importance of national guidance while allowing for state/local flexibility in implementation.

- Work Group proposes priority groups for COVID-19 vaccination, including healthcare/essential workers and persons at increased risk for severe disease.

- Prioritization will need to be refined as more information becomes available.
Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
COVID-19 MCM USG-WHO MCM COOPERATION CALL

FRIDAY, 29 MAY 2020

15:00 – 16:00 (Geneva) | 9:00 – 10:00 ET

NOTES

Participants:

WHO: Dr. Soumya Swaminathan, Chief Scientist; Dr. Bruce Aylward, Secretariat for ACT Accelerator; Dr. Mariangela Simão, Assistant Director-General for Drug Access, Vaccines and Pharmaceuticals; Dr. Sylvie Brian, Director for Global Infectious Hazard Preparedness; Dr. Vasee Moorhy, Coordinator for Research and R&D, WHO; Kate O’Brien, Director of the Department of Immunization, Vaccines and Biologicals; Emer Cooke, Director of Regulation of Medicines and other Health Technologies.
Withheld pursuant to exemption

(b)(6)

of the Freedom of Information Act
Withheld pursuant to exemption
(b)(6)
of the Freedom of Information Act
Withheld pursuant to exemption (b)(6) of the Freedom of Information Act
USG-WHO DIALOGUE ON COVID-19 MCMs
FRIDAY, 10 JULY 2020
15:00 – 15:45 (Geneva) | 9:00 – 9:45 ET

NOTES

Participants:

**WHO:** Dr. Soumya Swaminathan, Chief Scientist; Dr. Bruce Aylward, Secretariat for ACT Accelerator; Dr. Mariangela Simão, Assistant Director-General for Drug Access, Vaccines and Pharmaceuticals;

**USG:** ASPR: Christopher Houchens, Division Director of the CBRN Program; CDC: Rita Helfand, Senior Advisor for Science in NCEZID/Office of the Director; Terri Hyde, Global Immunization Division; FDA: David Cho, Senior Scientist for Emerging & Pandemic Threat Preparedness, CBER; Michael Mair; NIH: Christine Sizemore, Director of the Division of International Relations, Fogarty International Center, NIH; Sarah Scharf, Regional Program Director, Europe and Multilateral Organizations, Fogarty International Center, NIH; OGA: Garrett Grigsby, Director of Global Affairs; Larry Kerr, Director of Pandemic and Emerging Threats (PET); Emily Bleimund, Director of Trade and Health; OWS: Dr. Kevin Bugin, Director of Special Programs, Office of New Drugs, CDER, and OWS Therapeutics Program Manager;
Withheld pursuant to exemption
(b)(5)
of the Freedom of Information Act
FYI. Will forward the dial in info when I get it

Sent from my iPhone

Begin forwarded message:

From: "Carson, Tracy L (Geneva)" <CarsonTL@state.gov>
Date: September 16, 2019 at 5:20:46 PM GMT+3
To: "Smith, Steven T (Geneva)" <SmithST1@state.gov>, "Martin, Rebecca (CDC/DDPHSIS/CGH/OD)" <trm4@cde.gov>, "Kerr, Lawrence" <Lawrence.Kerr@hhhs.gov>, "Grigsby, Garrett (HHS/OS/OGA)" <Garrett.Grigsby@hhhs.gov>
Cc: "Locus, Tiffany" <tiffany.locus@hhhs.gov>, "Mceff, Colin (HHS/OS/OGA)" <Colin.Mceff@hhhs.gov>, "Gabrielle.Lamoureille@hhhs.gov" <Gabrielle.Lamoureille@hhhs.gov>, "Levine, Maya" <maya.levine@hhhs.gov>, "Wood, Rachel (HHS/OS/OGA)" <Rachel.Wood@hhhs.gov>

Subject: WHO CALL: Follow-up on Ebola Vaccine demand estimates and expansion of vaccine availability (Sept 19)

Dear all –

Sharing across HHS OGA and CDC given travel schedules – per Mike Ryan’s email below – USG is invited to an informal “Ebola Vaccine demand estimates and expansion of vaccine availability”
meeting/teleconference, to provide an update of our estimates, progress and challenges with the implementation of the ring vaccination and specific updates on the implementation of the SAGE recommendations. The meeting/call will be on Thursday, Sept 19 from, 13:00-14:00 GVA. When the call-in number is sent out, I will forward to this group.

Best,
Tracy

Tracy Carson
Tel: +41 (0) 22 749 4623 | Mobile: [Phone number]

Unclassified

From: RYAN, Michael J. <ryanm@who.int>
Sent: Monday, September 16, 2019 3:26 PM
To: Garrett.Grisby@hhs.gov; OLX1@cdc.gov; Healy, Jenifer L. (AID/A) <jhealy@usaid.gov>; Cassayre, Mark J (Geneva) <CassayreMJ@state.gov>; Moley, Kevin E <MoleyKE@state.gov>; julian.braithwaite@fco.gov.uk; D-Graymore@dfid.gov.uk; molyneux@dfid.gov.uk; Suzukiyasuhiro@mhlw.go.jp; hori-hiroyuki@mhlw.go.jp; naoki.akahane@mofa.go.jp; takato.koizumi@mofa.go.jp; wi-1-io@grenf.auswaertiges-amt.de; Dagmar.Reitenbach@bmg.bund.de; Bjoern.Kuemmel@bm.bund.de; cab-andriukaitis-webpage@ec.europa.eu; drtheresa.tam@canada.ca
Cc: Carson, Tracy L (Geneva) <CarsonTL@state.gov>; wi-s1-io@grenf.auswaertiges-amt.de; Roisin.Fegan@fco.gov.uk; HENAO RESTREPO, Ana Maria <henaoestrepoa@who.int>; HOLDEN, Robert Andrew <holdenr@who.int>; KABIR, Sophia <kabirso@who.int>; FARES, Christine Youssef <faresc@who.int>
Subject: Follow-up on Ebola Vaccine demand estimates and expansion of vaccine availability

Dear Partners,

We would like to invite you or your delegated experts to an informal “Ebola Vaccine demand estimates and expansion of vaccine availability” meeting/teleconference, to provide an update of our estimates, progress and challenges with the implementation of the ring vaccination and specific updates on the implementation of the SAGE recommendations.

The meeting will take place on 19 September, from 13.00-14.00pm in the lower SHOC room of WHO HQ. A dial-in number will be provided shortly.

If you have any specific items you would like to discuss or if you would like to present any information at the meeting, please let us know.

We would be pleased if you could participate or designate a focal point who should join the meeting.

Many thanks,

Dr Michael J Ryan
Executive Director
WHO Emergencies Programme
<table>
<thead>
<tr>
<th><strong>Sender:</strong></th>
<th>Kerr, Lawrence (HHS/OS/OGA) /o=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=6CE9DE2E7497472B8758F8FD6E262C86-KERR, LAWRE <a href="mailto:Lawrence.Kerr@hhs.gov">Lawrence.Kerr@hhs.gov</a></th>
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</thead>
<tbody>
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<td><strong>Recipient:</strong></td>
<td>Damon, Inger K. (CDC/DDID/NCEZID/DHCPP) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=02b00deb66dcb44f5aca3f26ed15cdd6a-Damon, Inge <a href="mailto:ted7@cdc.gov">ted7@cdc.gov</a>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5b45def6a4dc0bb45f8fac629cf09-Disbrow, Ga <a href="mailto:Gary.Disbrow@hhs.gov">Gary.Disbrow@hhs.gov</a>; Marston, Hilary (NIH/NAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93be476c17024bbcb5b44add01fe6a8-hilary.mar <a href="mailto:hilary.marston@nih.gov">hilary.marston@nih.gov</a>; OGA PET Ebola /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=34d6eb178464429aa80da05d5c5c245-OGA-PET-Ebo <a href="mailto:OGA-PET-Ebola@hhs.gov">OGA-PET-Ebola@hhs.gov</a>; Helfand, Rita (CDC/DDID/NCEZID/OD) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=28a17ce03de24abb3e9c9e1363c4017-Helfand, Ri <a href="mailto:rzh7@cdc.gov">rzh7@cdc.gov</a>; Abram, Anna (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5d498ef533e4d2ea760cacc22e3aeaa-anna.abram. <a href="mailto:Anna.Abram@fda.hhs.gov">Anna.Abram@fda.hhs.gov</a>; Marks, Peter (FDA/CBER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=df56588b970c43c8a2b9b31406746c-peter.marks <a href="mailto:Peter.Marks@fda.hhs.gov">Peter.Marks@fda.hhs.gov</a></td>
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The teams continue to vaccinate with rVSV ZEBOV GP (with informed consent) a large number of people at risk in the context of the outbreak

Data as of September 15 2019

### Total consented and vaccinated

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total consented and vaccinated</td>
<td>221'841</td>
<td></td>
</tr>
<tr>
<td>Contacts</td>
<td>54'921</td>
<td>24.7%</td>
</tr>
<tr>
<td>Contacts of contacts</td>
<td>152'646</td>
<td>69%</td>
</tr>
<tr>
<td>Possible Contacts</td>
<td>14'160</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

### Those vaccinated included the following populations:

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCWs/FLWS</td>
<td>45'927</td>
<td>20.7%</td>
</tr>
<tr>
<td>Children 6-11 months</td>
<td>1'157</td>
<td>0.5%</td>
</tr>
<tr>
<td>Children 1-17 year old</td>
<td>72'101</td>
<td>32.5%</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>796</td>
<td>0.4%</td>
</tr>
<tr>
<td>Breastfeeding Women</td>
<td>3'993</td>
<td>1.8%</td>
</tr>
<tr>
<td>Other groups</td>
<td>123'067</td>
<td>55.9%</td>
</tr>
</tbody>
</table>

---

**Total consented and vaccinated**

- Possible Contacts: 14,160 (6%)
- Contacts: 54,921 (25%)

**Contacts of contacts:**

- 152,646 (69%)
Cases of EVD with rings defined, ongoing or pending North Kivu, South Kivu and...
Vaccination activities - Daily number of doses administered

Date de vaccination

World Health Organization

HEALTH EMERGENCIES programme
Cases of EVD with rings defined, ongoing or pending North Kivu, South Kivu and

- Ring vax suspended
- Ring vax ongoing
- Ring definition ongoing
- Ring vax completed

<table>
<thead>
<tr>
<th>Location</th>
<th>Ring vax suspended</th>
<th>Ring vax ongoing</th>
<th>Ring definition ongoing</th>
<th>Ring vax completed</th>
</tr>
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<tbody>
<tr>
<td>BENI</td>
<td></td>
<td>10</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>BIENA</td>
<td></td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>BUTEMBO</td>
<td></td>
<td>14</td>
<td></td>
<td>11</td>
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<tr>
<td>KALUNGUTA</td>
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<tr>
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<td>17</td>
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<td>5</td>
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<tr>
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<td>3</td>
</tr>
<tr>
<td>MWENGA</td>
<td></td>
<td>2</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>
549 people vaccinated on Sept 15, 2019