

RESUME AND SUMMARY OF DISCUSSION:

(b) (5)

DESCRIPTION (provided by applicant): This project will examine the risk of future coronavirus (CoV) emergence from wildlife using in-depth field investigations across the human-wildlife interface in China, molecular characterization of novel CoVs and host receptor binding domain genes, mathematical models of transmission and evolution, and in vitro and in vivo laboratory studies of host range. Zoonotic CoVs are a significant threat to global health, as demonstrated with the emergence of pandemic severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002, and the recent and ongoing emergence of Middle East Respiratory Syndrome (MERS-CoV). Bats appear to be the natural reservoir of these viruses, and hundreds of novel bat-CoVs have been discovered in the last two decades. Bats, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a large scale human-wildlife interface, and high risk of future emergence of novel CoVs. This project aims to understand what factors increase the risk of the next CoV emerging in people by studying CoV diversity in a critical zoonotic reservoir (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China). The three specific aims of this project are to: 1. Assess CoV spillover potential at high risk human-wildlife interfaces in China. This will include quantifying the nature and frequency of contact people have with bats and other wildlife; serological and molecular screening of people working in wet markets and highly exposed to wildlife; screening wild-caught and market sampled bats from 30+ species for CoVs using molecular assays; and genomic characterization and isolation of novel CoVs. 2. Develop predictive models of bat CoV emergence risk and host range. A combined modeling approach will include phylogenetic analyses of host receptors and novel CoV genes (including functional receptor binding domains); a fused ecological and evolutionary model to predict host-range and viral sharing; and mathematical matrix models to examine evolutionary and transmission dynamics. 3. Test predictions of CoV inter-species transmission. Predictive models of host range (i.e. emergence potential) will be tested experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments across a range of cell cultures from different species and humanized mice.

PUBLIC HEALTH RELEVANCE: Most emerging human viruses come from wildlife, and these represent a significant threat to global public health and biosecurity - as demonstrated by the SARS coronavirus pandemic of 2002-03 and an ongoing SARS-like epidemic in the Middle East. This project seeks to understand what factors allow animal Coronaviruses to evolve and jump into the human population by studying virus diversity in a critical group of animals (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China).

CRITIQUE 1:

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Overall Impact:

(b) (5)

1. Significance:

(b) (5)

2. Investigator(s):

(b) (5)

(b) (5)



3. Innovation:

(b) (5)



4. Approach:

(b) (5)



5. Environment:

(b) (5)



(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2:

(b) (5)

(b) (5)

Overall Impact: (b) (5)

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1. Significance:

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2. Investigator(s):

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3. Innovation:

(b) (5)

4. Approach:

(b) (5)

5. Environment:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3:

(b) (5)

Overall Impact:

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1. Significance:

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2. Investigator(s):

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3. Innovation:

(b) (5)

4. Approach:

(b) (5)

5. Environment:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Budget and Period of Support:

(b) (5)

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume):

(b) (5)

PROTECTIONS FOR HUMAN SUBJECTS (Resume):

(b) (5)

(b) (5)

INCLUSION OF WOMEN PLAN (Resume):

(b) (5)

INCLUSION OF MINORITIES PLAN (Resume):

(b) (5)

INCLUSION OF CHILDREN PLAN (Resume):

(b) (5)

VERTEBRATE ANIMALS (Resume):

(b) (5)

BUDGETARY OVERLAP:

(b) (5)

COMMITTEE BUDGET RECOMMENDATIONS:

(b) (5)

RESUME AND SUMMARY OF DISCUSSION:

DESCRIPTION (provided by applicant): This project will examine the risk of future coronavirus (CoV) emergence from wildlife using in-depth field investigations across the human-wildlife interface in China, molecular characterization of novel CoVs and host receptor binding domain genes, mathematical models of transmission and evolution, and in vitro and in vivo laboratory studies of host range. Zoonotic CoVs are a significant threat to global health, as demonstrated with the emergence of pandemic severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002, and the recent and ongoing emergence of Middle East Respiratory Syndrome (MERS-CoV). Bats appear to be the natural reservoir of these viruses, and hundreds of novel bat-CoVs have been discovered in the last two decades. Bats, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs. This project aims to understand what factors increase the risk of the next CoV emerging in people by studying CoV diversity in a critical zoonotic reservoir (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China). The three specific aims of this project are to: 1. Assess CoV spillover potential at high risk human-wildlife interfaces in China. This will include quantifying the nature and frequency of contact people have with bats and other wildlife; serological and molecular screening of people working in wet markets and highly exposed to wildlife; screening wild-caught and market sampled bats from 30+ species for CoVs using molecular assays; and genomic characterization and isolation of novel CoVs. 2. Develop predictive models of bat CoV emergence risk and host range. A combined modeling approach will include phylogenetic analyses of host receptors and novel CoV genes (including functional receptor binding domains); a fused ecological and evolutionary model to predict host-range and viral sharing; and mathematical matrix models to examine evolutionary and transmission dynamics. 3. Test predictions of CoV inter-species transmission. Predictive models of host range (i.e. emergence potential) will be tested experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments across a range of cell cultures from different species and humanized mice.

PUBLIC HEALTH RELEVANCE: Most emerging human viruses come from wildlife, and these represent a significant threat to global public health and biosecurity - as demonstrated by the SARS coronavirus pandemic of 2002-03 and an ongoing SARS-like epidemic in the Middle East. This project seeks to understand what factors allow animal Coronaviruses to evolve and jump into the human population by studying virus diversity in a critical group of animals (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China).

CRITIQUE 1:

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Overall Impact:

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(b) (5)



1. Significance:

(b) (5)



2. Investigator(s):

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3. Innovation:

(b) (5)



4. Approach:

(b) (5)



5. Environment:

(b) (5)



Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2:

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(b) (5)

Overall Impact: A (b) (5)

1. Significance:

(b) (5)

2. Investigator(s):

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3. Innovation:

(b) (5)

4. Approach:

(b) (5)

(b) (5)

5. Environment:

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Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Resource Sharing Plans:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3:

(b) (5)

Overall Impact:

(b) (5)

1. Significance:

(b) (5)

2. Investigator(s):

(b) (5)

(b) (5)

3. Innovation:

(b) (5)

4. Approach:

(b) (5)

5. Environment:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Budget and Period of Support:

(b) (5)

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume):

(b) (5)

INCLUSION OF WOMEN PLAN (Resume):

(b) (5)

INCLUSION OF MINORITIES PLAN (Resume):

(b) (5)

INCLUSION OF CHILDREN PLAN (Resume)

(b) (5)

VERTEBRATE ANIMAL (Resume):

(b) (5)

COMMITTEE BUDGET RECOMMENDATIONS:

(b) (5)

RESUME AND SUMMARY OF DISCUSSION:

DESCRIPTION (provided by applicant): Project Summary This project will examine the risk of future coronavirus (CoV) emergence from wildlife using in-depth field investigations across the human-wildlife interface in China, molecular characterization of novel CoVs and host receptor binding domain genes, mathematical models of transmission and evolution, and in vitro and in vivo laboratory studies of host range. Zoonotic CoVs are a significant threat to global health, as demonstrated with the emergence of pandemic severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002, and the recent and ongoing emergence of Middle East Respiratory Syndrome (MERS-CoV). Bats appear to be the natural reservoir of these viruses, and hundreds of novel bat-CoVs have been discovered in the last two decades. Bats, and other wildlife species, are hunted, traded, butchered and consumed across Asia, creating a largescale human-wildlife interface, and high risk of future emergence of novel CoVs. This project aims to understand what factors increase the risk of the next CoV emerging in people by studying CoV diversity in a critical zoonotic reservoir (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China). The three specific aims of this project are to: 1. Assess CoV spillover potential at high risk human-wildlife interfaces in China. This will include quantifying the nature and frequency of contact people have with bats and other wildlife; serological and molecular screening of people working in wet markets and highly exposed to wildlife; screening wild-caught and market sampled bats from 30+ species for CoVs using molecular assays; and genomic characterization and isolation of novel CoVs. 2. Develop predictive models of bat CoV emergence risk and host range. A combined modeling approach will include phylogenetic analyses of host receptors and novel CoV genes (including functional receptor binding domains); a fused ecological and evolutionary model to predict host-range and viral sharing; and mathematical matrix models to examine evolutionary and transmission dynamics. 3. Test predictions of CoV inter-species transmission. Predictive models of host range (i.e. emergence potential) will be tested experimentally using reverse genetics, pseudovirus and receptor binding assays, and virus infection experiments across a range of cell cultures from different species and humanized mice.

PUBLIC HEALTH RELEVANCE: PROJECT NARRATIVE Most emerging human viruses come from wildlife, and these represent a significant threat to global public health and biosecurity - as demonstrated by the SARS coronavirus pandemic of 2002-03 and an ongoing SARS-like epidemic in the Middle East. This project seeks to understand what factors allow animal Coronaviruses to evolve and jump into the human population by studying virus diversity in a critical group of animals (bats), at sites of high risk for emergence (wildlife markets) in an emerging disease hotspot (China).

CRITIQUE 1:

(b) (5)



Principal Investigator(s): Daszak

Overall Impact:

(b) (5)



1. Significance:

(b) (5)



2. Investigator(s):

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3. Innovation:

(b) (5)



4. Approach:

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5. Environment:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2:

(b) (5)

Application #:

Principal Investigator(s):

Overall Impact

(b) (5)

1. Significance:

(b) (5)

2. Investigator(s):

(b) (5)

3. Innovation:

(b) (5)

4. Approach:

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5. Environment:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Resource Sharing Plans:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3:

(b) (5)

Application #:

Principal Investigator(s): Daszak

Overall Impact:

(b) (5)

1. Significance:

(b) (5)

2. Investigator(s):

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3. Innovation:

(b) (5)

(b) (5)

4. Approach:

(b) (5)

Weaknesses

(b) (5)

5. Environment:

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Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Budget and Period of Support:

(b) (5)

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume):

(b) (5)

INCLUSION OF WOMEN PLAN (Resume):

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INCLUSION OF MINORITIES PLAN (Resume):

(b) (5)

INCLUSION OF CHILDREN PLAN (Resume):

(b) (5)

VERTEBRATE ANIMAL (Resume):

(b) (5)

COMMITTEE BUDGET RECOMMENDATIONS:

(b) (5)

RESUME AND SUMMARY OF DISCUSSION:

DESCRIPTION (provided by applicant): Understanding the Risk of Bat Coronavirus Emergence
Novel zoonotic, bat-origin CoVs are a significant threat to global health and food security, as the cause of SARS in China in 2002, the ongoing outbreak of MERS, and of a newly emerged Swine Acute Diarrhea Syndrome in China. In a previous R01 we found that bats in southern China harbor an extraordinary diversity of SARSr-CoVs, some of which can use human ACE2 to enter cells, infect humanized mouse models causing SARS-like illness, and evade available therapies or vaccines. We found that people living close to bat habitats are the primary risk groups for spillover, that at one site diverse SARSr-CoVs exist that contain every genetic element of the SARS-CoV genome, and identified serological evidence of human exposure among people living nearby. These findings have led to 18 published peer-reviewed papers, including two papers in Nature, and a review in Cell. Yet salient questions remain on the origin, diversity, capacity to cause illness, and risk of spillover of these viruses. In this R01 renewal we will address these issues through 3 specific aims: Aim 1. Characterize the diversity and distribution of high spillover-risk SARSr-CoVs in bats in southern China. We will use phylogeographic and viral discovery curve analyses to target additional bat sample collection and molecular CoV screening to fill in gaps in our previous sampling and fully characterize natural SARSr-CoV diversity in southern China. We will sequence receptor binding domains (spike proteins) to identify viruses with the highest potential for spillover which we will include in our experimental investigations (Aim 3). Aim 2. Community, and clinic-based syndromic, surveillance to capture SARSr-CoV spillover, routes of exposure and potential public health consequences. We will conduct biological-behavioral surveillance in high-risk populations, with known bat contact, in community and clinical settings to 1) identify risk factors for serological and PCR evidence of bat SARSr-CoVs; & 2) assess possible health effects of SARSr-CoVs infection in people. We will analyze bat-CoV serology against human-wildlife contact and exposure data to quantify risk factors and health impacts of SARSr-CoV spillover. Aim 3. In vitro and in vivo characterization of SARSr-CoV spillover risk, coupled with spatial and phylogenetic analyses to identify the regions and viruses of public health concern. We will use S protein sequence data, infectious clone technology, in vitro and in vivo infection experiments and analysis of receptor binding to test the hypothesis that % divergence thresholds in S protein sequences predict spillover potential. We will combine these data with bat host distribution, viral diversity and phylogeny, human survey of risk behaviors and illness, and serology to identify SARSr-CoV spillover risk hotspots across southern China. Together these data and analyses will be critical for the future development of public health interventions and enhanced surveillance to prevent the re-emergence of SARS or the emergence of a novel SARSr-CoV.

PUBLIC HEALTH RELEVANCE: Most emerging human viruses come from wildlife, and these represent a significant threat to public health and biosecurity in the US and globally, as was demonstrated by the SARS coronavirus pandemic of 2002-03. This project seeks to understand what factors allow coronaviruses, including close relatives to SARS, to evolve and jump into the human population by studying viral diversity in their animal reservoirs (bats), surveying people that live in high-risk communities in China for evidence of bat-coronavirus infection, and conducting laboratory experiments to analyze and predict which newly-discovered viruses pose the greatest threat to human health.

CRITIQUE 1

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Overall Impact:

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1. Significance:

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2. Investigator(s):

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3. Innovation:

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4. Approach:

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5. Environment:

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Study Timeline:

(b) (5)

Protections for Human Subjects:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Renewal:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2

(b) (5)

Overall Impact:

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1. Significance:

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2. Investigator(s):

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3. Innovation:

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4. Approach:

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5. Environment:

(b) (5)



Study Timeline:

(b) (5)



Protections for Human Subjects:

(b) (5)



Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Renewal:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3

(b) (5)

Overall Impact:

(b) (5)

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS:

(b) (5)

INCLUSION OF WOMEN PLAN:

(b) (5)

INCLUSION OF MINORITIES PLAN:

(b) (5)

INCLUSION OF CHILDREN PLAN:

(b) (5)

VERTEBRATE ANIMALS:

(b) (5)

COMMITTEE BUDGET RECOMMENDATIONS:

(b) (5)

RESUME AND SUMMARY OF DISCUSSION: This outstanding application seeks to understand what factors allow coronaviruses, including close relatives to SARS, to evolve and emerge in the human population by studying viral diversity in their animal reservoirs (bats), surveying people that live in high-risk communities in China for evidence of bat-coronavirus infection, and conducting laboratory experiments to analyze and predict which newly-discovered viruses pose the greatest threat to human health. The renewal application follows a very productive and impressive founding period. The premise is strong. The goal of the application is highly significant; the knowledge gained will be very important for the future development of public health intervention. Other strengths are the productivity and the expertise of the investigator, the expertise of the enlisted collaborator, the innovative reverse genetic approach in aim 3, the rigorous sampling and the preliminary data. Although it is noted that sample size is optimistic, and the clinical valuation may not be powered, there remains high confidence in the ability of the investigative team and the impact of the proposed studies.

DESCRIPTION (provided by applicant): Understanding the Risk of Bat Coronavirus Emergence
Novel zoonotic, bat-origin CoVs are a significant threat to global health and food security, as the cause of SARS in China in 2002, the ongoing outbreak of MERS, and of a newly emerged Swine Acute Diarrhea Syndrome in China. In a previous R01 we found that bats in southern China harbor an extraordinary diversity of SARSr-CoVs, some of which can use human ACE2 to enter cells, infect humanized mouse models causing SARS-like illness, and evade available therapies or vaccines. We found that people living close to bat habitats are the primary risk groups for spillover, that at one site diverse SARSr-CoVs exist that contain every genetic element of the SARS-CoV genome, and identified serological evidence of human exposure among people living nearby. These findings have led to 18 published peer-reviewed papers, including two papers in Nature, and a review in Cell. Yet salient questions remain on the origin, diversity, capacity to cause illness, and risk of spillover of these viruses. In this R01 renewal we will address these issues through 3 specific aims: Aim 1. Characterize the diversity and distribution of high spillover-risk SARSr-CoVs in bats in southern China. We will use phylogeographic and viral discovery curve analyses to target additional bat sample collection and molecular CoV screening to fill in gaps in our previous sampling and fully characterize natural SARSr-CoV diversity in southern China. We will sequence receptor binding domains (spike proteins) to identify viruses with the highest potential for spillover which we will include in our experimental investigations (Aim 3). Aim 2. Community, and clinic-based syndromic, surveillance to capture SARSr-CoV spillover, routes of exposure and potential public health consequences. We will conduct biological-behavioral surveillance in high-risk populations, with known bat contact, in community and clinical settings to 1) identify risk factors for serological and PCR evidence of bat SARSr-CoVs; & 2) assess possible health effects of SARSr-CoVs infection in people. We will analyze bat-CoV serology against human-wildlife contact and exposure data to quantify risk factors and health impacts of SARSr-CoV spillover. Aim 3. In vitro and in vivo characterization of SARSr-CoV spillover risk, coupled with spatial and phylogenetic analyses to identify the regions and viruses of public health concern. We will use S protein sequence data, infectious clone technology, in vitro and in vivo infection experiments and analysis of receptor binding to test the hypothesis that % divergence thresholds in S protein sequences predict spillover potential. We will combine these data with bat host distribution, viral diversity and phylogeny, human survey of risk behaviors and illness, and serology to identify SARSr-CoV spillover risk hotspots across southern China. Together these data and analyses will be critical for the future development of public health interventions and enhanced surveillance to prevent the re-emergence of SARS or the emergence of a novel SARSr-CoV.

PUBLIC HEALTH RELEVANCE: Most emerging human viruses come from wildlife, and these represent a significant threat to public health and biosecurity in the US and globally, as was demonstrated by the SARS coronavirus pandemic of 2002-03. This project seeks to understand what factors allow coronaviruses, including close relatives to SARS, to evolve and jump into the human

population by studying viral diversity in their animal reservoirs (bats), surveying people that live in high-risk communities in China for evidence of bat-coronavirus infection, and conducting laboratory experiments to analyze and predict which newly-discovered viruses pose the greatest threat to human health.

CRITIQUE 1

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Overall Impact:

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1. Significance:

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2. Investigator(s):

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3. Innovation:

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4. Approach:

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5. Environment:

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Protections for Human Subjects:

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Inclusion of Women, Minorities and Children:

(b) (5)



Vertebrate Animals:

(b) (5)



Biohazards:

(b) (5)

Renewal:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2

(b) (5)

Overall Impact:

(b) (5)

1. Significance:

(b) (5)

(b) (5)



2. Investigator(s):

(b) (5)



3. Innovation:

(b) (5)



(b) (5)

4. Approach:

(b) (5)

5. Environment:

(b) (5)

Study Timeline:

(b) (5)

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Renewal:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3

(b) (5)



Overall Impact:

(b) (5)



Protections for Human Subjects:

(b) (5)



Inclusion of Women, Minorities and Children:

(b) (5)



Vertebrate Animals:

(b) (5)



Biohazards:

(b) (5)



Select Agents:

(b) (5)



Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

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PROTECTION OF HUMAN SUBJECTS:

(b) (5)

INCLUSION OF WOMEN PLAN:

(b) (5)

INCLUSION OF MINORITIES PLAN:

(b) (5)

INCLUSION OF CHILDREN PLAN:

(b) (5)

VERTEBRATE ANIMALS:

(b) (5)

COMMITTEE BUDGET RECOMMENDATIONS:

(b) (5)

RESUME AND SUMMARY OF DISCUSSION:

DESCRIPTION (provided by applicant):Project Summary: Understanding the Risk of Bat Coronavirus Emergence Novel zoonotic, bat-origin CoVs are a significant threat to global health and food security, as the cause of SARS in China in 2002, the ongoing outbreak of MERS, and of a newly emerged Swine Acute Diarrhea Syndrome in China. In a previous R01 we found that bats in southern China harbor an extraordinary diversity of SARSr-CoVs, some of which can use human ACE2 to enter cells, infect humanized mouse models causing SARS-like illness, and evade available therapies or vaccines. We found that people living close to bat habitats are the primary risk groups for spillover, that at one site diverse SARSr-CoVs exist that contain every genetic element of the SARS-CoV genome, and identified serological evidence of human exposure among people living nearby. These findings have led to 18 published peer-reviewed papers, including two papers in Nature, and a review in Cell. Yet salient questions remain on the origin, diversity, capacity to cause illness, and risk of spillover of these viruses. In this R01 renewal we will address these issues through 3 specific aims: Aim 1. Characterize the diversity and distribution of high spillover-risk SARSr-CoVs in bats in southern China. We will use phylogeographic and viral discovery curve analyses to target additional bat sample collection and molecular CoV screening to fill in gaps in our previous sampling and fully characterize natural SARSr-CoV diversity in southern China. We will sequence receptor binding domains (spike proteins) to identify viruses with the highest potential for spillover which we will include in our experimental investigations (Aim 3). Aim 2. Community, and clinic-based syndromic, surveillance to capture SARSr-CoV spillover, routes of exposure and potential public health consequences. We will conduct biological-behavioral surveillance in high-risk populations, with known bat contact, in community and clinical settings to 1) identify risk factors for serological and PCR evidence of bat SARSr-CoVs; & 2) assess possible health effects of SARSr-CoVs infection in people. We will analyze bat-CoV serology against human-wildlife contact and exposure data to quantify risk factors and health impacts of SARSr-CoV spillover. Aim 3. In vitro and in vivo characterization of SARSr-CoV spillover risk, coupled with spatial and phylogenetic analyses to identify the regions and viruses of public health concern. We will use S protein sequence data, infectious clone technology, in vitro and in vivo infection experiments and analysis of receptor binding to test the hypothesis that % divergence thresholds in S protein sequences predict spillover potential. We will combine these data with bat host distribution, viral diversity and phylogeny, human survey of risk behaviors and illness, and serology to identify SARSr-CoV spillover risk hotspots across southern China. Together these data and analyses will be critical for the future development of public health interventions and enhanced surveillance to prevent the re-emergence of SARS or the emergence of a novel SARSr-CoV.

PUBLIC HEALTH RELEVANCE

Program Director/Principal Investigator: Daszak, Peter Renewal: Understanding the Risk of Bat Coronavirus Emergence Project Narrative Most emerging human viruses come from wildlife, and these represent a significant threat to public health and biosecurity in the US and globally, as was demonstrated by the SARS coronavirus pandemic of 2002-03. This project seeks to understand what factors allow coronaviruses, including close relatives to SARS, to evolve and jump into the human population by studying viral diversity in their animal reservoirs (bats), surveying people that live in high-risk communities in China for evidence of bat-coronavirus infection, and conducting laboratory experiments to analyze and predict which newly-discovered viruses pose the greatest threat to human health.

CRITIQUE 1

(b) (5)

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Application #: 2 R01 AI110964-06

Principal Investigator(s): Daszak, Peter

Overall Impact:

(b) (5)

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1. Significance:

(b) (5)

A rectangular gray box used for redaction, located at the bottom of the page under the '1. Significance:' section header.

(b) (5)

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2. Investigator(s):

(b) (5)

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3. Innovation:

(b) (5)

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4. Approach:

(b) (5)

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(b) (5)

5. Environment:

(b) (5)

Study Timeline:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Resubmission:

(b) (5)

Renewal:

(b) (5)

Revision:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 2

(b) (5)

Application #: 2 R01 AI110964-06

Principal Investigator(s): Daszak

2

Overall Impact

(b) (5)

(b) (5)



1. Significance:

(b) (5)



2. Investigator(s):

(b) (5)



3. Innovation:

(b) (5)



4. Approach:

(b) (5)



5. Environment:

(b) (5)



(b) (5)

Study Timeline:

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Resubmission:

(b) (5)

Renewal:

(b) (5)

Revision:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

CRITIQUE 3

(b) (5)

Application #: PETER DASZAK R01 AI110964-06

Principal Investigator(s): PETER DASZAK

Overall Impact:

(b) (5)

Study Timeline:

(b) (5)

(b) (5)

Protections for Human Subjects:

(b) (5)

Inclusion of Women, Minorities and Children:

(b) (5)

Vertebrate Animals:

(b) (5)

Biohazards:

(b) (5)

Resubmission:

(b) (5)

Renewal:

(b) (5)

Revision:

(b) (5)

Applications from Foreign Organizations:

(b) (5)

Select Agents:

(b) (5)

Resource Sharing Plans:

(b) (5)

Authentication of Key Biological and/or Chemical Resources:

(b) (5)

Budget and Period of Support:

(b) (5)

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS:

(b) (5)

INCLUSION OF WOMEN PLAN: [REDACTED] (b) (5)

INCLUSION OF MINORITIES PLAN: [REDACTED] (b) (5)

INCLUSION OF CHILDREN PLAN: [REDACTED] (b) (5)

VERTEBRATE ANIMALS: [REDACTED] (b) (5)

COMMITTEE BUDGET RECOMMENDATIONS: [REDACTED] (b) (5)

From: Pyper, Joanna (NIH/CSR) [E]
Sent: Sat, 22 Jun 2013 16:34:26 -0400
To: [REDACTED] (b) (6)
Cc: Saadi, Soheyla (NIH/CSR) [E]
Subject: study section assignment of your NIH application

Dear Dr. Daszak,

I am writing with respect to your application "Understanding the Risk of Bat Coronavirus Emergence". I note that you request that VIRA review your application. CSR staff has carefully considered your application within the context of its scientific content, the focus of the individual study sections, and the expertise available in each of these study sections. The staff has determined that the most appropriate study section to review your application is [CRFS](#). Your application has been assigned to CRFS. Please rest assured that a competent team of reviewers will be assembled to assess the scientific merit of your application. If you have questions concerning this matter, please do not hesitate to communicate with me.

Sincerely,
Jody Pyper

Joanna M. Pyper, Ph.D.
Deputy Chief, Infectious Diseases and Microbiology IRG
Scientific Review Officer, Virology A (VIRA)
6701 Rockledge Drive, Room 3208, MSC 7808
Bethesda, MD 20892
(For delivery services, use 20817)
Telephone: [REDACTED] (b) (6)
FAX: 301-480-0940
e-mail: [REDACTED] (b) (6)

From: Saadi, Soheyla (NIH/CSR) [E]
Sent: Wed, 28 Aug 2013 11:13:05 +0000
To: (b) (6)
Subject: Review Process of Your NIH Application

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review, Bethesda, Maryland 20892

Soheyla Saadi, Ph.D

Phone (b) (6)

Email: (b) (6)

August 28, 2013

FROM: Soheyla Saadi, PhD, Scientific Review Officer, CRFS Study Section

TO: DASZAK, PETER

Application: 1R01AI110964-01

Title: Understanding the Risk of Bat Coronavirus Emergence

SUBJECT: Review Process of Your NIH Application

Dear Investigator:

I am the Scientific Review Officer (SRO) for CRFS study section which will review your NIH application on **October 7, 2013**. The purpose of this E-mail message is to provide you with some information concerning the review process. You may contact me about the review of your application **PRIOR** to the Study Section meeting. In addition, to a Study Section, your application is also assigned to a Program Officer who will be your primary point of contact **AFTER** the Study Section meeting.

Please note that the NIH has changed its policy on post-submission of grant application materials prior to Study Section meeting.

New policy can be found at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-115.html>

Under this policy, the following post-submission materials are NOT acceptable:

- Updated Specific Aims or Research Strategy pages
- Late-breaking research findings
- New letters of support or collaboration that do not result from a change in senior/key personnel due to the loss of an investigator

Acceptable post-submission materials include:

- **News** of an article accepted for publication (**DO NOT send a copy of the article**)
- Revised budget page(s) (e.g., change in budget request **due to new funding or institutional acquisition of equipment**)
- Biographical sketches (e.g., change in senior/key personnel **due to the hiring, replacement, or loss of an investigator**)
- Letters of support or collaboration resulting from a change in **senior/key personnel due to the hiring, replacement, or loss of an investigator**
- Adjustments resulting from natural **disasters** (e.g., loss of an animal colony)
- Adjustments resulting from **change of institution** (e.g., PI moves to another university)

Acceptable post-submission materials must be received by 5 pm ET, September 6 (30 calendar days prior to the peer review meeting). **Concurrence from the Authorized Organization Representative (AOR) of the applicant organization is required.** Although the content of post-submission materials may originate from the PD/PI, Contact PD/PI for multiple PD/PI applications, or organizational officials, the AOR must send the materials directly to **me**, or must send his/her concurrence to the PD/PI who will forward the materials and concurrence to the me. **A communication from the PD/PI only or with a "cc" to the AOR will not be accepted.**

Where can you find Rosters?

To see the previous rosters and the roster for the upcoming meeting roster, refer to CSR Study Section Roster Index "[Study Section Rosters](#)". Choose [Standing Study Section Rosters](#) from there you can reach the [CRFS](#) roster information links. The final roster for this meeting will be posted 30 day before the meeting.

Confidentiality of the Review Process

It is **inappropriate** for you, or anyone on your behalf, to contact a study section member regarding the review of your grant application either before or after the meeting of the study section. For a variety of reasons, **reviewers are instructed not to discuss anything about the review with anyone not at the study section meeting.** Questions and comments should be addressed to **me (SRO)** prior to the meeting and the Program Official after the meeting.

WHEN WILL SCORES / SUMMARY STATEMENTS BE AVAILABLE?

Scores will be released to the NIH computer within **three working** days after the meeting. Summary statements will be available within **30 days** after the meeting.

My goal is to facilitate a **fair** and **thorough** review of your application. If you have any questions or concerns, please contact me.

Sincerely,

Soheyla Saadi, Ph.D.

Scientific Review Officer

CRFS- [Clinical Research and Field Studies of Infectious Diseases Study Section](#)

ZRG1 IDM-R (50) International Research in Infectious Diseases including AIDS (IRIDA)

Infectious Diseases and Microbiology IRG

Center for Scientific Review, National Institutes of Health, DHHS

6701 Rockledge Dr, Room 3194 MSC 7808 Bethesda, MD 20892

Phone (b) (6) Fax 301-480-0940

Email: (b) (6)



From: Aleksei Chmura
Sent: Tue, 3 Sep 2013 13:50:10 +0000
To: Saadi, Soheyla (NIH/CSR) [E]
Cc: Peter Daszak; Megan Walsh
Subject: Post-Submission Letter for NIH Application "Understanding the Risk of Bat Coronavirus Emergence" (1R01AI110964-01)
Attachments: Daszak PI Understanding risk of bat coronavirus emergence - postsubmission letter.pdf, ATT00001.txt
Importance: High

Dear Dr. Saadi,

Please find attached to this email a short, post-submission letter (one-page) from lead PI, Dr. Peter Daszak, with news of two articles just accepted for publication providing additional support for our team's capacity to conduct significant international collaborative research on coronaviruses. Our proposal is entitled "Understanding the Risk of Bat Coronavirus Emergence" (1R01AI110964-01). As AOR, I concur with Dr. Daszak's news and approve of the letter.

If you have any questions or require modifications of the letter or this email, let me know anytime.

Many thanks most,

Sincerely,

Aleksei Chmura
Authorized Organizational Representative
EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(b) (6) (direct)

(b) (6) (mobile)

Visit our blog: www.ecohealthalliance.org/blog

EcoHealth Alliance integrates innovative science-based solutions and partnerships that increase capacity to achieve two interrelated goals: protecting global health by preventing the outbreak of emerging diseases and safeguarding ecosystems by promoting conservation.

From: Saadi, Soheyla (NIH/CSR) [E] (b) (6)
Sent: Wednesday, August 28, 2013 7:13 AM
To: Peter Daszak
Subject: Review Process of Your NIH Application

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Center for Scientific Review, Bethesda, Maryland 20892

Soheyla Saadi, Ph.D
Phone (b) (6)
Email: (b) (6)
August 28, 2013

FROM: Soheyla Saadi, PhD, Scientific Review Officer, CRFS Study Section
TO: DASZAK, PETER

Application: 1R01AI110964-01
Title: Understanding the Risk of Bat Coronavirus Emergence
SUBJECT: Review Process of Your NIH Application

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My goal is to facilitate a fair and thorough review of your application. If you have any questions or concerns, please contact me.

Sincerely,

Soheyla Saadi, Ph.D.

Scientific Review Officer

CRFS- Clinical Research and Field Studies of Infectious Diseases Study Section

ZRG1 IDM-R (50) International Research in Infectious Diseases including AIDS (IRIDA)

Infectious Diseases and Microbiology IRG

Center for Scientific Review, National Institutes of Health, DHHS

6701 Rockledge Dr, Room 3194 MSC 7808 Bethesda, MD 20892

Phone (b) (6) Fax 301-480-0940

Email: (b) (6)

<image002.jpg>



September 2, 2013

Post-submission acceptance of two manuscripts

Dear reviewers,

The status of two of our manuscripts has changed:

- 1) Our paper "**Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor**" has now been accepted by *Nature*. Dr. Peter Daszak (Lead PI on this proposal) & Dr. Zhengli Shi (PI on this proposal) are co-corresponding authors of this paper. Three other PIs (Drs. Ge, Epstein & Zhang) are authors. PI Dr. Ge is lead author.
- 2) Our paper "**Coronavirus diversity and evidence for MERS CoV infection in bats in Saudi Arabia**" has now been accepted by *Emerging Infectious Diseases* and published ahead of print: http://wwwnc.cdc.gov/eid/article/19/11/13-1172_article.htm. Lead PI Daszak and PI Epstein are co-authors of this paper.

We hope that you will consider the acceptance of these papers as providing additional support for our capacity to conduct significant international collaborative research on coronaviruses.

Yours sincerely,



Dr Peter Daszak

Lead PI

R01 proposal: "Understanding the Risk of Bat Coronavirus Emergence" (1R01AI110964-01)

From: Maheswar Mikki
Sent: Fri, 3 Apr 2020 00:38:41 -0400
To: (b) (6) Fauci, Anthony (NIH/NIAID) [E]; Lane, Cliff (NIH/NIAID) [E]; (b) (6) Bill Gates (via the Gates Notes)'; (b) (6) (b) (6) (b) (6)
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(b) (6) (b) (6) (b) (6)
Subject: asymptomatic

04/02/2020

Hi, All The Experts, especially expert Hertz from NASA (most ardent disciple of Einstein):

I hope you had a chance to look into my yesterday's message (if not, see below).

Here, I want to provide you with 'proof' in support the line 'Latitude 40N'—1st may I ask a simple Q:

I hope you have seen the News "Navy fires captain who sought help for virus-stricken ship.. The USS Theodore Roosevelt, with a crew of nearly 5,000, is docked in Guam, and the Navy has said as many as 3,000 will be taken off the ship and quarantined by Friday. More than 100 sailors on the ship have tested positive for the virus.."—when the Ship was sailing in Pacific-Sea.

So, if Navy or some would tell us the route it took to get to the Base in Guam, you all verify the 'Proof' I give you here.

Naval Base in Guam at ~latitude 13.5 N

Wuhan, China at ~latitude 30. N

Seattle, US at ~latitude 45. N

Rest of the Cities in Iran, Italy, Spain & Boston/NYC fall in close to a line---drawn a line from a point in the East at ~latitude 20. N to a point at ~latitude 47.5 N in the West (I hope Dr. Hertz knows how to do this without asking Einstein to provide Hubble-constant or Nobel Riess).

You may wonder—what is this line got to do with Virus?

Answer: this line from L ~20N to L ~47.5N represents the "present Tilt of earth's N. pole" (which I measured accurately in Nov. 2018—27.5d, not 23.5d per NASA: if Dr. Hertz or any astronomer know how to measure this Tilt, go ahead and verify—make sure to tell me about it).

You may wonder—how this Tilt of 27.5d relate to Virus?

Answer: this line at 27.5d defines a particular 'plane-of-surface in N. hemisphere' on the earth as earth rotates (once a day) & 365-days... and, this particular surface-plane (inclined at 27.5d towards Sun, at the present time is critical because, it connects the Ship to Wuhan to Iran to Italy

to Spain to Boston/NYC to Seattle...or the approx. line or region where the Virus was or is being 'created' by Nature !

The earth rotates from W to E on this plane as the wind going W to E wavering along the line (why wind weavers--let us ask genius Newton: it is force of gravity, not gravity-wave).

Hence, wind takes our-friendly Virus to places to visit for 'food'—like we look for food, shoot/kill/eat innocent/lovable/harmless animals (deer, goat, cow etc..). We forgot the message of Buddha.

Anyway, did I show the 'proof'?

See how The Nature, The Creator teaches us, the spoiled Brat?

Therefore, may I Beg you to show Kindness to all People & Animals That Belongs to The Creator !

When we leave from here, our next stop is either Hell or Heaven !

I will be Happy to show where one can find Hell or Heaven...

Be Kind—Thanks

Maheswar

From: Maheswar Mikki [mailto: (b) (6)]

Sent: Wednesday, April 01, 2020 10:08 AM

To: -----

Cc: -----

Subject: asymptomatic

04/01/2020

Hi, Dear WH science-advisor: Please send a copy of this message to Prof. Trump/Dr. Birx/Dr. Fauci (hope this will un-confuse on asymptomatic- issue)

Hi, Dear code-expert Gates: with love & respect to you, please learn 'more' about 'Virus' before you teach on TV or write to me..

Hi, Dear Chancellor: please contact me, I am waiting for an answer from you—we can design/develop Masks (with ventilator, if required) that can protect us, all.

Hi, Dear Amazon Bezos: did you place your \$10 B in a 'private Foundation'? Let us get to work on 'climate-change' problem—no one can take/carry \$ to Hell or Heaven !

My clear Message to All of you, Experts !

The Virus didn't Originate nor spread from Wuhan, China:

It is created by Nature (by Sun-Star, binary-star system in which we live: I have been saying/reporting for ~14 Yrs. to the astronomers/scientists, science-Journals/Media-moguls, Politicians & Pres. Obama/Prof. Trump...).

And, it appears asymptomatic because, we, all humans, are infected around the same time—most of us show 'no symptoms', some showed symptoms, and few died.

Sure, it, also, goes from one person to another person.

By mid-April, this will come to a stop below Latitude 40N—will continue for some more time above Latitude 40N to 90N & 40S to 90S.

When it is over, that's not The End—a new-cycle could begin in Nov.-April (next Yr. and/or for another ~300 Yrs.).

The only thing we can do is this: The Gates, Bezos etc. (& those with Trillions/Billions of \$ hidden in caves...) must come out to do something 'good'.

I hope the Chancellor likes are listening...

Thanks,

Maheswar

Deborah Birx, MD, an American family physician who's currently serving as the response coordinator for the White House Coronavirus Task Force, has also voiced concern about potential asymptomatic carriers of the coronavirus.

During a White House press conference Saturday, Dr. Birx mentioned that experts are still trying to understand people—mainly those under the age of 20—who don't have "significant symptoms":

"Until you really understand how many are asymptomatic and asymptotically passing the virus on, we think it's better for the entire American public to know that the risk of serious illness may be low, but they could be potentially spreading the virus to others," she said.

Captain of aircraft carrier struck by coronavirus wants sailors off ship

Cruise ships still trying to dock amid coronavirus pandemic

Iceland lab testing suggests 50% of coronavirus cases are asymptomatic

From: Goodtree, Hannah
Sent: Fri, 13 Mar 2020 19:51:29 +0000
To: Pavlin, Julie; (b) (6); Keusch, Gerald T; Lane, Cliff (NIH/NIAID) [E]; Nicole Lurie; Amponsah, Edith; Carver, Trea (NIH) [C]
Subject: GPMB Meeting with Cliff Lane

Hello,

Please see below for the call-in details for the GPMB meeting with Nicki Lurie, Jerry Keusch, and Cliff Lane, at Uncommon Grounds on 3/16 at 3 PM EST.

Join from PC, Mac, Linux, iOS or Android: <https://nasem.zoom.us/j/> (b) (6)

Or Dial

US: +1 646 558 8656 or 888 475 4499 (Toll Free)

Meeting ID: (b) (6)

International numbers available: <https://nasem.zoom.us/j/> (b) (6)

NOTICE: The Zoom service allows audio and any materials exchanged or viewed during the session to be recorded and shared. Please be aware that by participating in this activity, you consent to your voice, likeness, and any materials you provide, being recorded for use and dissemination, without payment of any compensation for such use, in any language, format, or media now known or later devised, and you release the National Academies of Sciences, Engineering, and Medicine from any and all claims, liability, or damages arising from any such use. The Academies will proceed in reliance upon such consent and release. If you do not consent to the foregoing, please do not join the session.

From: Alexander Semenov
Sent: Wed, 4 Mar 2020 11:29:59 +0300
To: Jong-koo Lee
Cc: AYLWARD Raymond Bruce J.;Chikwe IHEKWEAZU (chikwe.ihekw;Lane, Cliff (NIH/NIAID) [E];Zhou, Weigong (CDC/DDID/NCIRD/ID);Dale FISHER ((b) (6) Dr Hitoshi TAKAHASHI (takajin@;Natalia PSHENICHNAYA (natalia-;Tim ECKMANNNS ((b) (6) XING Jun;gmleung;Dr VAN KERKHOVE Maria;Zunyou Wu;(SPmig) LEI ZHOU; (b) (6) (b) (6) (b) (6)
Subject: Re: WITH ATTACHMENTS: WHO-China Joint Mission on CO

Wow! Thank you. Wish you good luck fighting the COVID-2019.

cp, 4 мар. 2020 г., 11:08 Jong-koo Lee < (b) (6)>

Dear All

FYI

----- 원본 메일 -----

보낸사람 : "AYLWARD, Raymond Bruce J." < (b) (6)>

받는사람 : (b) (6) < (b) (6)> "Alexander SEMENOV (alevxsemeno" < (b) (6)> "Chikwe IHEKWEAZU (chikwe.ihekw"

< (b) (6)> "Clifford LANE ((b) (6)"

< (b) (6)> "Zhou Weigong (CDC/DDID/NCIRD/" < (b) (6)> "Dale

FISHER ((b) (6) < (b) (6)> "Dr Hitoshi TAKAHASHI

(takajin@" < (b) (6)> "Natalia PSHENICHNAYA (natalia-" (b) (6).

(b) (6), "Tim ECKMANNNS ((b) (6)

< (b) (6)> "XING, Jun" < (b) (6)> gmleung < (b) (6)

참조 : "Dr VAN KERKHOVE, Maria" < (b) (6)> Zunyou Wu

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받은날짜 : 2020-03-03 (화) 04:32:31

제목 : RE: Possible SPAM detected: RE: WITH ATTACHMENTS: WHO-China Joint Mission on CO

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I attach summary of press briefing and informal contact of KCDC staffs for your understanding only

Thanks for your advice and WHO colleagues

Jong-koo LEE MD, MPH, PhD

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Professor, Department of Family Medicine

Seoul National University College of Medicine

Ihwajang-gil 71, Jongno-gu, Seoul, 110-810, Republic of Korea

Tel (b) (6)

Fax +82-2-766-1185

email : (b) (6) (b) (6)

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받은날짜 : 2020-03-02 (월) 03:44:04

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With very best regards to all,

Bruce

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Sent: Friday, February 28, 2020 10:58

To: GHEBREYESUS, Tedros Adhanom <(b) (6)>

Cc: KASAI, Takeshi <(b) (6)> GALEA, Gauden <(b) (6)>

<(b) (6)> <(b) (6)>; <(b) (6)>;

<(b) (6)> LI Juan (<(b) (6)> <(b) (6)>

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Importance: High

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From: (b) (6) on behalf of "Jong-koo Lee" <(b) (6)>
Sent: Wed, 4 Mar 2020 17:08:38 +0900
To: AYLWARD Raymond Bruce J.; (b) (6) Alexander SEMENOV (alexvsemeno;Chikwe IHEKWEAZU (chikwe.ihekw;Lane, Cliff (NIH/NIAID) [E];Zhou, Weigong (CDC/DDID/NCIRD/ID);Dale FISHER ((b) (6) Dr Hitoshi TAKAHASHI (takajin@;Natalia PSHENICHNAYA (natalia-;Tim ECKMANNS ((b) (6) XING Jun;gmleung
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Subject: RE: WITH ATTACHMENTS: WHO-China Joint Mission on CO
Attachments: Korea 0304.docx

Dear All

FYI

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Dear Dr Tedros,

It is my honor to share with you the attached, final version of the ***Report of the WHO-China Joint Mission on COVID-19***, on behalf of myself, my Co-Lead Dr LIANG Wannian, our Deputy Team Leader Dr WANG Bin, and the entire Joint Team of Chinese national and international members.

I am pleased to inform you that in the 24 hours since sharing a preliminary version of this report, the China and international members have fully aligned the language of the English and Chinese versions, allowing the release of both versions today.

It is agreed with our Chinese counterparts that the English version can be released immediately, given the urgency of sharing these findings with the international community. The Honorable Minister of Health, Dr MA Xiaowei, will release the Chinese version within hours.

In closing, I would like to reiterate my personal gratitude to Dr LIANG for his deep experience and guidance as we consolidated our findings, and to the entire Team for their tremendous contributions throughout. As you and I have discussed, this was truly a Joint Mission and the quality of this report reflects the world-class expertise of all team members, both national and international. The attached findings and recommendations reflect the collective opinion of the entire team, all of whom have been closely engaged in its writing and finalization.

It is our common hope and belief that the findings contained herein can inform the global work you are leading to stem the ongoing international spread of COVID-19.

Regards

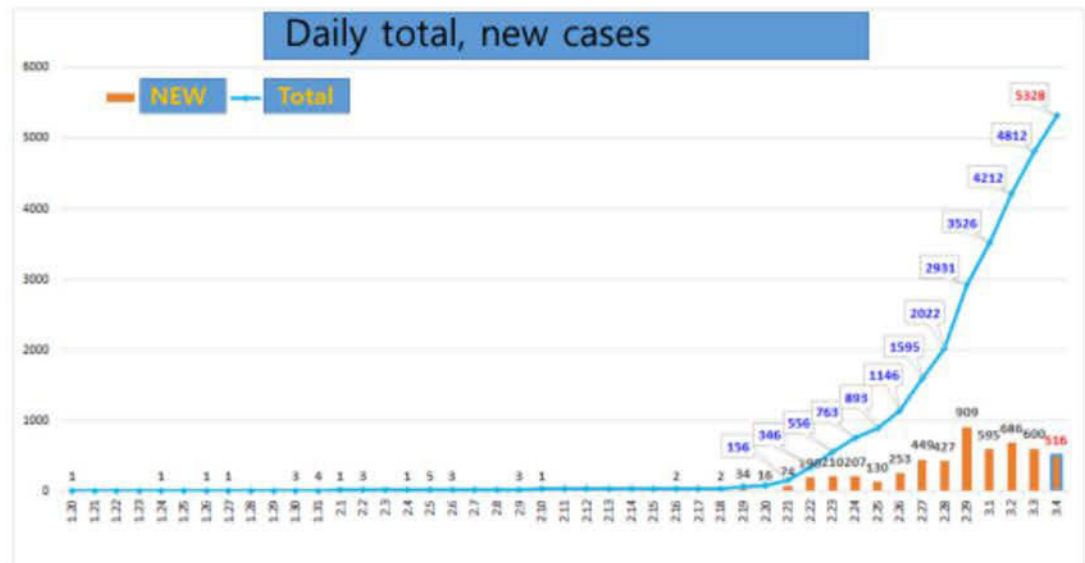
Bruce

Outbreak of ROK

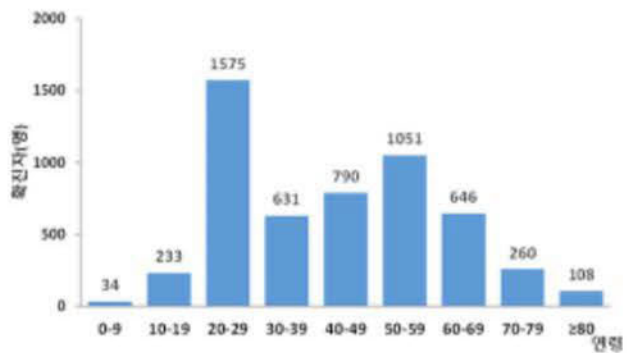
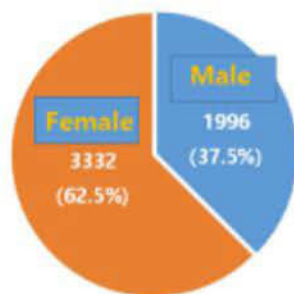
2020 4 Mach

1. Daily reporting cases

	Total	Confirmed cases				lab		
		subtotal	dischage	Iso	Death	total	processing	negative
2.26 09 AM	46,127	1,146	22	1,113	11	44,981	16,734	28,247
2.27 09 AM	57,990	1,595	24	1,559	12	56,395	21,097	35,298
2.28 09 AM	70,940	2,022 (+427)	26	1,983	13	68,918	24,751	44,167
2.29 09 AM	85,693	2,931 (+909)	27	2,888	16	82,762	29,154	53,608
3.1. 09 AM	96,985	3,526 (+595)	30	3,479	17	93,459	32,422	61,037
3.2. 00 AM	109,591	4, 212 (+686)	31	4,159	22	105,379	33,799	71,580
3.3. 00 AM	125,851	4,812 (+600)	34	4,750	28	121,039	35,555	85,484
3.4 00AM	136,707	5,328 (+516)	41	5,255	32	131,379	28,414	102,965



Sex and Age Distribution



Young(20-29), female : religious group

2. Geographic

■ Daegu : 4,006(positive cases(64.5%), 2,583 is religious group)

■ Kyoungbuk : 774(68% of positive is religious group(315), long-term mental hospital(115), pilgrim(49), social service facility(24)

- Cluster: 3,494(65.6%) : Religious group : 2,992

Others : are associated with other religious group, health workers, social workers and social service center, sports club, long-term care facility, small hospital

	Seoul	Busan	Daegu	Incheon	Gwangju	Daegu	Ulsan	Sejong	Gyeonggi	Gangwon	Chungbuk	Chungnam	Chonbuk	Chonnam	Gyeongbuk	Gyeongnam	Cholla	total
3,494	99	93	4006	9	13	15	23	1	101	21	11	82	7	5	774	65	3	5328

3. Measures

A. Contact tracing and isolation,

i. Religious group : Among about 210,000 believer(99% were traced by telephone),

1. 6,561 symptom person have being received test, positive rate is 62% in Daegu, other area is 1.7%.(03 March),
2. Self-quarantine is recommended to all believer (who have been to Daegu church)
3. Some believers have been to Wuhan before January (from August to January) and believers in China including Wuhan had a meeting in Korea mid Jan, but we did not yet confirm any association

- ii. Mental health hospital in Chengdo, near 80% inpatients, 115 patients were infected and late detection due to poor communication by drug and disease characteristic, made high case fatality
 - iii. Sporadic cases: traced by health center and quarantined strictly
- B. Triage for fever patients and PCR testing
- i. All district Health center(250) are designated fever patients evaluation
 - ii. Designated hospital with fever clinic are extended,
- C. Infection control and prevention
- i. PPE level D used in fever patient evaluation
- D. Hospital management of patents; being prioritized by severity
- I. Critical care – university affiliated hospital (negative pressure room)
 - II. Severe patient care – designated hospital (negative pressure room)
 - III. Mild and moderate pneumonia: general hospital and 6 dormitory on Daegu and Gyoungbuk
- E. Social distance and rigorous education
- i. Closing school, social service center (old age, toddler, handicapped etc)
 - ii. Recommend to restrict meeting with relatives, religious services
- F. Transmissibility
- i. Contact history: Among infected cases, contact history with early mild symptom case is frequently observed (religious group)
 - ii. Incubation period: 4-5d(shorter than China)
- G. Severity
- i. CFR : among 32, most of pt have underlying disease(transplantation, cancer, HT, DM,, CVD etc),

70 +y/o, : 4%, 80 +y/o 5.4% (03 March)

H. Market failure

- i. Mask, handwashing alcohol in market is closely observed by government

4. Perspective

- Now, lot of test is undergoing in religious group, confirmed case will be increased, but cases is decreasing
- Proportion of Sporadic cases, which is small cluster, is increasing, under being tracing and quarantined
-

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Dear All

This is progress of Korea situation

JK LEE

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" (b) (6) <(b) (6)

받은날짜 : 2020-03-03 (화) 04:32:31

제목 : RE: Possible SPAM detected: RE: WITH ATTACHMENTS: WHO-China Joint
Mission on CO

Dear Jong-Koo – really helpful to have this further information and insights on the Korea situation.
Thank you so much. B

From: (b) (6) <(b) (6)>
Sent: Monday, March 2, 2020 00:53
To: AYLWARD, Raymond Bruce J. <(b) (6)> "Alexander SEMENOV (alexvsemeno)"
<(b) (6)> "Chikwe IHEKWEAZU (chikwe.ihekw)" <(b) (6)>
"Clifford LANE (cliff.lane@nih.)" <(b) (6)> "Zhou Weigong (CDC/DDID/NCIRD/"
<(b) (6)> "Dale FISHER ((b) (6) <(b) (6)> "Dr Hitoshi TAKAHASHI
(takajin@" <(b) (6)> "LEE Jong-Koo ((b) (6) <(b) (6)> "Natalia
PSHENICHNAYA (natalia-" <(b) (6)> "Tim ECKMANN ((b) (6)
<(b) (6)> XING, Jun <(b) (6)> gmleung <(b) (6)>
Cc: Dr VAN KERKHOVE, Maria <(b) (6)> Zunyou Wu <(b) (6)> (SPmig) LEI
ZHOU <(b) (6)> ' (b) (6) <(b) (6)> ' (b) (6)
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I attach summery of press briefing and informal contact of KCDC staffs for your
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Thanks for your advice and WHO colleagues

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Director, Center for Healthy Society and Education

Professor, Department of Family Medicine

Seoul National University College of Medicine

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Tel (b) (6)

Fax +82-2-766-1185

email : (b) (6) (b) (6)

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받은날짜 : 2020-03-02 (월) 03:44:04

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 - in the section of WHO Coronavirus page:
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Sent: Friday, February 28, 2020 10:58

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< (b) (6) ALEXANDER, Nyka < (b) (6) STERN, Gabriella < (b) (6)

Subject: NEW - FOR PUBLIC RELEASE: WHO-China Joint Mission on COVID-19

Importance: High

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I am pleased to inform you that in the 24 hours since sharing a preliminary version of this report, the China and international members have fully aligned the language of the English and Chinese versions, allowing the release of both versions today.

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It is our common hope and belief that the findings contained herein can inform the global work you are leading to stem the ongoing international spread of COVID-19.

Regards

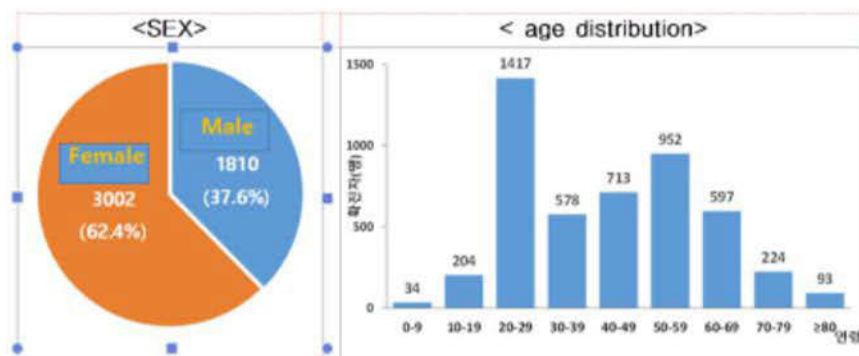
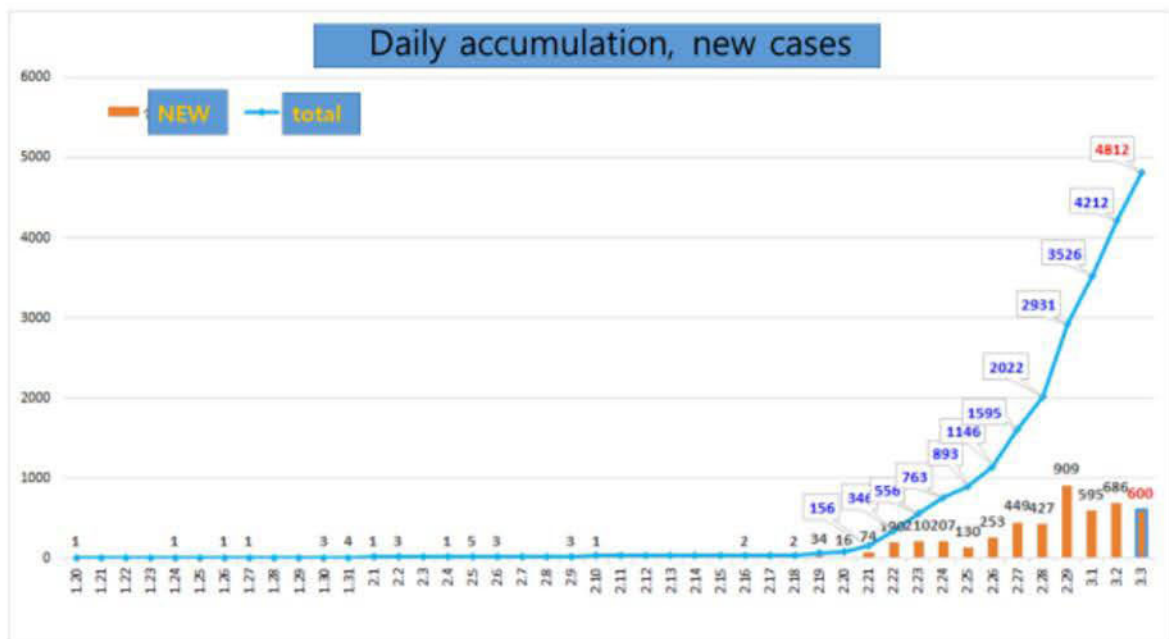
Bruce

Outbreak of ROK

2020 3 Mach

1. Daily reporting cases

	Total	Confirmed cases				lab		
		subtotal	discharge	Iso	Death	total	processing	negative
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2.29 09 AM	85,693	2,931 (+909)	27	2,888	16	82,762	29,154	53,608
3.1. 09 AM	96,985	3,526 (+595)	30	3,479	17	93,459	32,422	61,037
3.2. 00 AM	109,591	4, 212 (+686)	31	4,159	22	105,379	33,799	71,580
3.3. 00 AM	125,851	4,812 (+600)	34	4,750	28	121,039	35,555	85,484



- Young(20-29), female : religious group

2. Geographic

■ Daegu : 3,601(positive cases(66%) is religious group)

■ Kyoungbuk : 685(long-term mental hospital(115)and religious group(229), pilgrim(49)

- Cluster 3,161(65.7%)

Religious group : 2,698(56.1%), others(34.30)

Others : are associated with other religious group, health workers, social workers and social service center, sports club, long-term care facility, small hospital

	Se o ul	Bu sa n	Da eg u	Inc he on	Gw ang ju	Da eje on	Ul sa n	Sej on g	Gy ou ngi	Gan gwo n	Chu ngb uk	Chu ngb uk	Che onb uk	Che ona m	Gyou ngbu k	Gyou ngna m	C he ju	to ta l
3. 0 3	98	90	3, 6 0 1	7	11	14	20	1	94	20	11	81	7	5	685	64	3	4 8 1 4

3. Measures

A. Contact tracing and isolation,

i. Religious group : Among about 19,2634 believer(98.7% were traced by telephone),

1. 6,561 symptom person have been received test in Daegu, positive rate 62%(2,685) other area is 1.7% . ,
2. Self-quarantine is recommended to all believer (who have been to Daegu church)
3. Some believers have been to Wuhan before January (from August to January) and believers in China including Wuhan had a meeting

in Korea mid Jan, but we did not yet confirm any association

- ii. Mental health hospital in Chengdo, near 80% inpatients, 115 patients were infected and late detection due to poor communication by drug and disease characteristic, made high case fatality
- iii. Sporadic cases: traced by health center and quarantined strictly

B. Triage for fever patients and PCR testing

- i. All district Health center(250) are designated fever patients evaluation
- ii. Designated hospital with fever clinic are extended,

C. Infection control and prevention

- i. PPE level D used in fever patient evaluation

D. Hospital management of patents; being prioritized by severity

- I. Critical care – university affiliated hospital (negative pressure room)
- II. Severe patient care – designated hospital (negative pressure room)
- III. Mild and moderate pneumonia: general hospital or 3-5 dormitory on Daegu and Gyoungbuk

E. Social distance and rigorous education

- i. Closing school, social service center (old age, toddler, handicapped etc)
- ii. Recommend to restrict meeting with relatives, religious services

F. Transmissibility

- i. Contact history: Among infected cases, contact history with early mild symptom case is frequently observed (religious group)
- ii. Incubation period: 4-5d(shorter than China)

G. Severity

- i. CFR : among 28, most of pt have underlying disease(transplantation, cancer, HT, DM,, CVD etc), over
70 +y/o, : 4%, 80 +y/o 5.4%

H. Market failure

- i. Mask, handwashing in market is closely observed

4. Perspective

Now, lot of test is undergoing in religious group, confirmed case will be increased

From: (b) (6) on behalf of "Jong-koo Lee" <(b) (6)>
Sent: Mon, 2 Mar 2020 08:52:49 +0900
To: AYLWARD Raymond Bruce J.; Alexander SEMENOV (alexvsemeno;Chikwe IHEKWEAZU (chikwe.ihekwe;Lane, Cliff (NIH/NIAID) [E];Zhou, Weigong (CDC/DDID/NCIRD/ID);Dale FISHER ((b) (6)Dr Hitoshi TAKAHASHI (takajin@;LEE Jong-Koo ((b) (6)Natalia PSHENICHNAYA (natalia-;Tim ECKMANN ((b) (6)XING Jun;gmleung
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ZHOU; (b) (6) (b) (6) (b) (6)
Subject: RE: WITH ATTACHMENTS: WHO-China Joint Mission on COVID-19
Attachments: Korea 0301.docx

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2. Geographic

- Daegu : 2,569 (most of positive cases(73%) is religious group, young age)
- Kyoungbuk : 514(long-term mental hospital and religious group)
- Religious group : 2113(59.9%), mental hospital : 119(3.4%), others(35.8%)
- Others : are associated with other religious group, health workers, social workers, sports cub, pilgrim to Israel, prisons

	Se o ul	Bu sa n	Da eg u	Inc he on	Gw ang ju	Da eje on	Ul sa n	Sej on g	Gy ou ngi	Gan gwo n	Chu ngb uk	Chu ngb uk	Che onb uk	Che ona m	Gyou ngbu k	Gyou ngna m	C he ju	to ta l
3,011	82	81	2569	6	9	13	17	1	84	7	11	60	5	3	514	64	2	3,526

3. Measures

A. Contact tracing and isolation,

- i. Religious group in Daegu: Among about 230,000 believer in national wide, about 8,000 person have symptoms (by telephone call traced, mainly young people, who were attended on education program (education center of church),

1. PCT is 87% in positive who has symptoms (early data of 1,200)- very high attack rate
2. Self-quarantine is recommended to all believer (who went to Daegu church)
3. Some believers (near 40) have been to Wuhan on January by border record, but we did not yet confirm any association

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- III. Mild and moderate pneumonia: general hospital (considering home or dormitory)

E. Social distance and rigorous education

- i. Closing school, social service center (old age, toddler, handicapped etc)
- ii. Recommend to restrict meeting with relatives, religious services

F. Transmissibility

- i. Contact history: Among infected cases, contact history with early mild symptom case is frequently observed (religious group)
- ii. Incubation period: 4-5d(shorter than China)

G. Severity

- i. CFR : among 17, most of pt have underlying disease(transplantation, cancer, HT, DM,, CVD etc), over 70 y/o,

H. Market failure

- i. Mask in market is closely observed

4. Perspective

Now, lot of test is undergoing in religious group, confirmed case will be increased

From: AYLWARD, Raymond Bruce J.
Sent: Sun, 1 Mar 2020 22:00:16 +0000
To: Zhou, Weigong (CDC/DDID/NCIRD/ID); Alexander SEMENOV
(b) (6) Chikwe IHEKWEAZU (b) (6) Lane, Cliff
(NIH/NIAID) [E]; Dale FISHER (b) (6) Dr Hitoshi TAKAHASHI (b) (6); LEE Jong-Koo (b) (6) Natalia PSHENICHNAYA (b) (6) Tim ECKMANNNS
(b) (6); XING, Jun; gmleung
Cc: Dr VAN KERKHOVE, Maria; Zunyou Wu; (SPmig) LEI
ZHOU; (b) (6) (b) (6) (b) (6)
Subject: RE: WITH ATTACHMENTS: WHO-China Joint Mission on COVID-19

Good points both – just going for simplicity of messaging that people can remember (I usually say ‘about 15%’ and ‘about 5%’). Will be clearer.

Re the diagram – agree as well – we need to get this designed properly. B

From: Zhou, Weigong (CDC/DDID/NCIRD/ID) <(b) (6)>
Sent: Sunday, March 1, 2020 21:49’
To: AYLWARD, Raymond Bruce J. <(b) (6)> Alexander SEMENOV
(b) (6) <(b) (6)> Chikwe IHEKWEAZU
(b) (6) <(b) (6)> Clifford LANE (b) (6)
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ZHOU <(b) (6)> (b) (6) (b) (6) (b) (6)
Subject: RE: WITH ATTACHMENTS: WHO-China Joint Mission on COVID-19

One more quick not on slide 11. The proportions for severe and critical are reported at 13.8% and 6.1%, respectively in the joint mission report. So the 15% and 5% on slide 11 should be changed to 14% and 6%, respectively.

Thanks,
Weigong

From: Zhou, Weigong (CDC/DDID/NCIRD/ID)
Sent: Sunday, March 1, 2020 3:39 PM
To: AYLWARD, Raymond Bruce J. <(b) (6)> Alexander SEMENOV
(b) (6) <(b) (6)> Chikwe IHEKWEAZU
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< (b) (6)
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ZHOU < (b) (6) (b) (6) (b) (6) (b) (6)
Subject: RE: WITH ATTACHMENTS: WHO-China Joint Mission on COVID-19

Dear Bruce, Maria, and all,

I still think the figure in slide 7 is a bit misleading and those red arrow lines should be modified. The mild and moderate cases do not died directly, but a small portion of them progressed to the next level. I thought this was pointed out during our discussion on Sunday. The suggested change was to have the red arrow lines go to the next level instead of going to death directly except the one from critical to death.

Thanks,
Weigong

From: AYLWARD, Raymond Bruce J. < (b) (6)
Sent: Sunday, March 1, 2020 1:41 PM
To: Alexander SEMENOV ((b) (6) < (b) (6) Chikwe IHEKWEAZU
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<cliff. (b) (6) Zhou, Weigong (CDC/DDID/NCIRD/ID) < (b) (6) Dale FISHER
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< (b) (6) LEE Jong-Koo ((b) (6) < (b) (6) Natalia
PSHENICHNAYA ((b) (6) < (b) (6) Tim
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With very best regards to all,

Bruce

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Sent: Friday, February 28, 2020 10:58

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<(b) (6)> XING, Jun <(b) (6)> gmleung <(b) (6)> Dr VAN KERKHOVE,

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<(b) (6)> MINHAS, Raman <(b) (6)> SNIDER, Paige Anne

<(b) (6)> ALEXANDER, Nyka <(b) (6)> STERN, Gabriella <(b) (6)>

Subject: NEW - FOR PUBLIC RELEASE: WHO-China Joint Mission on COVID-19

Importance: High

Dr Tedros & colleagues,

Our eagle-eyed counterparts spotted a tiny edit I had inadvertently overlooked in the version just sent (an updated section now has six sub-sections but I had forgotten to say '6' instead of '5' in the preambular para).

I would be most grateful if the attached version be used as the 'final final' (with time stamp of 1100hr in the file name).

Apologies to all for any inconvenience.

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Subject: FOR PUBLIC RELEASE: WHO-China Joint Mission on COVID-19
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Regards

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Cc: Dr VAN KERKHOVE, Maria; Zunyou Wu; (SPmig) LEI ZHOU; (b) (6) (b) (6) (b) (6)
Subject: WITH ATTACHMENTS: WHO-China Joint Mission on COVID-19
Attachments: Joint Mission REPORT Chinese VERSION 29Feb2020.pdf, COVID Joint Mission Findings - at 29Feb2020.pptx
Importance: High

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Importance: High

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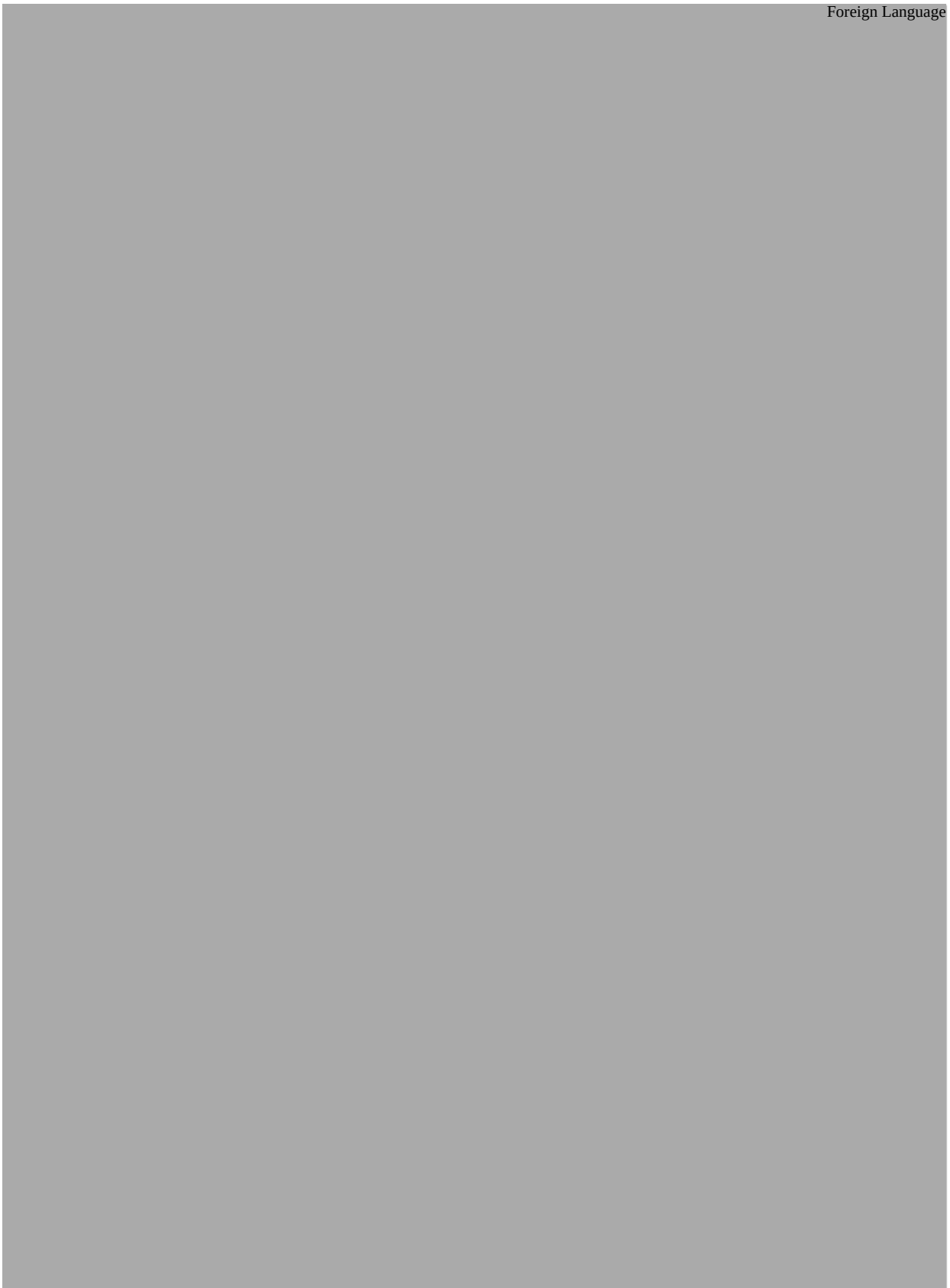
中国-世界卫生组织
新型冠状病毒肺炎（COVID-19）
联合考察报告

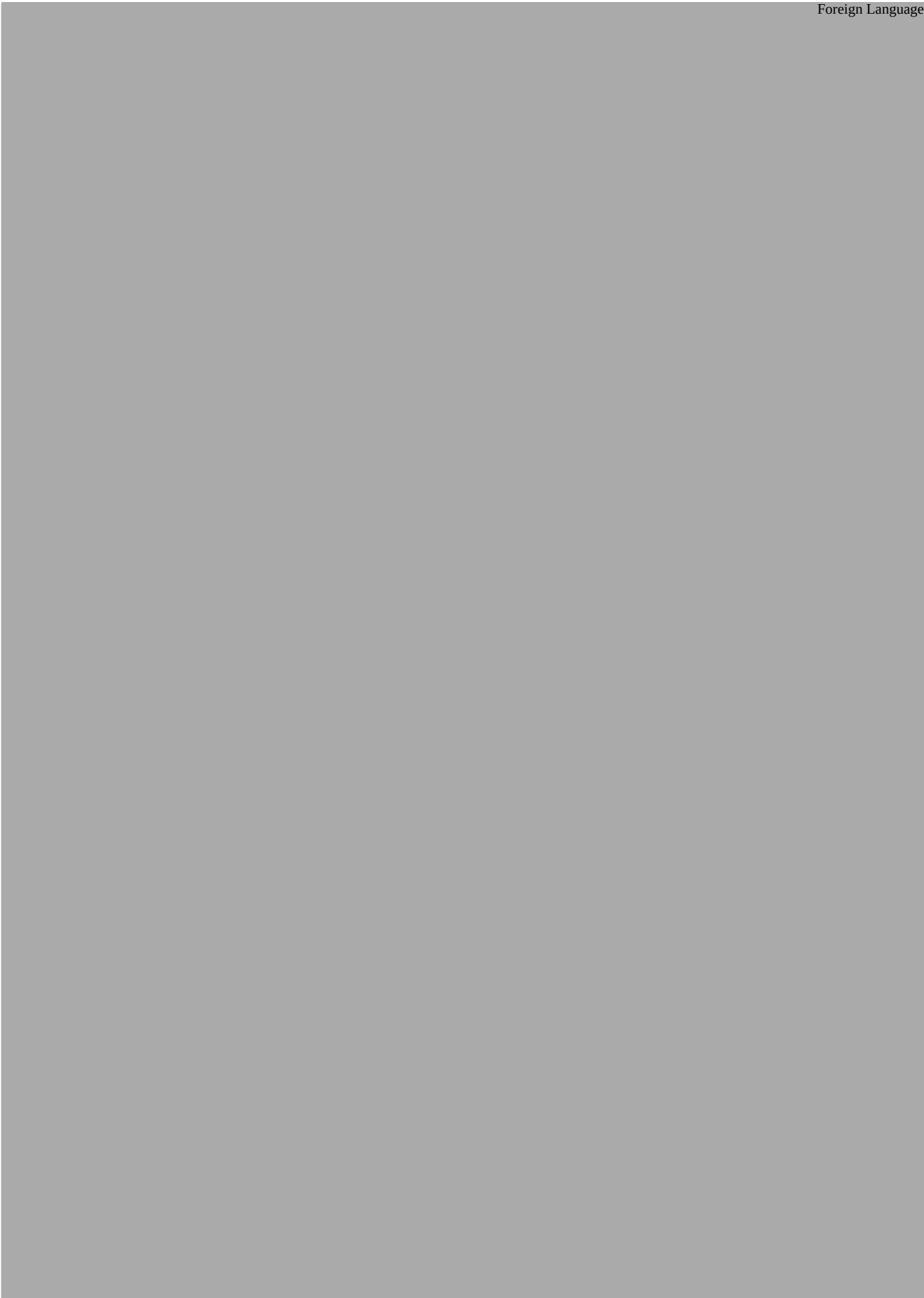
2020 年 2 月 16-24 日











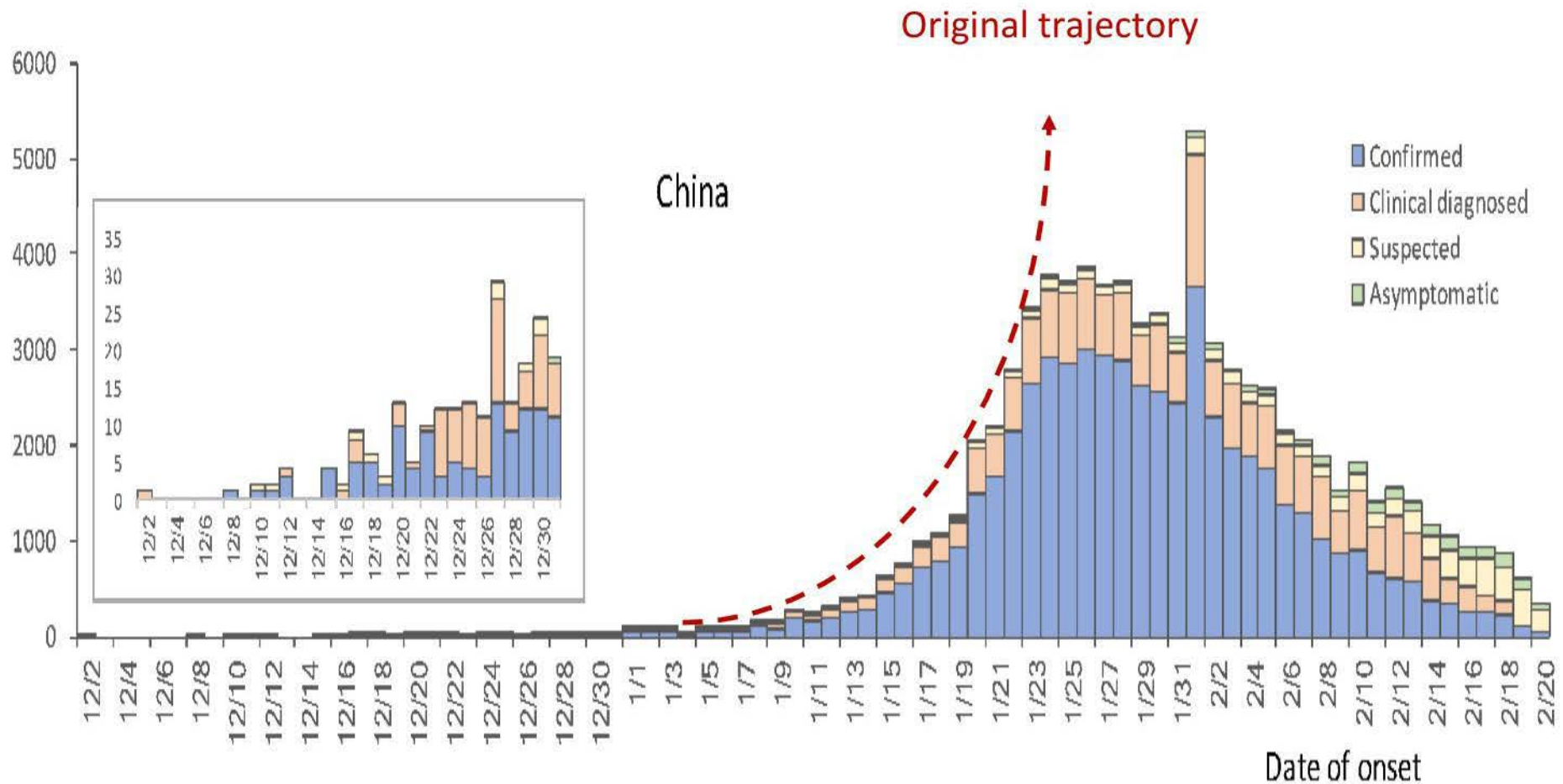




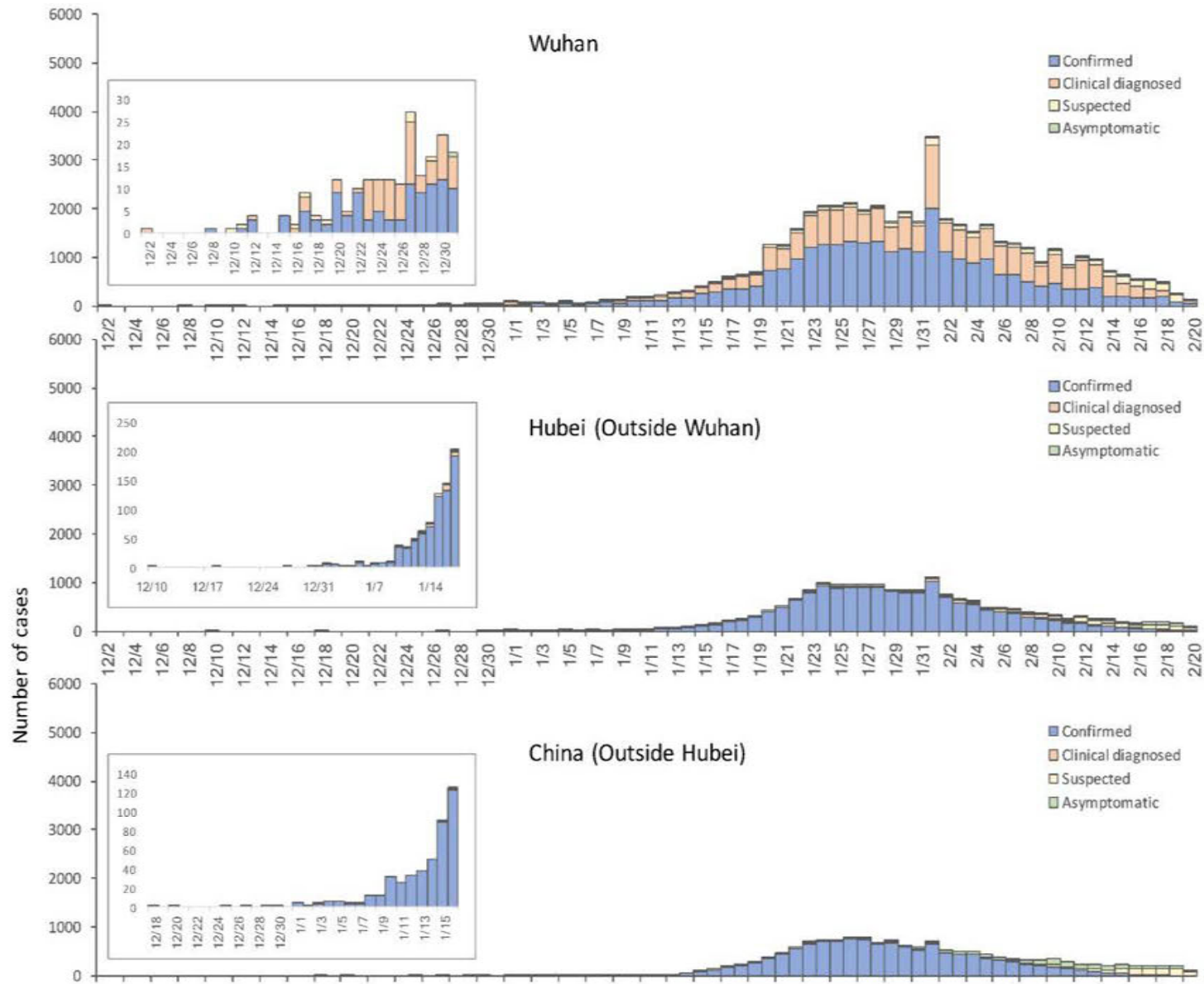
WHO-China Joint Mission on COVID-19

Key Findings at 29 February 2020

China proves it can change the course of COVID-19 outbreaks

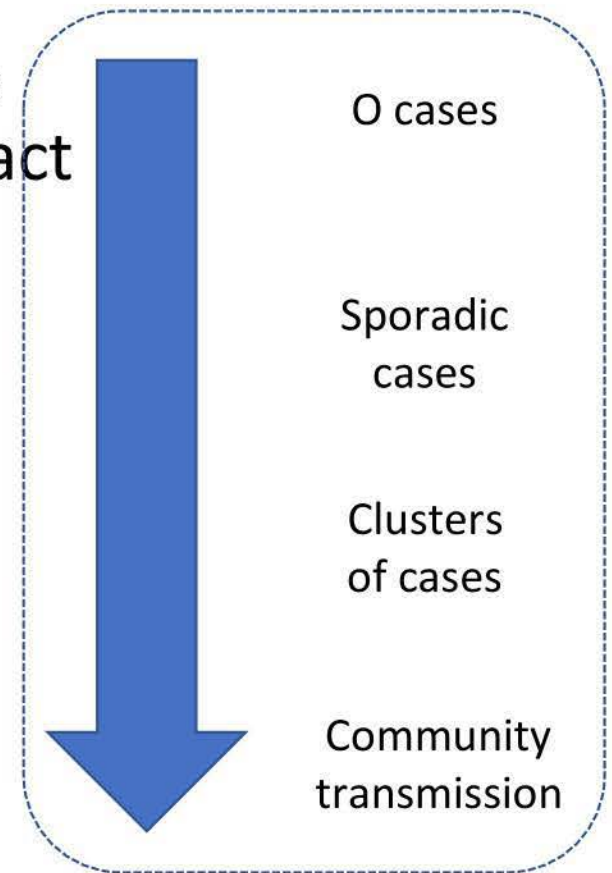


China's differentiated approach averted 100,000s of cases



China is using fundamental public health measures...

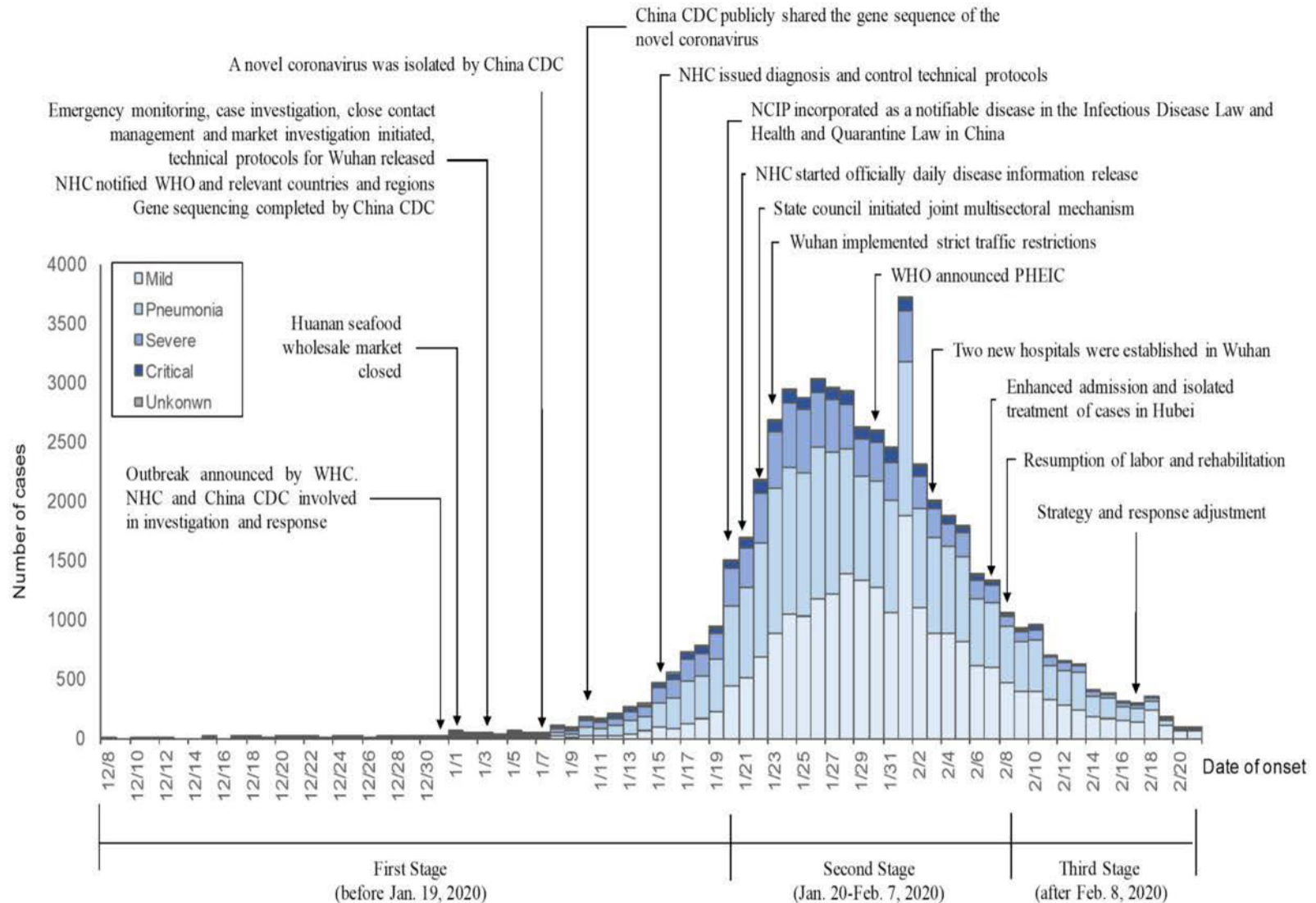
- Universal population measures
Case isolation & management
Close contact quarantine
Suspension of public gatherings
Movement restrictions



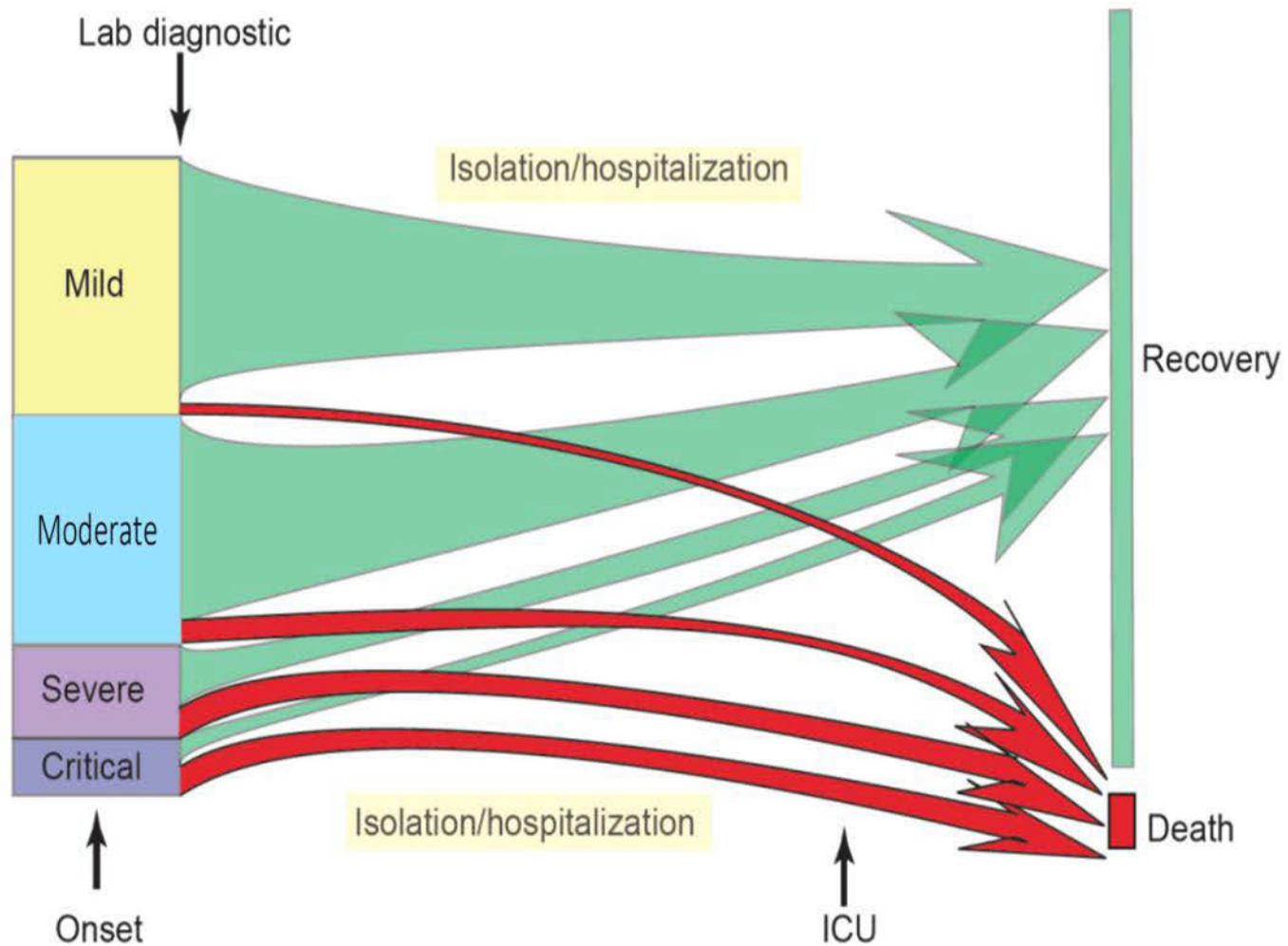
...with 5 key approaches to optimize for sustainability

- **differentiating to each context
mobilizing collective action
repurposing the machinery
of Government 'turbo-charging' with
technology agile driving with the latest
science**

What China's approach looks like in practice



China rapidly adapts strategy to its understanding of COVID-19



In China, COVID-19 readiness goes beyond pandemic flu preparedness

- the 'readiness mindset' immediate capacity (beds, oxygen, lab, CTs, PPE) massive workforces for case finding/contact tracing a fully aware & engaged population access to the best expertise

Some Epidemiologic & Technical Insights, China

Some key epi/technical insights from China (1 of 3)

Transmission dynamics: there does not appear to be substantial virus circulation in the community (e.g. only 0.14% of 320,000 samples in Guangdong from Jan-Feb) the vast majority of cases arise from close contacts of symptomatic cases; 1-5% of 38,000 close contacts develop COVID-19 (based on carefully followed contacts in 3 areas) transmission in most settings is driven by family-clusters (i.e. 75-85% of clusters); we found no examples of children transmitting to adults the most careful studies of 20 household attack rates suggest it was 10% early in the outbreak and fell to 3% with faster isolation transmission in other closed settings is happening but is not the major driver in China (e.g. nosocomial infections, nursing homes, prisons, restaurants) school outbreaks have not been a feature of this outbreak – this may simply be because of the closure of schools during most of this outbreak

Some key epi/technical insights from China (2 of 3)

Natural history: at diagnosis: approx. 80% are mild/moderate; 15% severe; 5% critical progression: approx. 10-15% of mild/moderate cases become severe, and approximately 15-20% of severe become critical average times: from exposure to symptom onset is 5-6 days after infection; from symptoms to recovery for mild cases is 2 weeks; from symptoms to recovery for severe cases is 3-6 weeks; from symptoms onset to death is from 1 week (critical) to 2-8 weeks. truly asymptomatic infection appears to be rare (e.g. 1-3%) an estimated 75% of 'asymptomatic' cases soon progress to disease children tend to have milder disease than adults; although COVID was less frequent in children & we did not see onward

Some key epi/technical insights from China (3 of 3)

Virology virus shedding is highest early in the course of disease (vs. SARS shedding which peaks at least 5 days post onset) virus shedding can be detected in the 24-48 hours prior to disease onset virus can be isolated from stool but there is not epidemiologic evidence of fecal-oral transmission virus shedding usually continues for 7-12 days in mild/moderate cases, and for >2 weeks in severe cases

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Sent: Sun, 1 Mar 2020 18:26:35 +0000
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<(b) (6)> ALEXANDER, Nyka <(b) (6)> STERN, Gabriella <(b) (6)>
Subject: NEW - FOR PUBLIC RELEASE: WHO-China Joint Mission on COVID-19
Importance: High

Dr Tedros & colleagues,

Our eagle-eyed counterparts spotted a tiny edit I had inadvertently overlooked in the version just sent (an updated section now has six sub-sections but I had forgotten to say '6' instead of '5' in the preambular para).

I would be most grateful if the attached version be used as the 'final final' (with time stamp of 1100hr in the file name).

Apologies to all for any inconvenience.

Bruce

From: AYLWARD, Raymond Bruce J.
Sent: Friday, February 28, 2020 10:22
To: GHEBREYESUS, Tedros Adhanom <(b) (6)>
Cc: KASAI, Takeshi <(b) (6)>; (b) (6) (b) (6) (b) (6)
(b) (6) LI Juan (b) (6) <(b) (6)>
(b) (6) Alexander SEMENOV (b) (6)
<(b) (6)> Chikwe IHEKWEAZU (b) (6)
<(b) (6)> Clifford LANE (b) (6) <(b) (6)> Zhou,
Weigong (CDC/DDID/NCIRD/ID) <(b) (6)> Dale FISHER (b) (6)
<(b) (6)> Dr Hitoshi TAKAHASHI (b) (6) <(b) (6)> LEE Jong-Koo

(b) (6) < (b) (6) Natalia PSHENICHNAYA (natalia-pshenichnaya@yandex.ru) < (b) (6) Tim ECKMANNS (b) (6)
< (b) (6) XING, Jun < (b) (6) gmleung < (b) (6) Dr VAN KERKHOVE,
Maria < (b) (6) RYAN, Michael J. < (b) (6) SCHWARTLANDER, Bernhard F.
< (b) (6) MINHAS, Raman < (b) (6) SNIDER, Paige Anne
< (b) (6) ALEXANDER, Nyka < (b) (6) STERN, Gabriella < (b) (6)

Subject: FOR PUBLIC RELEASE: WHO-China Joint Mission on COVID-19

Importance: High

Dear Dr Tedros,

It is my honor to share with you the attached, final version of the ***Report of the WHO-China Joint Mission on COVID-19***, on behalf of myself, my Co-Lead Dr LIANG Wannian, our Deputy Team Leader Dr WANG Bin, and the entire Joint Team of Chinese national and international members.

I am pleased to inform you that in the 24 hours since sharing a preliminary version of this report, the China and international members have fully aligned the language of the English and Chinese versions, allowing the release of both versions today.

It is agreed with our Chinese counterparts that the English version can be released immediately, given the urgency of sharing these findings with the international community. The Honorable Minister of Health, Dr MA Xiaowei, will release the Chinese version within hours.

In closing, I would like to reiterate my personal gratitude to Dr LIANG for his deep experience and guidance as we consolidated our findings, and to the entire Team for their tremendous contributions throughout. As you and I have discussed, this was truly a Joint Mission and the quality of this report reflects the world-class expertise of all team members, both national and international. The attached findings and recommendations reflect the collective opinion of the entire team, all of whom have been closely engaged in its writing and finalization.

It is our common hope and belief that the findings contained herein can inform the global work you are leading to stem the ongoing international spread of COVID-19.

Regards

Bruce

From: Lane, Cliff (NIH/NIAID) [E]
Sent: Sun, 23 Feb 2020 19:39:48 +0800
To: Dr VAN KERKHOVE, Maria
Cc: (b) (6)
Subject: COVID 19 References; second try!

Ref. 2 = 41 cases

Ref. 5 = 425 cases

The 1099 is still a pre-print. It is from Prof. Zhong's group.

I have deleted a few of the references but most of them contain one or more aspects of those things covered in the report.

Dr. Dong – please edit (add / subtract as appropriate)

Cliff

1. [A Novel Coronavirus From Patients With Pneumonia in China, 2019](#)
N Zhu et al. N Engl J Med 382 (8), 727-733. 2020. PMID 31978945.
In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was ...
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Ministry of Science and Technology, Chinese Academy of Medical Sciences, National Natural Science Foundation of China, and Beijing Municipal Science and Technology Commis ...
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17. [Preliminary Prediction of the Basic Reproduction Number of the Wuhan Novel Coronavirus 2019-nCoV](#)
T Zhou et al. J Evid Based Med. 2020. PMID 32048815.
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18. [Measures for Diagnosing and Treating Infections by a Novel Coronavirus Responsible for a Pneumonia Outbreak Originating in Wuhan, China](#)
F Yu et al. Microbes Infect. 2020. PMID 32017984.
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Wuhan City in central China was denoted as 2019-nCoV by the World Health Organization (WHO). As of 2 ...

19. [Origin and Evolution of the 2019 Novel Coronavirus](#)
L Zhang et al. Clin Infect Dis. 2020. PMID 32011673.
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KK To et al. Clin Infect Dis. 2020. PMID 32047895.
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23. [Therapeutic and Triage Strategies for 2019 Novel Coronavirus Disease in Fever Clinics](#)
J Zhang et al. Lancet Respir Med. 2020. PMID 32061335.
24. [Molecular and Serological Investigation of 2019-nCoV Infected Patients: Implication of Multiple Shedding Routes](#)
W Zhang et al. Emerg Microbes Infect 9 (1), 386-389. Dec 2020. PMID 32065057.
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N Tang et al. J Thromb Haemost. 2020. PMID 32073213.
The present study shows that abnormal coagulation results, especially

markedly elevated D-dimer and FDP are common in deaths with NCP.

From: Maria VAN KERKHOVE <(b) (6)>
Date: Sunday, February 23, 2020 at 6:59 PM
To: "Lane, Cliff (NIH/NIAID) [E]" <(b) (6)>
Cc: "(b) (6)" <(b) (6)>
Subject: Re: COVID 19 References

Hi Cliff,

I think we need to be more selective of the references that are identified. I would be grateful if we could pull some key ones from Zhong Nanshan's group, China CDC, the report of 41 cases, then of 425 cases, then 1099 cases – some on clinical features (as you have below), lab diagnostics and phylogenetics, clinical trial protocols, etc.

Thanks in advance for your work on this,
Maria

From: Cliff Lane <(b) (6).gov>
Date: Sunday, 23 February 2020 at 09:47
To: Maria Van Kerkhove <(b) (6)>
Cc: "(b) (6)" <(b) (6)>
Subject: Fwd: COVID 19 References

Below are some of the key references regarding COVID 19. I pulled these from PubMed. There may be other documents (esp. governmental guidelines) we should add.

Cliff

Begin forwarded message:

From: NLM NCBI nobody <nobody@ncbi.nlm.nih.gov>
Date: February 23, 2020 at 4:42:09 PM GMT+8
To: "Lane, Cliff (NIH/NIAID) [E]" <(b) (6)>
Subject: COVID 19 References

This message contains search results from the National Center for Biotechnology Information ([NCBI](#)) at the U.S. National Library of Medicine ([NLM](#)). Do not reply directly to this message

Sent On: Sun Feb 23 03:42:03 2020

30 selected items

PubMed Results

Items 1-30 of 30 ([Display the 30 citations in PubMed](#))

1. [A Novel Coronavirus From Patients With Pneumonia in China, 2019](#)
N Zhu et al. N Engl J Med 382 (8), 727-733. 2020. PMID 31978945.
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H Nishiura et al. J Clin Med 9 (2). 2020. PMID 32054045.

Reanalysis of the epidemic curve from the initial cluster of cases with novel coronavirus (2019-nCoV) in December 2019 indicates substantial human-to-human transmission. ...

24. [CT Manifestations of Two Cases of 2019 Novel Coronavirus \(2019-nCoV\) Pneumonia](#)

Y Fang et al. Radiology 200280. 2020. PMID 32031481.

25. [Emergence of a Novel Coronavirus Causing Respiratory Illness From Wuhan, China](#)

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In December 2019, a novel coronavirus (2019-nCoV) caused an outbreak in Wuhan, China, and soon spread to other parts of the world. It was believed that 2019-nCoV was tran ...

28. [Estimation of the Transmission Risk of the 2019-nCoV and Its Implication for Public Health Interventions](#)

B Tang et al. J Clin Med 9 (2). 2020. PMID 32046137.

Since the emergence of the first cases in Wuhan, China, the novel coronavirus (2019-nCoV) infection has been quickly spreading out to other provinces and neighboring coun ...

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N Tang et al. J Thromb Haemost. 2020. PMID 32073213.

The present study shows that abnormal coagulation results, especially markedly elevated D-dimer and FDP are common in deaths with NCP.

Dear All,

We sincerely look forward to speaking with you tomorrow for the consultation on ***Financing Coronavirus Disease 2019 (COVID-19) Vaccine Development***. In anticipation of this important meeting, kindly find attached a background paper for the consultation titled “Funding the development and manufacturing of COVID-19 vaccines” as well as a meeting agenda. These documents have also been circulated through the calendar invitation, for your convenience.

Please do not hesitate to reach out with any questions.

Many thanks,
Gabrielle Williams
WBG Health Team

From: WB Health Events
Sent: Thu, 20 Feb 2020 15:13:38 +0000
To: NkengasongJ@africa-union.org; (b) (6); (b) (6); (b) (6)pete
(b) (6); (b) (6); Glass, Roger (NIH/FIC) [E]; (b) (6); Fauci, Anthony (NIH/NIAID) [E]; Lane, Cliff (NIH/NIAID) [E]; Higgs, Elizabeth (NIH/NIAID) [E]; (b) (6) Dan Peters; (b) (6); (b) (6); (b) (6)ogbuabo
(b) (6); (b) (6); (b) (6); (b) (6); (b) (6)
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(b) (6); Fernandez, Jose (OS/OGA); (b) (6); (b) (6); (b) (6)Michael Kent Ranson; (b) (6)Andreas Seiter; Alexandru Valeriu Cebotari; Daniel Dulitzky; Dirk Reinermann; Ernest E. Massiah; Magnus Lindelow; Michael S. Bennett; Trina S. Haque; Ira Marina; Lydia Ndebele; Piot Carol; (b) (6)Bright, Rick (OS/ASPR/BARDA); Ming Xu; Chai, Shuen (OS/OGA); Weinberger, Collin (OS/OGA); LaHood, Natalie (OS/OGA); (b) (6)Anne Margreth Bakilana; Frederik Kristensen; Clara Ana Coutinho de Sousa; Angelique DePlaa; Peishan Yeo; Alida Uwera; Alexandra Humme; Anna Carroll
Cc: (b) (6); Muhammad Ali Pate; Feng Zhao; Mukesh Chawla; Rocio Schmunis; Adrienne Kate Mcmanus; Gabrielle Lynn Williams
Subject: Presentation | Consultation on Financing Coronavirus Disease (COVID-19) Vaccine Development | Thursday, February 20 from 9:30am to 1:30pm
Attachments: Yamey COVID-19 presentation Feb 20.pptx

Dear All,

Kindly find attached the power point presentation for today's meeting for your ready reference.

Many thanks,
Gabrielle

From: WB Health Events
Sent: Wednesday, February 19, 2020 2:49 PM
To: (b) (6) <(b) (6)> (b) (6) <(b) (6)>
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Funding the development and manufacturing of COVID-19 vaccines



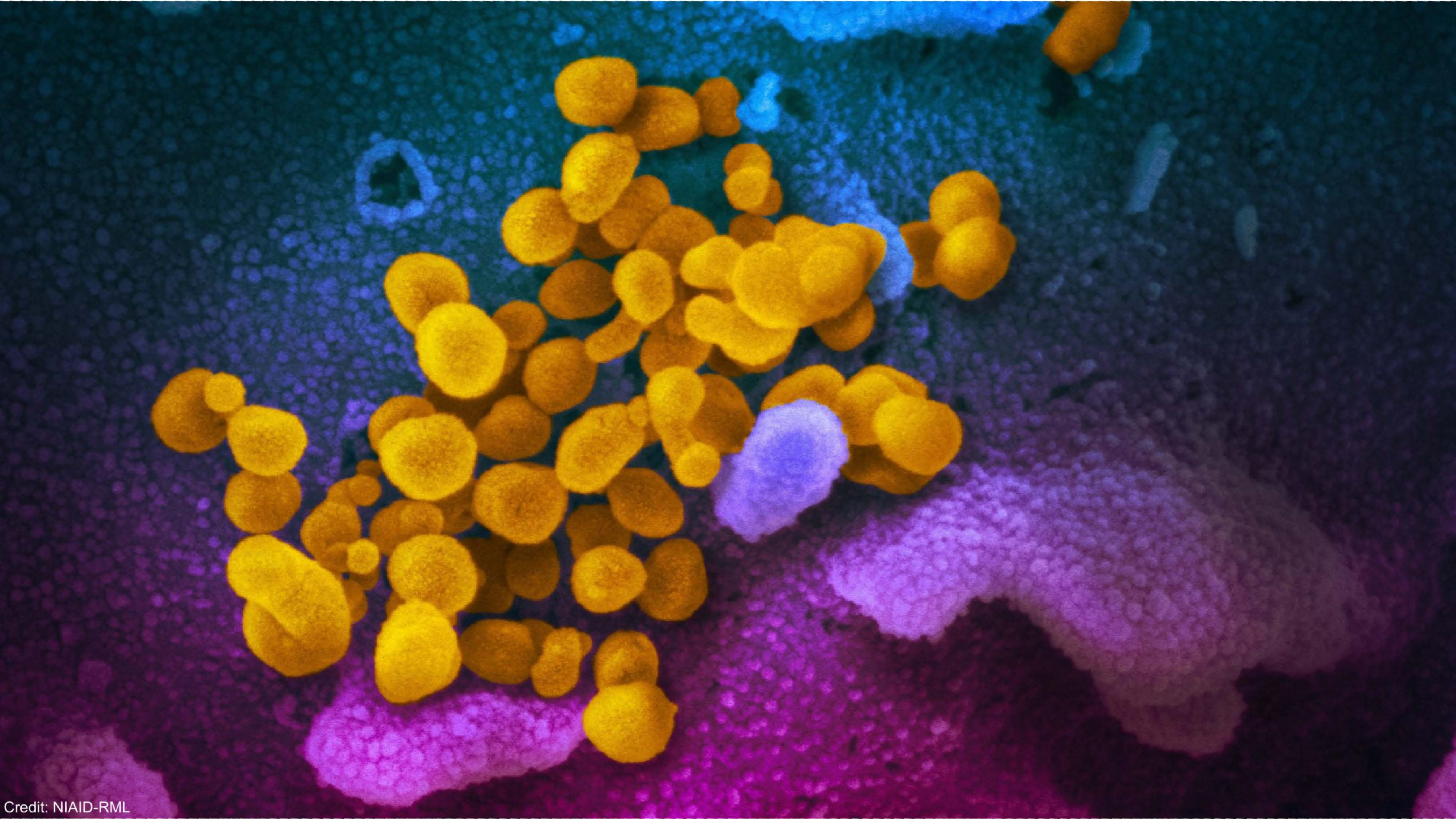
World Bank/CEPI financing of COVID-19 vaccine development consultation
World Bank
Office, Washington D.C. | February 20, 2020

Gavin Yamey
Professor of the Practice of Global Health and Public
Policy
Director, Center for Policy Impact in Global Health, Duke
University



— THE CENTER FOR —
POLICY IMPACT IN
GLOBAL HEALTH

 OPEN
CONSULTANTS



Structure of this presentation

3





1. Why do we need a COVID-19 vaccine?

Key messages

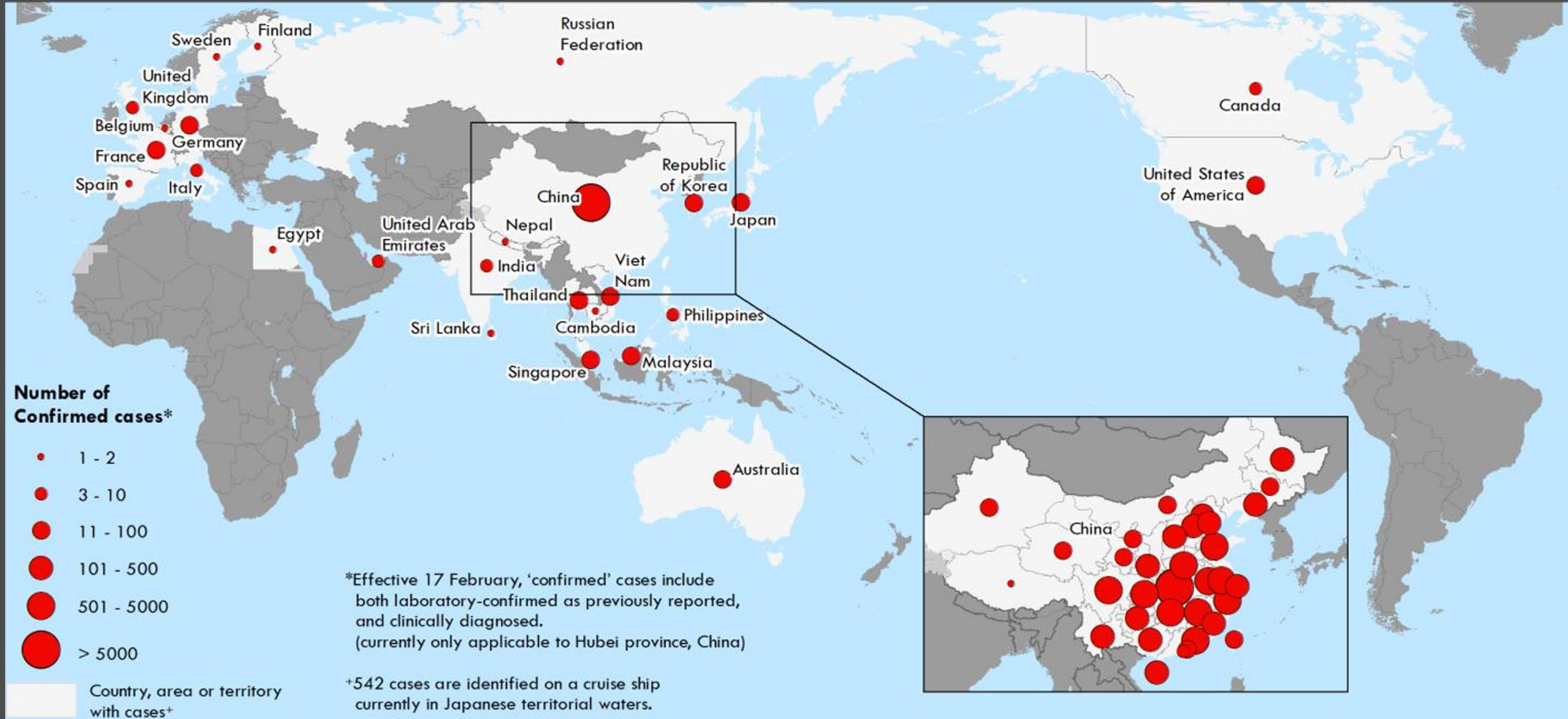
All governments must
prepare for transmission

Could become a pandemic
with waves of COVID-19
over years *and/or* a global
endemic virus

Vaccine critical for
reducing illness, deaths,
and economic impact

Compare costs (\$2B)
against likely losses
(\$280B in Q1 alone)

Distribution of COVID-19 cases as of 19 February 2020



Data Source: World Health Organization, National Health Commission of the People's Republic of China

Map Production: WHO Health Emergencies Programme

0 2,500 5,000 km
© World Health Organization 2020. All rights reserved.

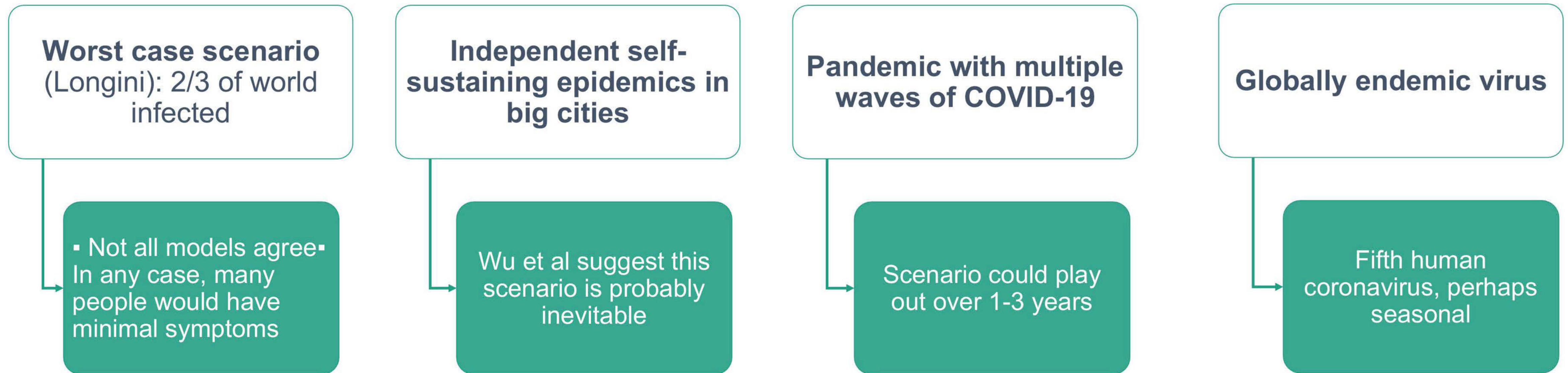
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Morbidity and mortality – no specific treatment

- **Cases and deaths: Over 75,000 laboratory-confirmed cases and over 2,000 deaths**
Compare with 774 reported deaths from SARS (2003)
Case fatality rate (CFR) unclear: 2.2% outside China, ~15% in Wuhan (?detection bias)
High risk of complications once in hospital: 1/4 patients to ICU in one study
Health workers at high risk: 1,746 Chinese health workers have been infected
Hard to track spread: lack of RDTs and the mildness of the symptoms in some infected people
No specific treatment: WHO estimates 82 trials of various MCMs are being conducted in China alone

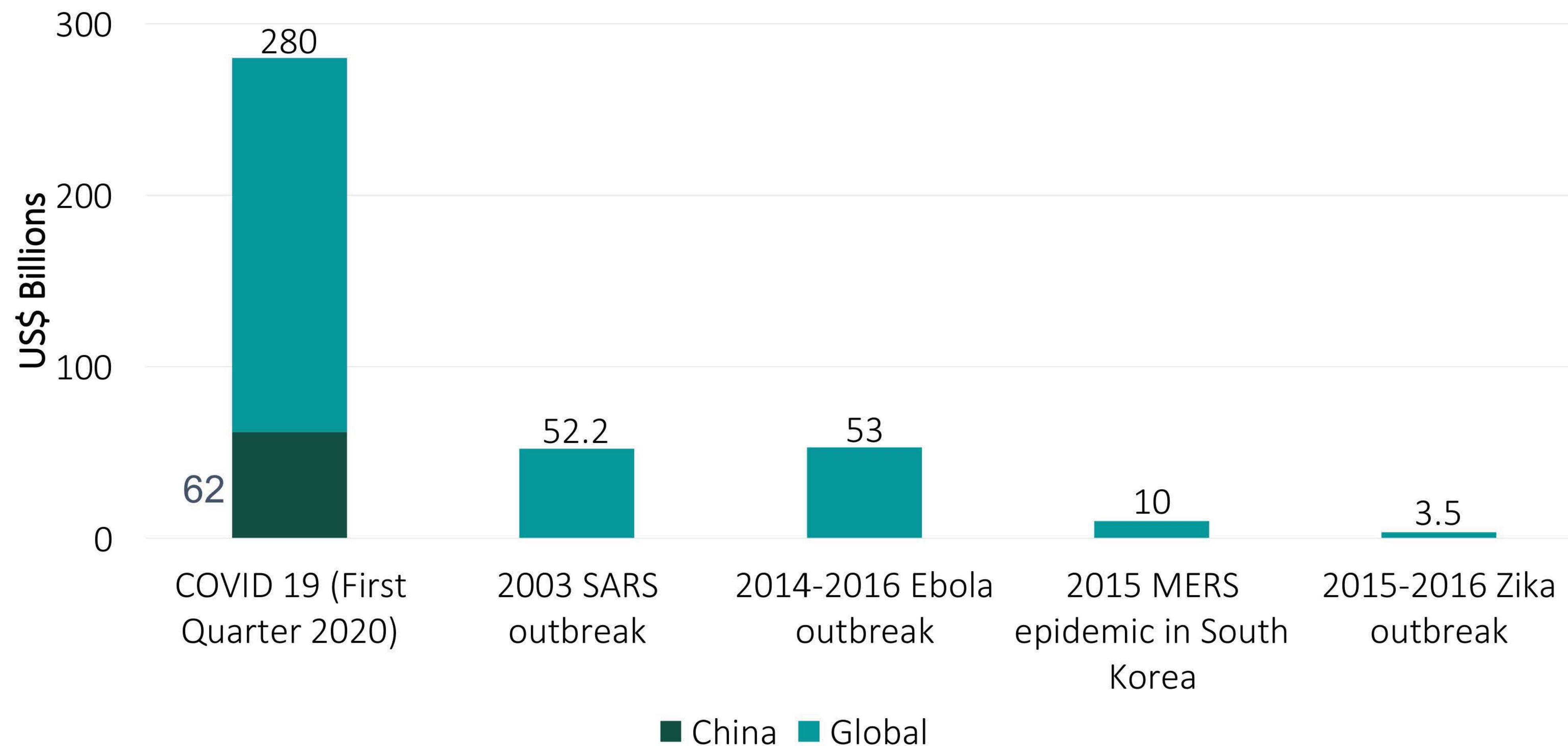
Potential future scenarios of COVID-19

Containment has likely slowed transmission but experts doubt that eradication can be achieved – future scenarios are highly uncertain, so vaccines are critical



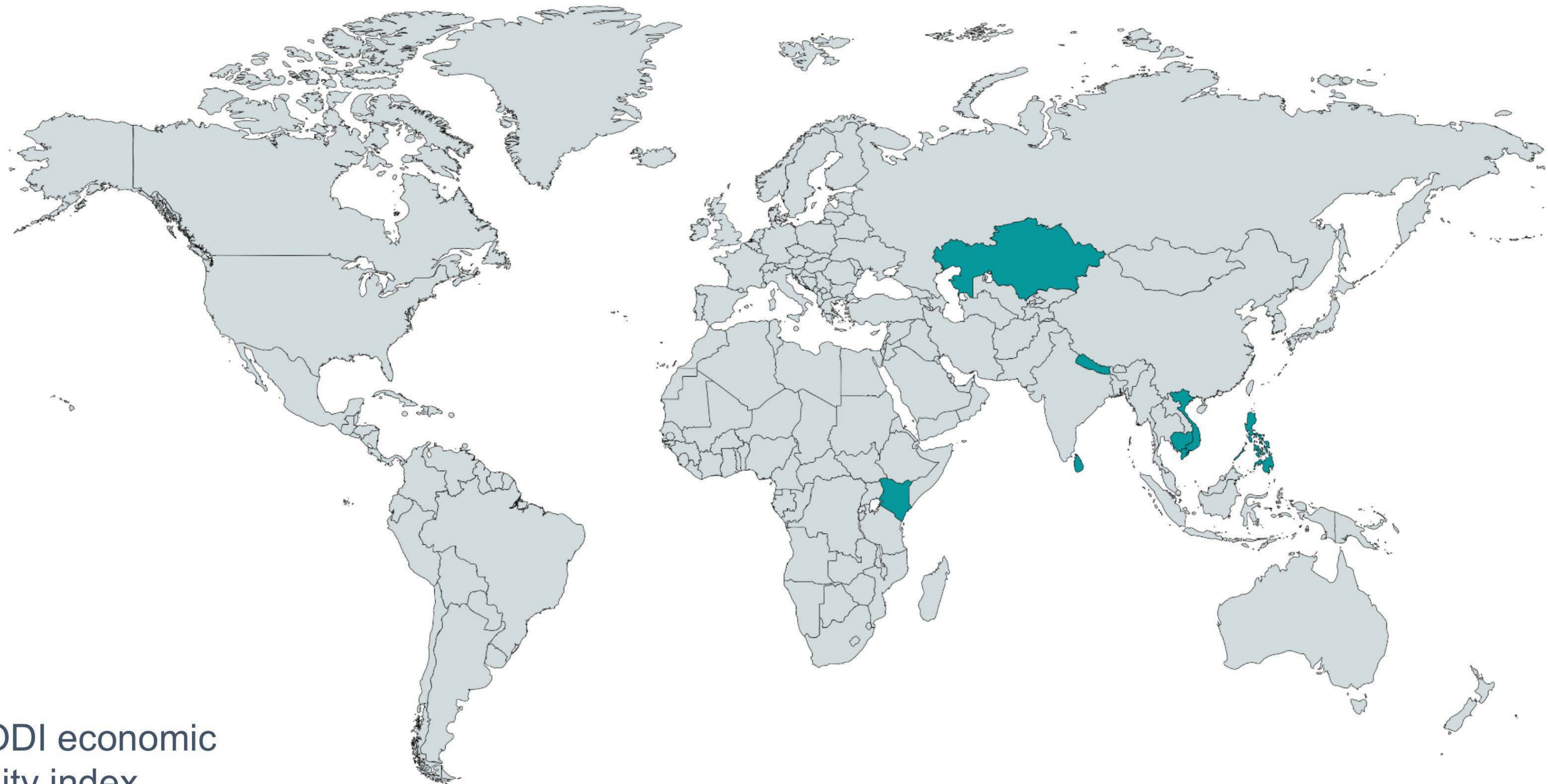
Economic losses from outbreaks

Additional rationale for COVID-19 vaccine development



The most vulnerable countries in economic terms

10



Source: ODI economic
vulnerability index

Need to act *now*

COVID-19 vaccine candidates are in pre-clinical development but could be ready for clinical trials in next few months

CEPI-funded candidates: 4 vaccine candidates funded through Phase 1. CEPI wants 6-8 because: Attrition rates

Current partners do not have production facilities to make a commercial product in bulk at a scale commensurate with needs in a pandemic

Other candidates: BARDA collaborations with J&J and Sanofi; candidates under development by Chinese government research organizations (funded by Jack Ma)

Why mobilize funds now: Since trials could begin by spring, investments in process development and scale up of manufacturing could begin immediately

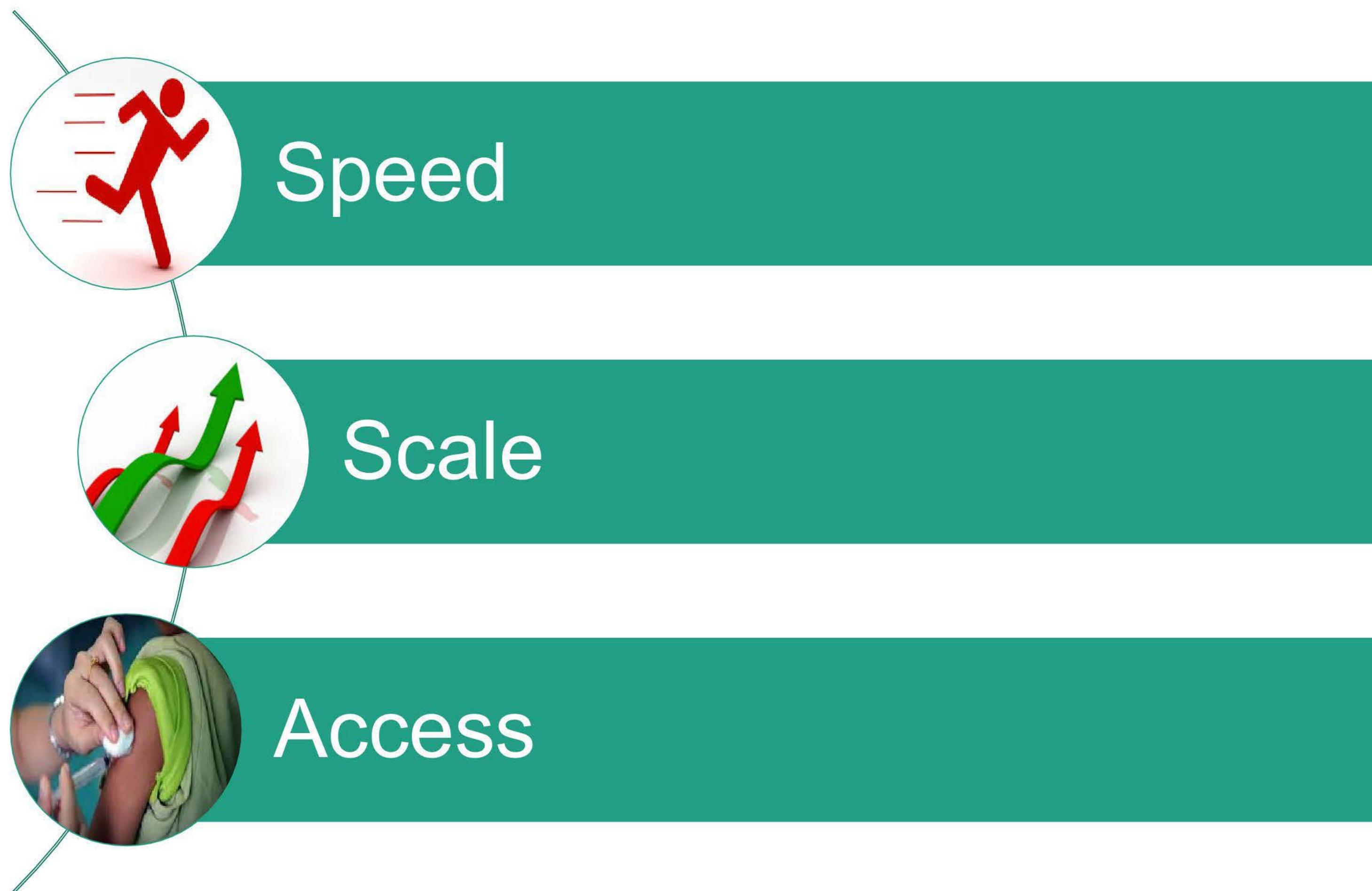
Best case scenario: Vaccines deployed, whether as licensed product or under appropriate 'emergency use provisions', within 12-18 months

Four COVID-19 candidate vaccines funded by CEPI

12

Vaccine candidate	Developer	Funding from CEPI
INO-4800	Inovio Pharmaceuticals, Inc.USA	US\$ 8.9 million
Molecular-clamp vaccine platform <i>(Protein sub-unit)</i>	University of QueenslandAustralia	<i>Up to</i> US\$ 4.5 million
mRNA based vaccine	CureVac AGGermany	US\$ 8.4 million
mRNA based vaccine <i>(mRNA-1273)</i>	Moderna Inc. and NIAIDUSA	US\$ 0.9 million for manufacturing (clinical trial costs covered by NIAID)

Core goals of a vaccine funding push



Goals entail large investments, short timelines, tolerance for risk

COVID-19 vaccine funding push: broader global health funding context



- **Future outbreaks:** We have an opportunity to establish a new epidemic vaccine funding mechanism that is “ready to go” for any future outbreak
Emerging infections and neglected diseases: first step in developing a sustained mechanism to mobilize new financing for phase 3 trials & product manufacturing for broad range of diseases
Complementarity: this effort should be complementary to other fund-raising processes (e.g., WHO’s mobilization of resources for pandemic response and preparedness, upcoming Gavi replenishment)

2. How much funding is needed?

Key messages

\$2B to develop 1 or more vaccine

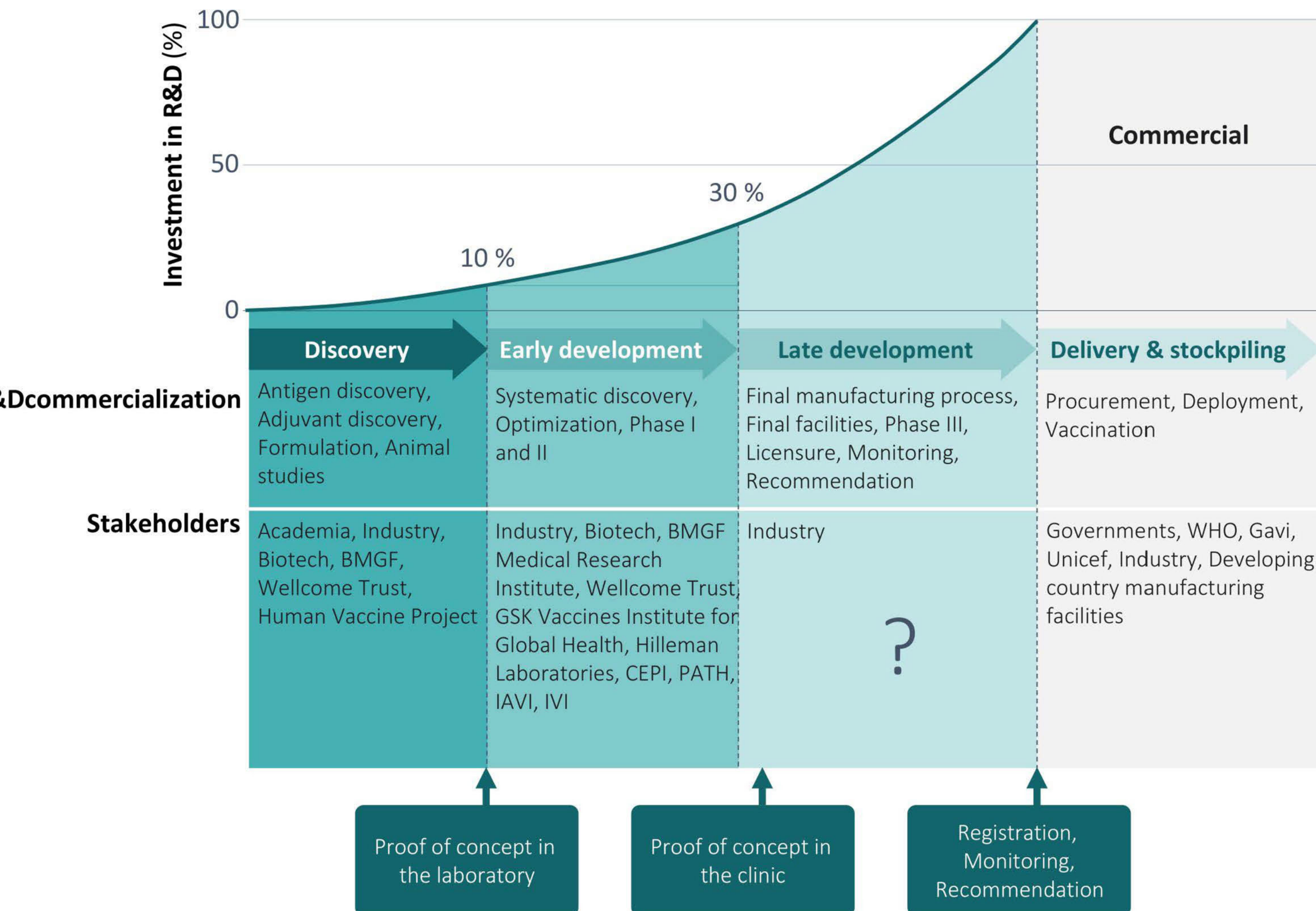
Costs are for development up to point at which vaccine can be licensed or used under emergency provisions

Does not include costs for subsequent manufacturing, delivery, or administration

Funding is needed for all stages of development (CEPI used \$100M of unprogrammed funds)

Late stage vaccine development: a valley of death

17



- 📍 Late development is responsible for ~70% of total development costs. There is a major gap in the financing architecture for late development (denoted by “?”). Phase IV costs can also be substantial (not shown in the graphic).
- 📍

Up to \$2 billion is needed

CEPI estimates that up to \$2bn is needed to accelerate the development of, scale up, and preparation to roll out vaccines against COVID-19 (indicative estimates)

Progress 8 candidates from pre-clinical to phase 1: clinical development cost up to \$10m for each candidate

Support for scale up, process development and manufacturing, at risk, while candidates are in phase 1: allows for rapid initiation of phase 2/3 trials. Assumes initial investments would be required in all 8 candidates, for an average of \$70m per candidate

Progress 6 vaccine candidates through phase II/III: clinical development costs of up to \$150m each including clinical trial material cost

Licensure: If CEPI were to progress 3 vaccine candidates to full licensure there would be additional costs of up to \$100m per candidate

Does not include costs for subsequent manufacturing, delivery, or administration



3. How to mobilize funding?

Key messages

“All of the above approach”—public, philanthropic, & private sectors

Strong case for investment from national health budgets as part of health system preparedness

Role for innovative financing (IFFIm, AMCs, PEF) and World Bank mechanisms

May be valuable to match different financing instruments with different development stages

New financial commitments are needed to close the \$2bn funding gap

Closing the \$2 billion gap will require new contributions from all sectors – no funds should be diverted from other key global health investments

OECD governments: Alongside new ODA (e.g. UK, Norway), there is a strong rationale for these governments to tap into budgets of their health and science ministries to fund development and deployment of COVID-19 vaccines (health system preparedness)

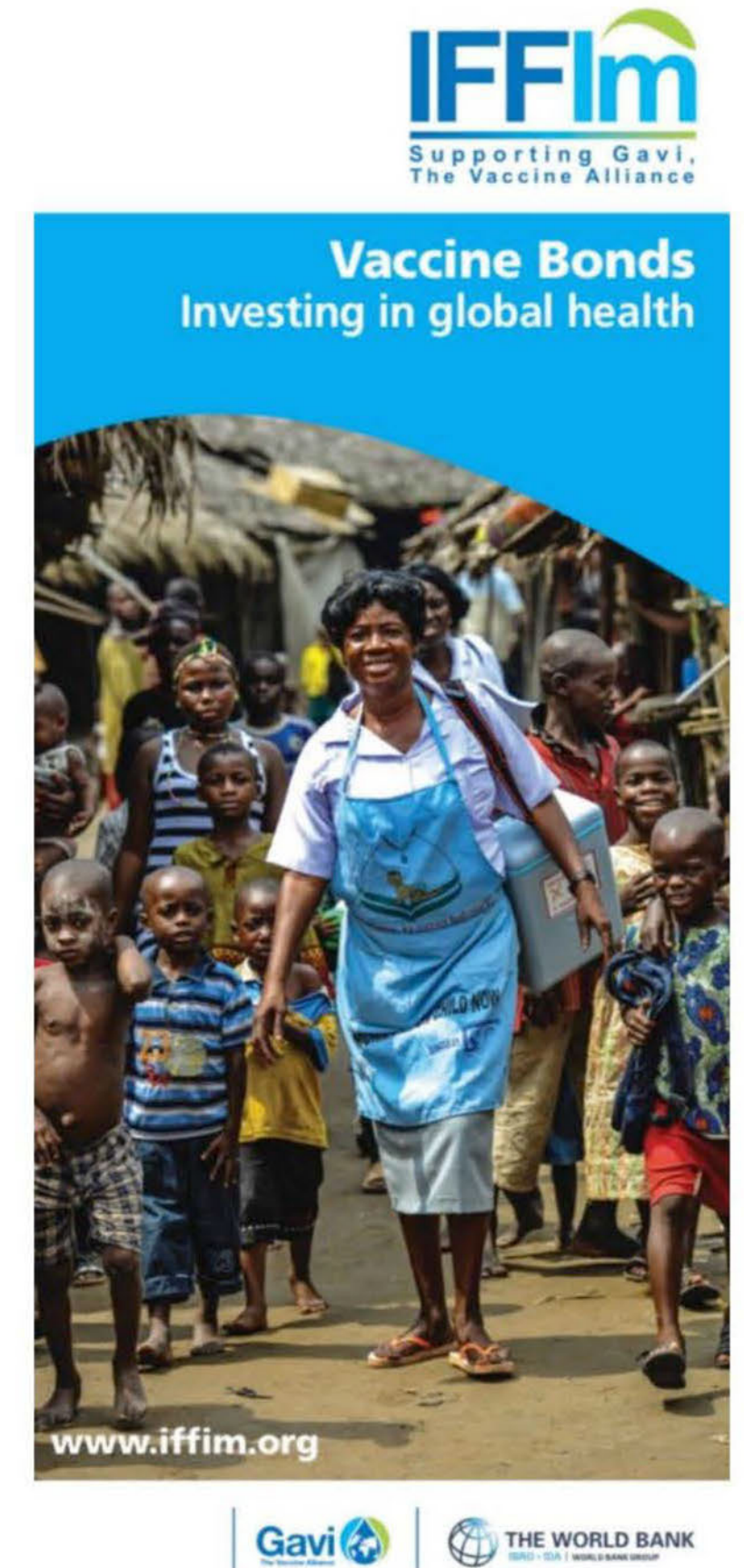
Emerging economies: Face the same threat and should support COVID-19 vaccine funding window

Philanthropists: Philanthropic funders should follow the lead of Bill & Melinda Gates Foundation (\$100m pledge in response to the epidemic) and the Wellcome Trust (GBP 10m)

Private sector: Cascading consequences of COVID-19 in China show that companies are highly dependent on global supply chains & have a strong economic incentive to invest in vaccine development (in addition to moral compulsion)

Innovative financing approaches

Vaccine bonds are an existing model that could be used to help finance the development and deployment of COVID-19 vaccines. IFFIm uses financial markets—through issuance of bonds—to turn long-term contributions by donor countries into current, or “frontloaded,” cash. IFFIm supports Gavi’s vaccine programs & has received legally binding pledges from 10 donors totaling US\$6.6 billion spanning 23 years to 2030. The World Bank is IFFIm’s treasury manager. In June 2019, Norway pledged NOK600 million (US\$66 million) to IFFIm to support CEPI’s vaccine development efforts. As an existing model, IFFIm bonds could easily be used to help finance the development and deployment of COVID-19 vaccines. Bonds could be blended with direct contributions from donors.



Innovative financing approaches *cont'd*

The Pandemic Emergency Financing Facility (PEF) An alternative bond-based mechanism, with cash and insurance windows. Undergoing review - “PEF 2.0” is due to be launched by May 2020 Cash window could potentially be used for development and/or manufacturing and delivery of a pandemic vaccine, but this approach has not been fully tried and tested

Advanced market commitment (AMC) Gavi’s AMC for pneumococcal vaccines guarantees the price of vaccines once they have been developed. Funding commitments by donors provide manufacturers the incentive they need to expand manufacturing capacity (and perhaps invest in R&D?). In exchange, companies sign legally binding commitment to provide the vaccines at a price affordable to developing countries in long term

Another example: advanced purchase commitment (APC) between Gavi and Merck. Based on a pre-payment made by Gavi, Merck committed to create a stockpile of its Ebola vaccine

World Bank instruments A number of instruments within the World Bank’s health portfolio, such as contingent emergency response components, could also be leveraged

4. How could CEPI be leveraged as a funding vehicle?

Key messages

Existing platform with scientific expertise and networks; low transaction costs to expand this platform

If resourced for COVID-19, could support pre-clinical development, clinical development & “scale out”

Already supported by a World Bank FIF—highly flexible model

Equitable access policy & governance arrangements easily adapted

Vehicle for funding first 3 steps in COVID-19 development

26



Why CEPI?

Using CEPI as an existing platform to finance advanced development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access:

Mission: Stimulate and accelerate development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks

Current funding focus: Early development (to phase 2b). However, it can fund phase 3 in certain circumstances (e.g., it will fund late stage trials of two Chikungunya candidate vaccines):

Clear need: Funding for phase 3 trials can be mobilized

Transaction costs for “add-on” functions: By using an existing platform as an “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism

Why CEPI? *cont'd*

- **Expanding expertise:** Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments
- Benefits of being supported by a World Bank FIF**
- FIFs allow for contributions from non-government stakeholders**
- FIF recipients are not limited to Bank-eligible countries**
- Flexibility in World Bank's role** (pass-through, program management functions and implementation support) and in governance and design
- Can channel funding rapidly**
- CEPI's governance:** flexible enough to adapt to expanded scope of work contemplated by this new financing window for COVID-19 vaccine development (e.g. expanding SAC to include experts on late stage trials and manufacturing, adding new investors to the council)
- Long term mechanism:** Once a funding window for late stage development is in place, it would be “ready to go” for future outbreaks



5. Manufacturing, global access, and regulatory concerns

Key messages

Making large volumes (e.g. 1B doses) will require consortium of manufacturers (MNCs, CMOs, DCVMs) ♦ PPP model of bulk manufacturing

*Affordability and access must be bedrock of COVID-19 vaccine funding push
→ GPG approach*

Use public \$ to procure vaccine & allocate it pro rata to countries (prevents HICs monopolizing vaccine)

Regulatory bodies recognize urgency of providing a simplified/expedited joint regulatory review of COVID-19 MCMs

Manufacturing

Establishing large-scale manufacturing capacity for COVID-19 vaccines: Number of doses: In worst-case scenario, very large number of COVID-19 vaccine doses will need to be manufactured in short time period (e.g. 1 billion doses in 12-18 months time) **Role of MNCs:** To produce needed volumes of vaccine, large MNCs will likely have to be engaged in some way. Yet such MNCs are wary of being asked to manufacture epidemic and pandemic vaccines (e.g., high opportunity costs, IP concerns) **Consortium model:** To ensure the large-scale production of the vaccine, a new public private partnership model for bulk manufacturing of the COVID-19 vaccine by a consortium of manufacturers (MNCs, CMOs, and DCVMs) will probably be needed **Profit motive:** If COVID-19 becomes an endemic global pathogen, it would highly profitable for MNCs to manufacture vaccine and sell it using a tiered pricing model

Global access: equitable access licensing

32

CEPI does not take ownership of IP



“stage-gate reviews” to review compliance with the equitable access mandate

Can use “step-in rights” to move candidate forward
awardee is “unable or unwilling to further vaccine development and equitable access”

If company cannot keep commitment to making a product available or affordable, CEPI could identify a new awardee to which to transfer the IP

Call for phase 3 COVID-19 testing could embed its own unique access requirements into the agreement (including triggers for step-in rights)

Global access: COVID-19 vaccine as a GPG

33

Poor are hit “first and worst” by outbreaks

One option is a global public good model



Global Public Good

Any model in which only HICs can access COVID-19 vaccine would be unacceptable

Procure vaccine with public \$ and allocate pro rata to countries

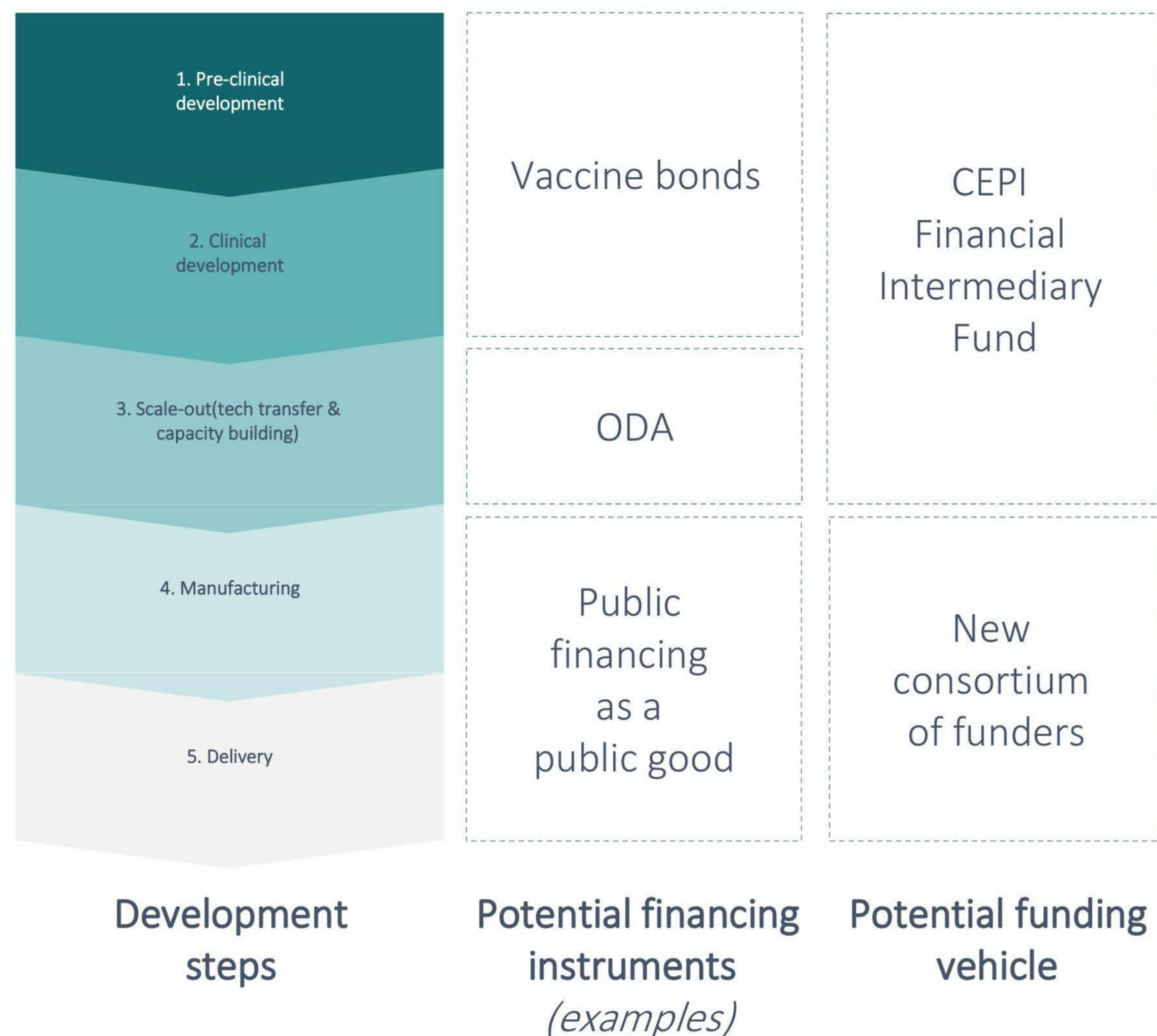
Must avoid scenario in which HIC governments enter into bilateral purchase contracts with manufacturers (monopoly)

Consortium of manufacturers ideally provides “cost plus” contract for sales to a global purchasing agent for a time-limited period

If COVID-19 transitions to become a globally endemic pathogen, a tiered pricing model could then be adopted

Funding approach to COVID-19 vaccine development

Pandemic scenario with multiple waves of COVID-19 over years



📍 Different financing instruments may be better suited to different steps in the process

📍 Figure is just an illustrative schematic

📍 How to mix and match funding instruments requires further exploration

Expediting regulatory approval



- **Ebola epidemic exposed hurdles: During the 2014-2016 Ebola epidemic in west Africa, there was widespread agreement that a new mechanism was needed to rapidly agree on trial designs and collaborate across borders on fast-track scientific assessment, regulatory approval, and roll-out** Cannot be “business as usual” for **COVID-19 MCMs: Regulatory agencies recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs**

6. Conducting trials during outbreaks

Key messages

Need to learn lessons from trials conducted during Ebola in West Africa

Designing such trials can be challenging; new approaches have been developed (e.g. adaptive trials)

Ethical issues and community participation should not be an afterthought

Need an ethical, collaborative approach to conducting research during COVID-19 outbreak

Conducting trials during an epidemic

Challenges
Unpredictability: The unpredictability of the duration of an epidemic makes enrolling and completing a trial difficult
Patient numbers: Enrolling a sufficient number of patients is often impossible
Capacity: Often no capacity to conduct clinical trials in low-resource settings
Funding: Often not enough funding to cover costly, large phase III trials
Ethical challenges: Ethics of using investigational new drugs
WHO advisory panel: compassionate use is “justified as an exceptional emergency measure” Such use should not “preclude or delay the initiation of more conclusive investigations of the intervention(s) in properly designed clinical studies”

Conducting trials during an epidemic *cont'd*

Solutions
Adaptive clinical trials Use results emerging in the trial to modify trial's course in accordance with pre-specified rules
Stepped wedge trials Introduce intervention by random allocation at regular intervals to a cluster of participants until all clusters eventually receive the intervention
Non-randomized trials
Capacity building programs
CREDO (Clinical REsearch During Outbreaks) program: TDR, International Severe Acute Respiratory & Emerging Infections Consortium, UK
Public Health Rapid Support Team

Ethical concerns conducting trials during an outbreak

40

Research should be guided by three key values: equal respect, help reduce suffering, and fairness
Calls for action by research funders, governments, and others to:
Not support research unless basic health needs of participants are addressed through the response effort
Involve communities in community engagement mechanisms during emergency research
Promote fair and equitable collaborations between ALL research organizations
Support emergency planning for properly resourced preparedness between emergencies



7. Key takeaways

Key takeaways

- **We need a vaccine:** Given uncertain trajectory of COVID-19, must prepare for a worst-case scenario ◇ vaccine would be a critical MCMWe need a funding push: Without this push, COVID-19 vaccine candidates will languish ◇ how will public, philanthropic, and private funding commitments be made? **Advantages of CEPI:** Funding early development through phase 3 trials and “scale-out” under CEPI, an existing platform, offers the advantages of speed, flexibility, and low transaction costs **Who will fund manufacturing and delivery?** CEPI isn’t the right mechanism for funding manufacturing, purchasing, delivery ◇ what will a new funding consortium for these steps look like?

Key takeaways *cont'd*

- **Tailoring financing mechanisms:** Need to better understand how different mechanisms may be suited to financing different steps in COVID-19 vaccine development process
A new approach: New funding approach for COVID-19 vaccine could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics, to break “cycles of panic and neglect” Could be an important step in building a broader ecosystem to fund phase 3 and manufacturing for EIDS and neglected diseases
Complementarity: Must be a complementary effort (e.g., must not siphon ODA from WHO or Gavi)
Using vaccine bonds or an IFFIm mechanism for COVID-19 effort could be one way to take pressure off these other mobilization efforts
Current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts

Thank You

Authors: A collaborative team of authors from Duke University's Center for Policy Impact in Global Health (**Gavin Yamey**), Open Consultants (**Marco Schäferhoff**), the World Bank's Health, Nutrition and Population Global Practice (**Muhammad Pate, Mukesh Chawla, Kent Ranson, and Feng Zhao**), and CEPI (**Richard Hatchett, Richard Wilder**) wrote the background paper.

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Many thanks,
Gabrielle Williams
WBG Health Team

Consultation on Financing Coronavirus Disease 2019 (COVID-19) Vaccine Development

Thursday, February 20, 2020 | 9:30am – 1:30pm
World Bank Main Complex, Floor C2, Conference Room MC C2-125

AGENDA

- | | |
|-----------------|--|
| 9:30 – 9:45am | Welcome and Opening Remarks <ul style="list-style-type: none">- <i>Muhammad Ali Pate, Global Director, Health, Nutrition & Population, WBG</i>- <i>Richard Hatchett, CEO, CEPI</i> |
| 9:45 – 9:55am | Overview of the Coalition for Epidemic Preparedness Innovations (CEPI) in the Context of COVID-19 <ul style="list-style-type: none">- <i>Richard Hatchett, CEO, CEPI</i> |
| 9:55 – 10:05am | Overview of World Bank's Response to COVID-19 <ul style="list-style-type: none">- <i>Mukesh Chawla, Adviser, Health, Nutrition and Population, WBG</i> |
| 10:05 – 10:35am | Presentation of Background Paper:
<i>"Funding the development and manufacturing of COVID-19 vaccines"</i> <ul style="list-style-type: none">- <i>Gavin Yamey, Public Policy Director, Center for Policy Impact, Duke University</i> |
| 10:35 – 10:50am | <i>Coffee break</i> |
| 10:50 – 12:20pm | Discussion on Background Paper <ul style="list-style-type: none">- <i>Moderated by Feng Zhao, Practice Manager, Health, Nutrition and Population, WBG</i>- <i>All participants</i> |
| 12:20 – 12:30pm | Closing and Next Steps <ul style="list-style-type: none">- <i>Richard Hatchett, CEO, CEPI</i>- <i>Muhammad Ali Pate, Global Director, Health, Nutrition & Population, WBG</i> |
| 12:30 – 1:30pm | Lunch |

Funding the development and manufacturing of COVID-19 vaccines

Background paper for the World Bank/CEPI financing COVID-19 vaccine development consultation on February 20, 2020

Authors

A collaborative team of authors from Duke University's [Center for Policy Impact in Global Health](#) (Gavin Yamey), [Open Consultants](#) (Marco Schäferhoff), the World Bank's Health, Nutrition and Population Global Practice (Muhammad Pate, Mukesh Chawla, Kent Ranson, and Feng Zhao), and [CEPI](#) (Richard Hatchett, Richard Wilder) wrote this paper. The paper aims to enhance discussions at the consultation.

Executive summary

► **Why do we need a vaccine?** The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide and has the potential to become a pandemic. The WHO has declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and has advised all governments to prepare for transmission in their countries. There is uncertainty about what will happen next, e.g., there could be a pandemic, with multiple waves of COVID-19 over 1-3 years, and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production.

► **How much funding do we need and what are the core goals of this funding push?** CEPI has proposed three core goals for its vaccine development efforts—*speed*, *scale*, and *access*—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of \$2 billion. It must be noted that these costs are much lower than the costs of inaction—the economic costs of COVID-19 in China *alone* are estimated to be \$62 billion in the first quarter of 2020. These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery, or administration.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of emerging infectious diseases (EIDs) and neglected diseases.

► **How could the funding gap for COVID-19 vaccine development and deployment be closed?** Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and deployment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds and advanced market commitments, and instruments within the World Bank's health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine

development and deployment process (Figure 1). For example, vaccine bonds could be used to finance clinical and process development; official development assistance (ODA) could fund tech transfer from multinational companies to manufacturers in middle-income countries (MICs), including capacity building; public funds could be used to procure vaccines as a global public good (GPG).

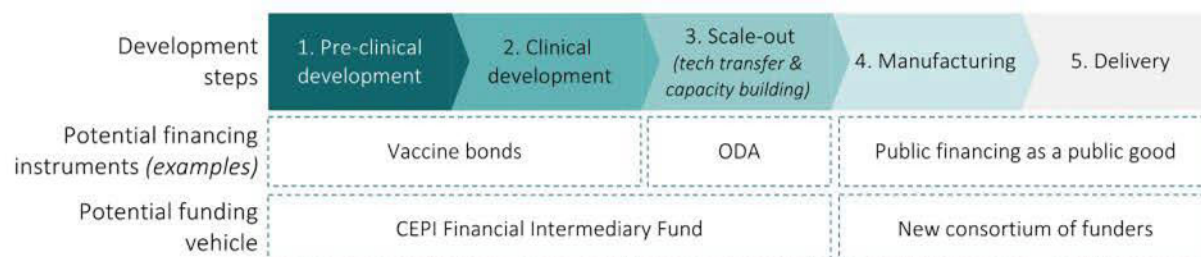


Figure 1. Schematic of a funding approach to COVID-19 vaccine development (pandemic scenario with multiple waves of COVID-19 over 1-3 years)

► **Why would CEPI be an appropriate venue for a new financing window for the development of COVID-19 vaccines?** If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out” (i.e. tech transfer and capacity building in MICs). It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit (Figure 1). CEPI funds the development of vaccines against a range of WHO’s Blueprint priority pathogens. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Using CEPI as the platform would mitigate concerns about fragmentation and “cannibalization” of R&D funding for EIDs/neglected diseases. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. Even if the COVID-19 outbreak wanes, opening this new window at CEPI will help to sustain attention to the importance of epidemic vaccine development. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Similarly, CEPI’s existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

► **How would manufacturing and delivery of COVID-19 vaccines be funded?** The fourth and fifth steps in the COV-19 vaccine development process—manufacturing and delivery—would require a separate financing mechanism outside of CEPI. A consortium of public and philanthropic funders is likely to be needed.

► **How would the manufacturing challenges be addressed?** For COVID-19 vaccines under development through CEPI funding, none of the current partners has experience in bulk

manufacturing and they have not previously licensed a vaccine. CEPI is in the process of reviewing additional proposals and anticipates expanding its portfolio with additional vaccine candidates, and it is hoped that some of these will be sponsored by experienced manufacturers. For manufacturing at scale, it is likely that a consortium of manufacturers—including multinational companies (MNCs), contract manufacturing organizations (CMOs), and developing country vaccine manufacturers (DCVMs)—will be needed to produce the large numbers of doses that may be required (e.g., a billion doses 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed.

► **How would regulatory challenges be addressed?** Regulatory agencies and bodies, including the WHO, the US Food and Drug Administration, the European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. There is widespread recognition that a “business as usual” approach is not tenable given the speed at which a pandemic may spread.

► **How would global access to COVID-19 vaccines be ensured?** Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit “first and worst” by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In a pandemic scenario, with multiple waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this scenario, countries would probably need some additional way to prioritize who receives the vaccine. The consortium of manufacturers discussed earlier (MNCs, CMOs, and DCVMs) would ideally provide a “cost plus” contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would then be free at the point of care. If COVID-19 then becomes a globally endemic pathogen, successful vaccines could transition to commercial sales and a tiered pricing model could be adopted.

► **How can we ensure that a COVID-19 vaccine funding push does not siphon off funding needed for other global health priorities?** Additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be *complementary* to other fund-raising processes (e.g., WHO’s mobilization of resources for pandemic response and preparedness as well as the upcoming Gavi replenishment). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.

Abbreviations

AMC	Advanced Market Commitment
APC	Advanced Purchase Commitment
BMGF	Bill & Melinda Gates Foundation
CEPI	Coalition for Epidemic Preparedness Innovations
CFR	Case Fatality Rate
CREDO	Clinical REsearch During Outbreaks
DCVMs	Developing Country Vaccine Manufacturers
EIDs	Emerging Infectious Diseases
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FIF	Financial Intermediary Fund
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
IAVI	International AIDS Vaccine Initiative
IFFIm	International Finance Facility for Immunisation
IP	Intellectual Property
IVI	International Vaccine Institute
MCM	Medical Countermeasure
MICs	Middle-income Countries
MNC	Multinational Company
NOK	Norwegian Crone
NRAs	National Regulatory Authorities
ODA	Official Development Assistance
ODI	Overseas Development Institute
PATH	Program for Appropriate Technology in Health
PEF	Pandemic Emergency Financing Facility
PHEIC	Public Health Emergency of International Concern
R0	Basic Reproductive Number
SAC	Scientific Advisory Committee
SARS	Severe Acute Respiratory Syndrome
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Structure of this background paper

This paper is organized into eight sections. **Section 1** makes the case for why we urgently need a COVID-19 vaccine. **Section 2** argues that new funding for COVID-19 vaccine development is required for all development stages and gives estimates of how much funding is needed. **Section 3** examines ways to mobilize such funding. **Section 4** explores potential funding vehicles. It makes the case that CEPI is well placed to be the vehicle for funding pre-clinical development, clinical development, and “scale out,” but that a different vehicle would be needed for funding manufacturing and delivery. **Section 5** discusses governance of a CEPI funding window for development of COVID-19 vaccines. **Section 6** highlights vaccine manufacturing, IP, global access, and regulatory approval, and **Section 7** highlights issues (including ethical considerations) in conducting trials in the midst of the COVID-19 outbreak. **Section 8** briefly summarizes our main conclusions.

1. Introduction: the urgent need to develop and manufacture COVID-19 vaccines

Key messages: The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide and has the potential to become a pandemic. The WHO has declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and has advised all governments to prepare for transmission in their countries. There is uncertainty about what will happen next, e.g., there could be a pandemic, with multiple waves of COVID-19 over 1-3 years and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production. While the costs of development may be high (CEPI estimates the costs of clinical development and “scale-out” alone as up to \$2 billion), the costs of inaction are much larger (the economic costs of COVID-19 in China alone are estimated to be \$62 billion in the first quarter of 2020).

1.1 Current status of COVID-19

As of February 19 2020 at 16.00 (CET), the WHO [reports](#) that there have been 75,285 laboratory-confirmed cases of COVID-19 infection in 26 countries and 2,009 deaths. In comparison, there were [774 reported deaths](#) from the 2003 SARS outbreak. China’s National Health Commission [reports](#) that 1,716 health workers have been infected.

An initial [assessment](#) of the outbreak by Li and colleagues estimated that in the early phase of the COVID-19 outbreak in China, the epidemic doubled in size every 7.4 days and the basic reproductive number (R_0) was 2.2. It has been challenging to accurately track the spread, because of factors such as the lack of rapid diagnostic tests and the mildness of the symptoms in some infected people.

The case fatality rate (CFR) has been the subject of much debate. The CFR for cases outside China is [estimated](#) to be 2.2% (95% confidence interval, 0.6%-5.8%). The [first clinical study](#) of COVID-19 in patients in Wuhan reported a much higher CFR, of about 15%, though this estimate may be [prone to detection bias](#). Hospitalized patients in Wuhan have a high rate of transfer to the intensive care unit: a [study](#) by Wang and colleagues of 138 hospitalized patients found that 36 patients (26.1%) were transferred to the intensive care unit because of complications. There is no specific treatment, though a [large number of treatment trials](#) are now underway; the WHO [estimates](#) that there are 82 trials of various MCMs (including of antiretrovirals and traditional Chinese medicines) being conducted in China.

1.2 Potential future scenarios

The likely pattern of global spread is [debated](#) and is highly uncertain. For example, [modeling](#) by Ira Longini, co-director of the Center for Statistics and Quantitative Infectious Diseases at the University of Florida, an adviser to the WHO, suggests that up to two-thirds of the world could become infected. But other modelers argue this is a worst-case scenario, which even if true would be mitigated by the many people who would be minimally or mildly symptomatic. Models and estimates will be refined as new information becomes available.

A [study](#) by Wu and colleagues using flight data suggested that Beijing, Shanghai, Guangzhou, and Shenzhen are all at risk of substantial numbers of cases, and that “independent self-sustaining

outbreaks in major cities globally could become inevitable because of substantial exportation of pre-symptomatic cases.” Bogoch and colleagues [project](#) a high risk of spread from the Chinese mainland to Taipei, Bangkok, Tokyo, Seoul, Singapore, London, Sydney, Los Angeles, New York, Paris, San Francisco, Moscow, and Cairo. Efforts to contain the virus have clearly slowed its transmission, but at extraordinary cost, and it is unclear how long the quarantines and other measures employed can be maintained. While containment efforts continue for the time being, many experts now doubt that eradication can be achieved.

In addition to the possibility of multiple waves of COVID-19, there is also a [possibility](#) that COVID-19 becomes a globally endemic virus. Given this range of potential scenarios—a global pandemic, independent self-sustaining epidemics, or a globally endemic pathogen—vaccine development has become an urgent priority.

1.3 Economic consequences of inaction

In addition to their major health consequences, previous epidemics and pandemics have also been associated with [large economic losses](#):

- The global economic loss from SARS in 2003 was US\$52.2 billion (more than US\$6 million per case)
- The 2014-2016 Ebola outbreak led to a direct loss of US\$2.8 billion across Guinea, Liberia, and Sierra Leone and an estimated global social and economic burden in excess of US\$53 billion (more than \$1.8 million per case)
- The 2015 MERS epidemic in South Korea was estimated at the time to have resulted in economic losses approaching US\$10 billion (more than \$50 million a case)
- The 2015-2016 Zika outbreak led to an estimated loss of US\$3.5 billion in the Latin American and Caribbean region.

If the COVID-19 outbreak continues on its current trajectory, China is expected to lose up to [\\$62 billion](#) in the first quarter of 2020. The global loss is estimated to be \$280 billion within the same period. Oxford Economics [predicts](#) that China’s economic growth in the first quarter of 2020 will be 4% lower than in the first quarter of 2019. It also expects the global economy to grow by 0.2 percentage points less as a result of COVID-19. The anticipated economic losses are another reason why vaccine development is so urgent.

The Overseas Development Institute (ODI) [developed](#) a “vulnerability index” to estimate which countries are likely to be the most economically vulnerable to COVID-19. Based on countries’ likely exposure to COVID-19 and their poor preparedness to address the economic impacts, the index predicts that the most vulnerable countries in economic terms are Sri Lanka, the Philippines, and Vietnam, followed by Kazakhstan, Kenya, Cambodia, and Nepal.

2. Why funding is needed for the development of COVID-19 vaccines

Key messages: CEPI has proposed three core goals for its vaccine development efforts—*speed*, *scale*, and *access*—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of \$2 billion. These cost estimates presume development to the point at which the

vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery or administration.

Funding is needed for *all stages* of COVID-19 vaccine development. The first \$100M that CEPI is spending has come from unprogrammed funds already allocated to other projects (CEPI does not have an emergency response lockbox), so this funding also needs to be recouped.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of EIDs and neglected diseases.

2.1 The valley of death in funding late stage development for EIDs and neglected diseases

[Research](#) led by the Center for Policy Impact in Global Health at Duke University has illustrated a valley of death in the development of technologies to control both EIDs and neglected diseases. There is a large drop-off in the pipeline of candidates from phase II to III, which partly reflects the very high costs of phase III trials. For example, as of August 31, 2017, just 38 out of the 538 candidates (7%) in the pipeline for neglected diseases were in phase III.

At baseline, there is currently too little funding for late-stage trials, there are too few funders, and the financing is highly fragmented, creating inefficiencies. The result is that for many fatal or disabling conditions, the prospects for developing urgently needed control tools are very poor.

For vaccine development specifically, Rappuoli and colleagues have recently [shown](#) the high costs of late stage trials (Figure 2). While there have been improvements in early stage development, thanks to investments by the Bill & Melinda Gates Foundation, CEPI, PATH, and others, “these improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase.” Late development is responsible for about 70% of total development costs. There is a major gap in the financing architecture for such late development (Figure 2 shows this gap, which is denoted by “?”). The large costs and time commitments are explained by the need to (a) produce vaccine candidates according to good manufacturing practice (GMP) standards in purpose-built production facilities, (b) conduct large-scale phase III trials, (c) submit data to regulators, and (d) conduct post-marketing surveillance. Although not shown in the figure, phase IV costs can also be [substantial](#).

As described below, there are a number of promising COVID-19 vaccines in early development. However, unless dedicated funding is mobilized to fund this development, and then for late stage trials and manufacturing, these candidates will never be developed and deployed. As mentioned, CEPI has no emergency funds set aside, and so all stages of COVID-19 vaccine development need emergency funding.

While the acute, urgent focus is on funding for COVID-19 vaccine development, the current crisis reveals once again that we need to mobilize new financing, especially for phases III and manufacturing, for a broad range of health technologies for both EIDs and neglected diseases.

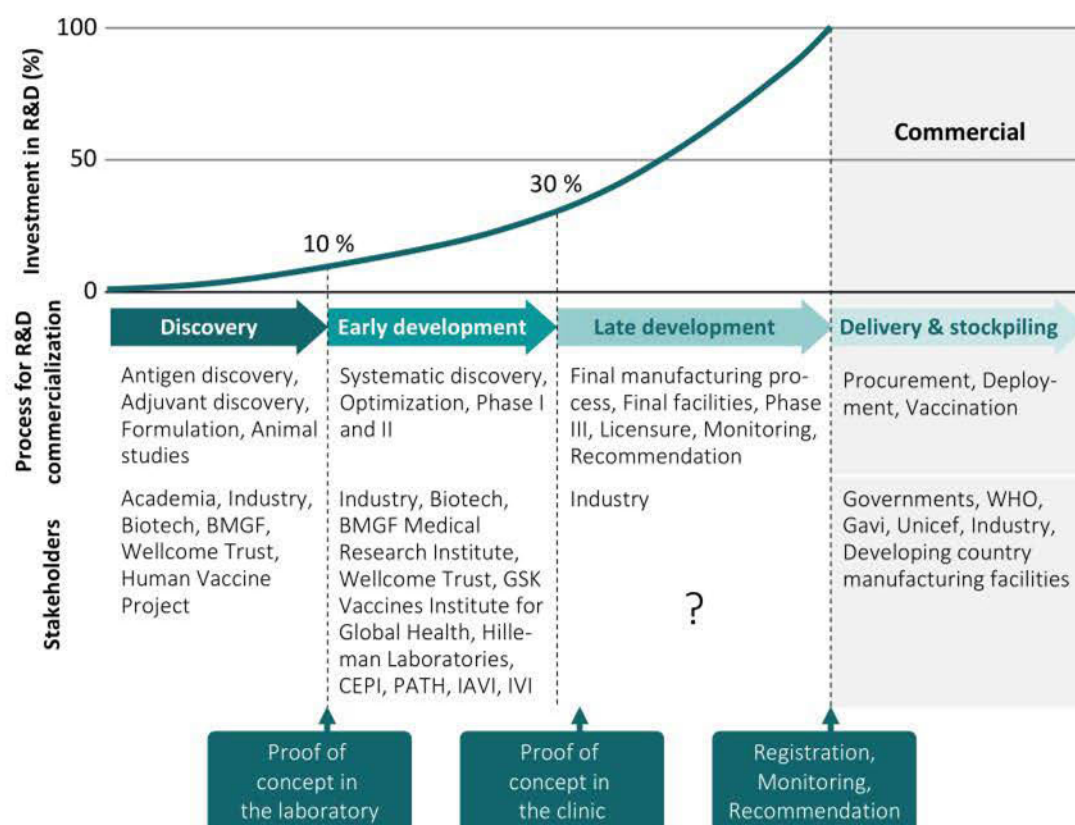


Figure 2. Stages of vaccine development and delivery

The figure shows three stages of vaccine development: discovery (10% of the R&D budget), early development (20% of the budget), and late development (70% of the budget). Under the graph are the funders and stakeholders involved at each step. A major gap can be seen in the financing architecture for late development (denoted by "?"). Figure adapted from a figure in: Rappuoli R, et al. Vaccines and global health: In search of a sustainable model for vaccine development and delivery. *Sci Transl Med.* 2019 Jun 19;11(497).¹

2.2 Status of current COVID-19 vaccines

CEPI is currently funding four candidates through Phase 1, all of which are still in pre-clinical development (Table 1). The platforms supporting these candidates are also being used to develop vaccines for other indications, several of which have reached clinical trials. CEPI recently issued a new call for proposals (the deadline was February 14, 2020), with the aim of expanding the portfolio to a total of 6-8 candidates. The portfolio needs such expansion, given (i) standard attrition rates during development, and (ii) the fact that the current CEPI-funded development efforts involve partners [that](#) do not have the production facilities to make a commercial product in bulk at a scale commensurate with the needs in a pandemic. While all are using innovative techniques to fast track vaccine candidate development, none have licensed a vaccine. Thus, there are substantial barriers ahead with respect to manufacturing and licensure (see below).

¹ **Abbreviations:** BMGF: Bill & Melinda Gates Foundation; CEPI: Coalition for Epidemic Preparedness Innovations; Gavi: Gavi, the Vaccine Alliance; GSK: GlaxoSmithKline; IAVI: International AIDS Vaccine Initiative; IVI: International Vaccine Institute; PATH: Program for Appropriate Technology in Health; UNICEF: United Nations Children's Fund; WHO, World Health Organization

There are [reports](#) of other COVID-19 vaccines being developed, including through a [collaboration](#) between Johnson & Johnson and BARDA, a [collaboration](#) between Sanofi and BARDA, and by Chinese government research organizations through [funding](#) by Jack Ma, Alibaba's founder.

COVID-19 vaccine candidates could potentially be ready for clinical trials in the next few months, and investments in process development and scale up of manufacturing could begin immediately, albeit at risk—hence the urgency to mobilize financing immediately.

Table 1. The four COVID-19 candidate vaccines funded by CEPI as of February 19, 2020

COVID-19 vaccine candidate	Developer	Funding from CEPI for COVID-19 vaccine development
INO-4800	Inovio pharmaceuticals	US\$ 8.9 million
Protein sub-unit (molecular-clamp vaccine platform)	University of Queensland	Up to US\$ 4.5 million
mRNA based vaccine	CureVac	US\$ 8.4 million
mRNA based vaccine (mRNA-1273)	Moderna Inc. in partnership with NIAID	US\$ 0.9 million for manufacturing (clinical trial costs covered by NIAID)

2.3 Costs to develop and deploy a COVID-19 vaccine

Key message: Up to \$2bn is needed to accelerate the development of, scale up, and prepare to roll out vaccines against COVID-19.

On February 14, 2020, CEPI provided a background paper called “Investment Case: Rapid Vaccine Development for COVID-19,” which it shared with us for the development of this paper. CEPI estimates that:

- Up to \$2bn is needed to “accelerate the development of, scale up, and prepare to roll out vaccines against 2019-nCoV [now called COVID-19]
- The best-case scenario would see vaccines that could potentially be deployed, whether as a licensed product or under appropriate ‘emergency use provisions’ within 12-18 months.”

The \$2bn estimate is based on the following:

- “Funding for an initial 8 vaccine candidates from preclinical through phase I, with clinical development cost up to \$10m for each.
- Support for scale up, process development and manufacturing, at risk,² while candidates are in phase I. Such investment will allow for the rapid initiation of phase 2/3 trials. The

² “At risk” in this context means beginning the investment in process development and scale-up without even knowing whether the vaccine candidate works. The process development and scale-up, in theory, are agnostic of the vaccine candidate, so that if a particular candidate failed and a new construct has to be developed, the

assumption is that initial investments would be required in all 8 candidates for an average of close to \$70m for each of those candidates.

- CEPI progresses 6 vaccine candidates through phase II/III, with clinical development costs up to \$150m each including Clinical Trial Material cost.
- If CEPI were to progress 3 vaccine candidates to full licensure there would be additional costs of up to \$100m per candidate.”

CEPI cautions that these are indicative budget estimates based on professional judgment and do not reflect specific budgets from the current set of performers.

These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery or administration.

3. Mobilizing an additional \$2 bn for COVID-19 vaccine development and deployment

Key messages: Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors, including from official development assistance (ODA) and domestic health investments. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and employment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds, advanced market commitments, as well as instruments within the World Bank’s health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine development and deployment process.

3.1 Public, philanthropic, and private sources

Given the scale of the threat, and the urgent need for additional financing, an “all of the above” approach is needed to close the funding gap, including new and additional ODA commitments (ODA should not be diverted or “cannibalized” from other key health investments). Many donors have already shown their commitments to the COVID-19 vaccine response, [including](#) to the WHO’s COVID-19 appeal. Norway [pledged](#) NOK 36 million and the United Kingdom [pledged](#) £20m to CEPI for COVID-19 vaccine development

All governments need to prepare for transmission of the SARS-CoV-2 virus in their countries, and investment in the development and deployment of a vaccine against COVID-19 is a critical component of preparedness. Thus alongside *new* ODA, there is a strong rationale for OECD governments to tap into the budgets of their health ministries (as part of their health systems investments aimed at pandemic preparedness) and their ministries of science and technology to fund advanced development and deployment of a COVID-19 vaccine. For those emerging economies with the means to do so, there is a similar rationale for these governments to also support the COVID-19 vaccine funding window.

investment has not gone to waste. It only goes to waste if the particular development program is cancelled altogether (which it might be if the candidate failed while others succeed).

Following the lead of the Bill & Melinda Gates Foundation, which recently [committed](#) US\$100 million in response to the epidemic, and the Wellcome Trust, which [pledged](#) GBP 10 million, philanthropic funding can help close the gap.

There is an important role for the private sector, not just in providing in-kind expertise but also as co-investors—along with the public and philanthropic sectors—in vaccine development and deployment. As the cascading consequences of the COVID-19 epidemic in China demonstrate, private sector companies are increasingly dependent on global supply chains (or on parts of the supply chain located in low-income countries and MICs) and they have a strong economic incentive to invest in the development of vaccines, in addition to any moral compulsion they may feel.

3.2 Innovative financing approaches

Vaccine bonds: The International Finance Facility for Immunisation (IFFIm) was launched in 2006 to rapidly accelerate the availability and predictability of funds for immunization. IFFIm uses the financial markets—through the issuance of bonds—to turn long-term contributions by donor countries into current, or “frontloaded,” cash. IFFIm supports Gavi’s vaccine programs and to date has received legally binding pledges from ten donors totaling about US\$6.6 billion spanning 23 years to 2030. The World Bank is IFFIm’s treasury manager. In June 2019, Norway pledged NOK 600 million (US\$66 million) to IFFIm to support CEPI’s vaccine development efforts. IFFIm bonds are therefore an existing finance model that could be used to help finance the development and deployment of a COVID-19 vaccine. Such IFFIm bonds could be blended with direct contributions from donors.

The Pandemic Emergency Financing Facility (PEF). An alternative bond-based mechanism is the PEF, [launched](#) in July 2017, which includes both a cash window and an insurance window. The PEF is currently undergoing review, including a review of the activation criteria for the insurance window (which have been [criticized](#) for being too narrow). “PEF 2.0” is due to be launched by May 2020. While PEF’s cash window could potentially also be used for funding the development and/or manufacturing and delivery of a pandemic vaccine, this is not an approach that has been fully tried and tested.

Advanced market commitments (AMCs). To de-risk the efforts of manufacturers (described further in Section 6.1), an AMC could be used. Gavi’s AMC for pneumococcal vaccines, for example, guarantees the price of vaccines once they have been developed.³ Funding commitments by donors provide vaccine manufacturers with the incentive they need to expand manufacturing capacity (there is some debate on whether AMCs could potentially also stimulate R&D). In exchange, companies sign a legally binding commitment to provide the vaccines at a price affordable to developing countries in the long term. Another example is the advanced purchase commitment (APC) between Gavi and Merck. Based on a pre-payment made by Gavi, Merck committed to create a stockpile of its Ebola vaccine, which is being used in the DRC today.

World Bank instruments. A number of instruments within the World Bank’s health portfolio, such as contingent emergency response components, could also be leveraged.

³ Though CEPI itself CEPI would not issue an AMC—it would hand off products ready for stockpiling to other partners in the ecosystem, such as Gavi.

3.3 Matching different financing instruments with different steps in vaccine development

Each of the different financing instruments discussed above may be better suited to funding particular stages of COVID-19 vaccine development. An illustrative schematic of this kind of matching is shown in Figure 1 on page 2. How to mix and match funding instruments requires further exploration.

4. CEPI as a venue for funding late stage development of COVID-19 vaccines

Key messages: If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out.” It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond and its existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance advanced development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

4.1. The advantages of CEPI as a venue for funding late stage development of COVID-19 vaccines

Although CEPI is only three years old (Box 1), it has established expertise in financing the development of a broad suite of epidemic and pandemic vaccines. It has already shown that it can very quickly fund COVID-19 vaccine developers and expand the portfolio of candidates under development. It has strong relationships with key stakeholders in ensuring the late stage development and deployment of a vaccine, including regulators, WHO, Gavi, the Vaccine Alliance, industry, academics, and foundations. CEPI has some experience already with funding phase III trials. Assuming the collaboration of the private sector partner, CEPI can target its investments to complement those of governmental institutions such as BARDA that may also be making substantial investments in COVID-19 vaccine development.

Furthermore, CEPI is supporting rapid response vaccine platform technologies partnerships (e.g. with Imperial College London, CureVac, and University of Queensland) that could potentially shorten the time it takes to develop vaccines from years to weeks.

Using CEPI, as an existing institution, for the first three steps in COVID-19 vaccine development makes strategic sense in terms of speed and keeping transaction costs down. There is existing expertise and institutional capacity within CEPI that could be further strengthened without large investments or substantial amounts of time. Once such a window is established, it could be leveraged for other future outbreaks.

Box 1: About CEPI

- CEPI's mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks.
- CEPI was launched in January 2017 at the World Economic Forum in Davos, Switzerland.
- Its current focus is on early development. However, it can fund phase III trials in certain circumstances where there is a clear need and when it can mobilize funding (e.g., it will fund [late stage trials](#) of two Chikungunya candidate vaccines).
- CEPI's first call for proposals was for the development of vaccines against MERS-CoV, Nipah virus, and Lassa virus, all of which are on the WHO's [R&D Blueprint list for Action to Prevent Epidemics](#). These three pathogens were [prioritized](#) "based on a set of criteria including the risk of an outbreak occurring, transmissibility of the pathogen, burden of disease, and feasibility of vaccine development."
- Its second call was [for](#) "the development of platforms that can be used for rapid vaccine development against unknown pathogens." This call has now been re-opened to invite additional partners to apply. Of the four COVID-19 vaccine candidates under development funded by CEPI (Table 1), one was funded from the first call (Inovio, which had a MERS Co-V vaccine in phase I trials), two were funded from the second call (CureVac and the University of Queensland), and one was from a new call (Moderna Inc.).
- Its [third](#) call was for the development of vaccines against Chikungunya and Rift Valley fever.
- CEPI has received unrestricted multi-year funding from Norway, Germany, Japan, the United Kingdom, Canada, Australia, Ethiopia, the Bill & Melinda Gates Foundation, Wellcome, and the European Commission. It has received restricted multi-year funding from India, a single-year investment from the government of Belgium, and co-funding from EDCTP. It has reached ~US\$ 850 million of its US\$ 1 billion funding target for the period 2017-2021.

4.2. The advantages of using a World Bank financial intermediary fund (FIF)

CEPI is supported by a World Bank FIF. As the beneficiary of a FIF, there would be many advantages to using CEPI as a vehicle for funding both early and late stage development of COVID-19 vaccines. Unlike IDA/IBRD, FIFs allow for contributions from non-government stakeholders, such as private philanthropy or the private sector. FIF recipients are not limited to Bank-eligible countries. The World Bank's role in FIFs is flexible: at a minimum, a FIF is a financial pass-through where use of funds is solely determined by the governing body. The World Bank can also provide program management functions and implementation support. The governance arrangements and design of FIFs are also highly flexible. FIFs can disburse funds rapidly.

Core IBRD/IDA programs can accept contributions only from governments, but FIFs can accept funding from the private sector. FIFs have several other benefits. For example:

- They can channel funding to countries that are not members of the Bank or do not choose to invest in global public goods. For example, from 2006-2013 [the Avian and Human Influenza Facility](#) raised \$126m for avian influenza surveillance and control and allocated some of this funding to “weak link” countries that were not prioritizing influenza control interventions.
- FIFs are usually able to disburse funds more rapidly than core IBRD/IDA funding mechanisms because they sidestep traditional bank administrative and operational processes. For example, unlike in core lending, the bank’s board of executive directors usually are not required to approve FIF proposals. This ability to harness political momentum has been crucial in launching many global health programs targeting infectious diseases.
- The narrowly defined goals and measurability of outcomes of projects funded by FIFs make them attractive to funders.

4.3 A funding vehicle for manufacturing and procurement

CEPI does not have expertise in funding or managing the fourth and fifth steps in vaccine development (Figure 1), which are outside of its remit. A distinct consortium of public and philanthropic funders is likely to be needed.

4.4 Breaking the cycles of panic and neglect: towards a sustained funding approach

Establishing the kind of funding approach for development and deployment of COVID-19 vaccines shown in Figure 1 could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics. Once established, this approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics (antivirals and monoclonals).

The “valley of death” in funding phase III trials and manufacturing of health tools for controlling EIDs also applies to neglected diseases more broadly. This new approach for COVID-19 vaccine financing could be an important step in developing a sustained pooled funding platform for late stage development and deployment of new technologies to control other EIDs and diseases of poverty. In other words, this new approach would set a precedent and it would lay the groundwork to fund late stage development/deployment of technologies to control an array of diseases of poverty.

5. Governance of new COVID-19 vaccine funding channeled through CEPI

Key messages: CEPI’s existing governance arrangements—a Board with 12 voting members that is guided by a Scientific Advisory Committee (SAC) and a Joint Coordination Group— have flexibility to adapt to the expanded scope of work contemplated by this new financing for late stage COVID-19 development.

Since its launch, CEPI has announced three calls for proposals (Box 1), and CEPI’s Board approves all funded projects. The [Board](#) has 12 voting members (“four investors and eight independent members representing competencies including industry, global health, science, resource mobilisation, finance”) and five observers (including WHO and the World Bank). Currently, one third of Board members are based in low- or middle-income countries. There are four Board committees: Executive and Investment, Compensation and Nomination, Audit and Risk, and Equitable Access. The Board receives support and advice from the SAC and a Joint Coordination Group.

Investor Board members are invited to join CEPI's [Investors Council](#), which “nominates Investor representatives to the Board and has some rights including approval of any single investment over \$100 m.” The [SAC](#) has 24 voting members and five non-voting members. It provides scientific support and advice, e.g. it provides scientific guidance on CEPI's calls for proposals and it recommends which pathogens should be prioritized for vaccine development. The SAC does not have decision-making authority over CEPI's operations. CEPI's [Joint Coordination Group](#) is a “roundtable of independent institutions with an interest in seeing CEPI's vaccines successfully developed and deployed in an outbreak.”

It would be relatively straightforward to modify these arrangements, e.g. by expanding the SAC's expertise to include experts on late stage trials and manufacturing and potentially adding new investors to the Investors Council.⁴ CEPI considers the inclusion of strong representation of LICs and MICs in its development programs essential and such representation should be reflected in any expanded governance and oversight arrangements related to the management of the COVID-19 portfolio.

6. Addressing challenges in manufacturing, intellectual property, access, and regulatory approval

Key messages: For the current set of COVID-19 vaccines supported by CEPI funding, none of the partners has experience in bulk manufacturing and they have not previously licensed a vaccine. For manufacturing at scale, it is likely that a consortium of manufacturers—including MNCs, CMOs, and DCVMs—will be needed to produce the large numbers of doses that may be required (e.g. a billion doses in 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed. CEPI's existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Regulatory agencies and bodies recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In a pandemic scenario, with waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries.

6.1. Manufacturing the COVID-19 vaccine

In a worst-case scenario, a very large number of COVID-19 vaccine doses will need to be manufactured in a short time period. Establishing large-scale manufacturing capacity for a coronavirus vaccine is a key challenge to be overcome. To produce the needed volumes of vaccine, a large MNC (or several companies) will likely have to be engaged in some way. Yet the large MNCs are wary of being asked to manufacture epidemic and pandemic vaccines because of the high opportunity costs (they have to take a commercially successful product off one of their manufacturing lines); they also fear that tech transfer could lead to them losing commercially

⁴ CEPI's Investors Council has made it clear that only investors making *unrestricted* donations gain full governance privileges (investors who restrict their donations to do gain such privileges). CEPI could adapt, however, to provide appropriate transparency and oversight to investors in the COVID-19 vaccine development effort, perhaps by establishing some kind of “COVID-19 Investors Board,” but this would require discussions with the CEPI Board.

valuable IP. Such companies [feel](#) “burned by the string of vaccine pleas,” and are unsure that they can “afford these costly disruptions to their profit-seeking operations.”

However, as discussed below (section 6.2), COVID-19 could end up being an endemic global pathogen, and in this scenario it could be highly profitable for MNCs to manufacture the vaccine and sell it using a tiered pricing model. Thus in comparison to other outbreaks, such as Ebola, we may see MNCs being much more willing to manufacture a vaccine for COVID-19.

There is also vaccine manufacturing capacity in many MICs, such as China and India, and these companies could be highly incentivized to step up their role. CEPI has recently conducted a global survey of such capacity. Rapid tech transfer to these companies in MICs for manufacturing is likely to be part of the solution.

For COVID-19 vaccines under development, CEPI has forged partnerships with biotech companies, a government scientific agency, and a university. CEPI has entered a partnership with one MNC already, GSK, to make its adjuvant technology available. However, to ensure the large-scale production of the vaccine, a new public private partnership model for bulk manufacturing of the COVID-19 vaccine by a consortium of manufacturers (MNCs, CMOs, and MICs) will probably be needed.

6.2 Intellectual property

CEPI outlines its commitment to access in its [equitable access policy](#) (Box 2), which can be applied to ensure global access to a COVID-19 vaccine. CEPI [revised](#) its original equitable access policy last year. The impetus for this change was its desire to provide greater flexibility as to the means of ensuring equitable access to vaccines and to attract more potential industry partners. Although the overarching principles of the original equitable access policy remain intact, the new policy takes a more “principles-based” than “rules-based” approach. This approach allows CEPI to have more flexibility in negotiations with partners, although the shift has attracted [scrutiny](#) from some stakeholders.

In both the new and the old policy, CEPI does not take ownership over IP. However, it can use its [“step-in rights”](#) to move a candidate forward if the awardee is “unable or unwilling to further vaccine development and equitable access.” The triggers that would cause such an action are unique to the negotiated contract for a particular product.

Under the new policy, “stage-gate reviews” are to be used to review compliance with the equitable access mandate (Box 2) at each major stage of development and testing. If a company cannot keep its commitment to making a product available or affordable, CEPI could, according to its negotiated terms, identify a new awardee to which to transfer the IP.

Moving forward, CEPI [intends](#) to adapt the terms of negotiation for each call for proposal round. CEPI’s equitable access policy can probably accommodate the unique elements of funding phase III trials and manufacturing. Based on CEPI’s [existing model](#), a call for phase 3 COVID-19 testing could embed its own unique requirements, different from those for other products. The flexibility of CEPI’s access policy also ensures both CEPI and the awardee are in alignment regarding both the price and the terms that would be used to activate CEPI’s “step-in rights.”

Box 2: CEPI's equitable access policy

Equitable access is at the heart of CEPI's mandate, and was defined in its 2019 revised equitable access [policy](#): *"Equitable access to epidemic vaccines in the context of an outbreak means that appropriate vaccines are first available to populations when and where they are needed to end an outbreak or curtail an epidemic, regardless of ability to pay."* CEPI's approach is grounded in several guiding principles that allow for flexibility in partner agreements and negotiations, all of which must meet agreed upon thresholds for ensuring equitable access.

CEPI aims to facilitate equitable access to epidemic and pandemic vaccines by:

- "(1) Funding the development of vaccines and maintaining investigational stockpiles, to be used free of charge when an outbreak occurs
- (2) Coordinating with others in the global health community to enable licensure of vaccines funded by CEPI, including by securing resources for pivotal clinical trials
- (3) Collaborating with others in the global health community to ensure the procurement, allocation, deployment and administration of licensed vaccines to protect global health, at a price that does not limit equitable access and is sustainable to the manufacturer."

6.3 Ensuring global access

Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit "first and worst" by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine.

In a pandemic scenario, with waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this scenario, countries would probably need some additional way to prioritize who receives the vaccine. The consortium of manufacturers discussed earlier (MNCs, CMOs, and MICs) would ideally provide a "cost plus" contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would be free at the point of care. If COVID-19 then transitions to become a globally endemic pathogen, a tiered pricing model could be adopted.

6.4 Expediting regulatory approval

During the 2014-2016 Ebola epidemic in west Africa, there was widespread agreement that a [new mechanism](#) was needed to rapidly agree on trial designs and to collaborate across borders on fast-track scientific assessment, regulatory approval, and roll-out. For example, the African Vaccine Regulatory Forum [proposed](#) that this mechanism would cover

- "Clear pathways and timelines for expedited ethical and regulatory review of clinical trial applications and approval of products;
- Agreement on timelines and joint safety and efficacy assessments of the new products to fast-track national registration;

- Endorsement of a panel of safety experts for expedited review of safety data of new products with relevant communication to National Regulatory Authorities (NRAs);
- Technical assistance from the World Health Organization (WHO) to facilitate these processes.”

Regulatory agencies and bodies, including the WHO, US Food and Drug Administration, European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. There is widespread recognition that a “business as usual” approach is not tenable.

7. Conducting late stage trials in the midst of the outbreak

Key messages: International experience of conducting phase III trials during epidemics, including Ebola (Box 3), has highlighted several key lessons and principles that should be adopted by the new funding window. These lessons relate to issues such as trial design (including the use of adaptive trials), the ethics of trial conduct, and being sensitive to the needs of communities. In light of the COVID-19 outbreak, on January 20 2020, the Nuffield Council on Bioethics [issued](#) a “Call for Action to research funders, governments, and others involved in health research systems for a more ethical and collaborative approach to conducting research during emergencies such as infectious disease outbreaks.”

Box 3: Conducting trials during outbreaks: what can we learn from the 2014-2016 Ebola epidemic in West Africa?

By the end of the 2014-2016 Ebola epidemic, more than ten therapeutic trials had been designed but none had been fully completed. As of 2019, there were 42 ongoing Ebola vaccine trials. For highly infectious and deadly diseases such as Ebola virus disease and COVID-19, conducting conventional clinical trials is very challenging. The Merck vaccine rVSV-ZEBOV is currently the only approved vaccine against Ebola virus; phase I trials started shortly after WHO declared the West Africa Ebola virus outbreak as a PHEIC. Regulatory approval came five years later. In addition to the common challenges of time and cost, there are ethical challenges in conducting vaccine trials in outbreaks. For example, it is difficult to justify processes such as randomization when only some patients receive a potentially lifesaving intervention. The Ebola trials pointed to the need for adopting new, more efficient clinical trial designs. One of these designs is an alternative platform trial using a “response adaptive randomization strategy” that allows for re-allocation of study participants based on treatment response, as was [proposed](#) during the Ebola epidemic.

7.1 Design of trials conducted during emergencies

There are several challenges in conducting clinical trials during epidemics:

- [Time to enroll and complete a trial](#): The duration of an epidemic is unpredictable, and control efforts are aimed at shortening the duration. Unless trials are started early, these factors make it difficult for trials to reach a conclusion before the epidemic burns out.
- [Enrolling a sufficient number of patients](#): Clinical trials require minimum sample sizes in order to be sufficiently powered to make scientific conclusions. Enrolling enough patients is

often impossible in short-run epidemics. A trial run by Gilead in Wuhan, China, of an antiretroviral to treat COVID-19 is [struggling](#) to recruit patients,

- Capacity for conducting clinical trials: When epidemics occur in low-resource settings, the capacity to conduct a clinical trial may not exist and researchers do not have the luxury of time to build capacity before conducting the trial.
- Resources: Large phase III trials are very costly, which is one rationale for launching a new funding window.
- [Ethical challenges of using investigational new drugs](#): There are often major arguments about compassionate use versus waiting for trial results. A WHO advisory panel [stated](#) that compassionate use is “justified as an exceptional emergency measure” but said that it should not “preclude or delay the initiation of more conclusive investigations of the intervention(s) in properly designed clinical studies.”

Policymakers face a number of important decisions, including (a) choosing the right candidates for inclusion in a trial (limited numbers of patients and resources mean that candidate selection is critical), and (b) choosing the right trial design (some trial designs work better for different situations). A number of solutions and advances have been developed to help meet these challenges, e.g.

- [Adaptive clinical trials](#): Adaptive trials, which use “results accumulating in the trial to modify the trial’s course in accordance with pre-specified rules,” are widely believed to be an important design advance for future outbreaks. Most evidence to date has been based on simulation studies, which show that adaptive trials have a higher potential to reach a decision during the outbreak than regular trials. Nevertheless, adaptive trial designs must take into account a [number of issues](#) (e.g. “whether the adaptation process has led to design, analysis, or conduct flaws that have introduced bias that increases the chance of a false conclusion that the treatment is effective”).
- [Stepped wedge trials](#): in such trials, the intervention is introduced by random allocation at regular intervals to a cluster of participants until all clusters eventually receive the intervention. This design primarily addresses the ethical challenge of enrolling some affected populations in trials while excluding others.
- Non-randomized trials: these remain controversial and hard to interpret, but they could allow trials to be conducted when the capacity to conduct randomized trials is absent.
- Capacity building: An example is the [Clinical REsearch During Outbreaks \(CREDO\) program](#), jointly funded/implemented by TDR, the International Severe Acute Respiratory and Emerging Infections Consortium, and the UK Public Health Rapid Support Team.

7.2 Ethical concerns in conducting trials in an outbreak situation

Too often, the ethical issues involved in conducting trials during epidemics or pandemics—including those related to community consultation and participation—have not been carefully considered *before* trials begin. These issues should not be an “afterthought” but should be front and center of this new vaccine funding window.

In January 2020, after a two-year study conducted by an international working group, the Nuffield Council on Bioethics published its [report](#), “*Research in global health emergencies: ethical issues*.” The report argued that research in emergencies should be guided by an “ethical compass” comprising

three key values: equal respect (treating others as moral equals), helping reduce suffering (acting on duties founded on solidarity and humanity), and fairness (duties of non-discrimination and of “the equitable distribution of benefits and burdens”).

The report makes wide-ranging recommendations to research funders, WHO and other international agencies, governments, researchers, research ethics committees, and other stakeholders. These are summarized in a [Call for Action](#) (Box 4) that has been endorsed by many research organizations and international institutions, including the Wellcome Trust, the African Academy of Sciences, and the International Rescue Committee.

Box 4: Nuffield Council of Bioethics’ [Call for Action](#) on the ethical conduct of health research in emergencies

“We are issuing a call for action to research funders, governments and others to:

- Ensure that research is not supported unless the basic health needs of research participants are being addressed through the response effort. Research funders will need to work in partnerships with humanitarian organisations and ministries of health to ensure this.
- Invest in putting community engagement mechanisms into emergency research to make them a reality. In the longer term, engagement must be a central part of local healthcare systems to ensure sustainability and preparedness.
- Promote fair and equitable collaborations between research organisations, particularly between external research institutions and their local partners in high- and low-income settings.
- Support emergency planning - including securing robust health and health research systems - given the vital importance of properly resourced preparedness between emergencies. ”

8. Conclusions

Given the uncertain trajectory of COVID-19, the global health community must prepare for a worst-case scenario, in which a vaccine will be a critical control tool. While there are several promising vaccine candidates, these could languish in early stage development unless new funding is mobilized to fund all stages of COVID-19 vaccine development and to manufacture the large number of doses that could be needed.

Funding early development through phase 3 trials and “scale-out” under CEPI, an existing platform, offers the advantages of speed, flexibility, and low transaction costs. Additional capacities required to support the later stages of development could be quickly added. CEPI’s existing governance arrangements and equitable access policies could be adapted for phase III/manufacturing without major obstacles. But manufacturing and delivery would require a separate financing mechanism outside of CEPI; a consortium of public and philanthropic funders is likely to be needed. Different financing instruments are likely to be better suited to financing different steps in the COVID-19 vaccine development process.

Ethical conduct of trials, participation of LICs and MICs in governance arrangements, and global access to the vaccine must all be cornerstones of this new funding approach. Innovations in trial designs (e.g. adaptive trials) and manufacturing (e.g. modular approaches) and joined-up approaches to expediting regulatory approval could help to streamline development and deployment of the vaccine.

A new funding approach for late stage trials and manufacturing of a COVID-19 vaccine could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics, one that helps to break [the cycles of panic and neglect](#). Once established, the approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics. It could also be an important step in developing a sustained and consolidated pooled funding platform for late stage development and deployment of new technologies to control a broad range of diseases, including EIDs and poverty-related and neglected diseases. Due to the lack of a well-resourced funding mechanism for late-stage trials, the prospects for developing urgently need control tools for many fatal or disabling conditions are very poor.

Finally, additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be *complementary* to other fund-raising processes (e.g. the Gavi replenishment and WHO’s mobilization of resources for pandemic response and preparedness). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.

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Subject: (Update: Background paper and agenda provided) Consultation on Financing Coronavirus Disease (COVID-19) Vaccine Development | Thursday, February 20 from 9:30am to 1:30pm
Attachments: image002.png, image003.png, COVID19 vaccine fund_final background paper Feb 19 2020.pdf, Consultation on Financing COVID-19 Vaccine Development_February 20, 2020_Agenda.pdf, Consultation on Financing COVID-19 Vaccine Development_February 20, 2020_Logistics Note.pdf

Dear All,

On behalf of the World Bank health team, in coordination with the Coalition for Epidemic Preparedness Innovations (CEPI), it is our pleasure to host you for a half-day consultation on **Financing Coronavirus Disease 2019 (COVID-19) Vaccine Development**. The meeting is set to take place on **Thursday, February 20, 2020 from 9:30am to 1:30pm** at the **World Bank Offices in Washington DC** (located at 1818 H St NW) on **floor C2, conference room MC C2-125**.

As you know, the novel Coronavirus outbreak, which started in Wuhan, China, is evolving rapidly. As of today, the number of confirmed cases has increased significantly to over 60,000 and the virus has reached 25 countries. The outbreak, a Public Health Emergency of International Concern (PHEIC), poses a threat to countries worldwide, especially those with weak health systems and low levels of pandemic preparedness.

It is of urgent importance that we move quickly to finance the development of the appropriate countermeasures for a disease that risks becoming endemic across the globe. Two critical issues are necessary to address: i) immediate financing for the development and scale-up of a diversified portfolio of vaccines, and ii) financing the manufacturing and procurement of vaccine for global distribution.

In this context, we take this opportunity to share with you pertinent information regarding some logistics for the meeting; please see below for further details. We note that logistical information is also provided in the attached document for your convenience.

Please find in the attached a background note as well as the agenda for the meeting.

Finally, we thank all participants who have so far RSVP'd to the meeting. For those who have not yet RSVP'd, kindly confirm your participation to Ms. Gabrielle Williams, Health, Nutrition and Population Global Practice, World Bank (wbhealthevents@worldbank.org).

Please do not hesitate to reach out with any questions.

Many thanks,
Gabrielle
WBG Health Team

LOGISTICS NOTE

It is our distinct pleasure to host you on the occasion of **Thursday, February 20, 2020 from 9:30am – 1:30pm** at the **World Bank Headquarters in Washington, DC**. Please find in the below pertinent information regarding logistics (including instructions for connecting remotely as needed):

Venue & Location

The meeting will be held at the **World Bank Headquarters (Main Complex) in Washington, DC, USA** (located at 1818 H Street NW, 20433) on the **Floor C2**, in conference room number **MC C2-125**. Please see map below for building location and nearest Metro stations:



Security Clearance & Building Access

Please enter the building through the **WB visitor's entrance located on the 18th street side of the building**. Please **bring a valid form of photo identification**, such as a passport or a Government issued ID. Upon entering, please go through the security checkpoint. A member of our team will be waiting for you to provide you with your building pass and to escort you to the room. Please note that you will need to show your building pass every time you enter or exit the building.

Transportation

- **Arrival in Washington, DC:** A one-way taxi fare from Dulles International Airport (IAD) to downtown Washington, DC costs approximately US\$75. The trip takes about 45 minutes depending on traffic. A one-way taxi fare from Reagan National Airport (DCA) costs approximately US\$25, and the trip takes about 20 minutes.
- **To the airport:** Taxis are readily available from the World Bank Headquarters or from your hotel, whichever is most conducive to your travel arrangements.
- **For more information on public transportation:** please visit [WMATA – Metro/Bus/Train andService Near Me](#)

Coffee & Lunch

- Coffee and tea will be available upon arrival
- Lunch will be provided; vegetarian options will be available

Connecting Remotely

For those who will be connecting remotely, please find instructions on how to connect via Webex in the below:

To join via computer or electronic device:

- Kindly select the 'join meeting' button below
- Meeting number (access code): (b) (6)
- Meeting password: (b) (6)

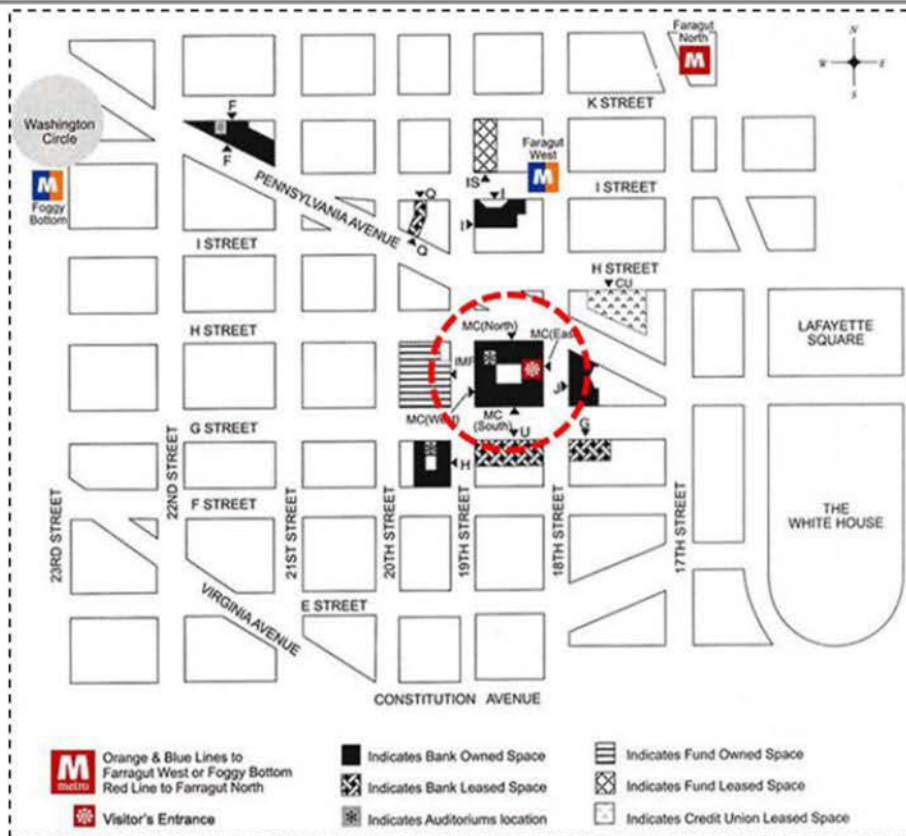
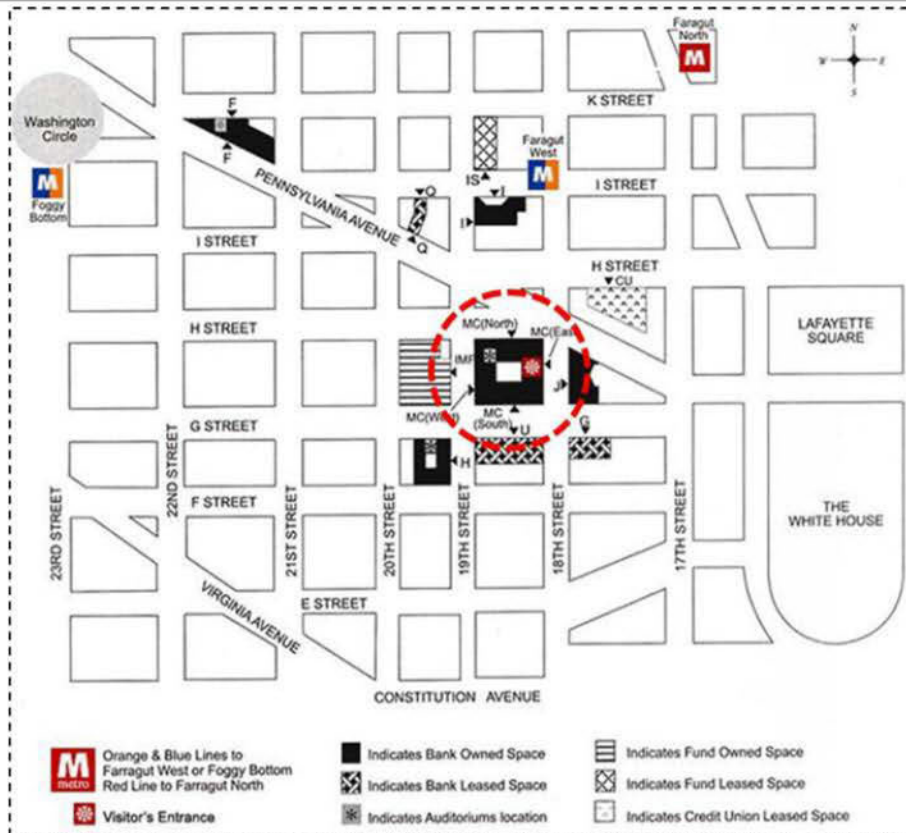
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To join via phone, please use the following dial-in and access code:

- Dial in: [1-650-479-3207](tel:1-650-479-3207) (Call-in toll number (US/Canada)) or click here for [Global call-in numbers](#)
- Meeting number (access code): (b) (6)

Enquires or questions

If you have any further questions or enquiries regarding the meeting, please do not hesitate to contact the World Bank Health Team directly at Wbhealthevents@worldbank.org.





Orange & Blue Lines to
Farragut West or Foggy Bottom
Red Line to Farragut North



Visitor's Entrance



Indicates Bank Owned Space



Indicates Bank Leased Space



Indicates Auditoriums location



Indicates Fund Owned Space



Indicates Fund Leased Space



Indicates Credit Union Leased Space

Washington Circle



23RD STREET

22ND STREET

21ST STREET

20TH STREET

19TH STREET

18TH STREET

17TH STREET

VIRGINIA AVENUE

E STREET

CONSTITUTION AVENUE

I STREET

H STREET

G STREET

F STREET

PENNSYLVANIA AVENUE

K STREET

I STREET

H STREET

LAFAYETTE SQUARE

THE WHITE HOUSE



Orange & Blue Lines to
Farragut West or Foggy Bottom
Red Line to Farragut North



Visitor's Entrance



Indicates Bank Owned Space



Indicates Bank Leased Space



Indicates Auditoriums location



Indicates Fund Owned Space



Indicates Fund Leased Space



Indicates Credit Union Leased Space

Funding the development and manufacturing of COVID-19 vaccines

Background paper for the World Bank/CEPI financing COVID-19 vaccine development consultation on February 20, 2020

Authors

A collaborative team of authors from Duke University's [Center for Policy Impact in Global Health](#) (Gavin Yamey), [Open Consultants](#) (Marco Schäferhoff), the World Bank's Health, Nutrition and Population Global Practice (Muhammad Pate, Mukesh Chawla, Kent Ranson, and Feng Zhao), and [CEPI](#) (Richard Hatchett, Richard Wilder) wrote this paper. The paper aims to enhance discussions at the consultation.

Executive summary

► **Why do we need a vaccine?** The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide and has the potential to become a pandemic. The WHO has declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and has advised all governments to prepare for transmission in their countries. There is uncertainty about what will happen next, e.g., there could be a pandemic, with multiple waves of COVID-19 over 1-3 years, and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production.

► **How much funding do we need and what are the core goals of this funding push?** CEPI has proposed three core goals for its vaccine development efforts—*speed*, *scale*, and *access*—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of \$2 billion. It must be noted that these costs are much lower than the costs of inaction—the economic costs of COVID-19 in China *alone* are estimated to be \$62 billion in the first quarter of 2020. These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery, or administration.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of emerging infectious diseases (EIDs) and neglected diseases.

► **How could the funding gap for COVID-19 vaccine development and deployment be closed?** Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and deployment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds and advanced market commitments, and instruments within the World Bank's health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine

development and deployment process (Figure 1). For example, vaccine bonds could be used to finance clinical and process development; official development assistance (ODA) could fund tech transfer from multinational companies to manufacturers in middle-income countries (MICs), including capacity building; public funds could be used to procure vaccines as a global public good (GPG).

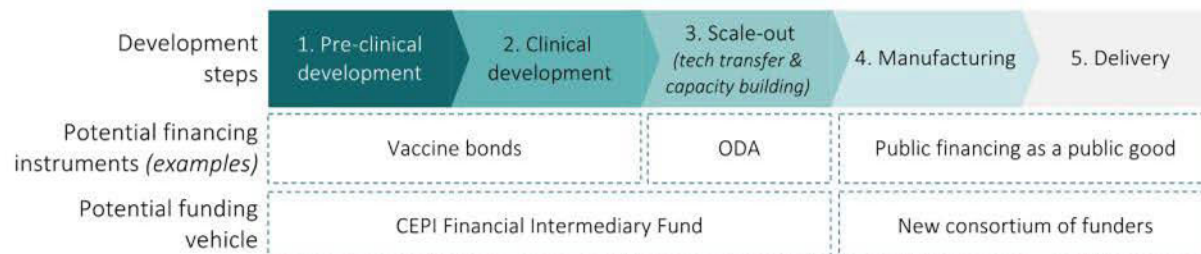


Figure 1. Schematic of a funding approach to COVID-19 vaccine development (pandemic scenario with multiple waves of COVID-19 over 1-3 years)

► **Why would CEPI be an appropriate venue for a new financing window for the development of COVID-19 vaccines?** If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out” (i.e. tech transfer and capacity building in MICs). It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit (Figure 1). CEPI funds the development of vaccines against a range of WHO’s Blueprint priority pathogens. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Using CEPI as the platform would mitigate concerns about fragmentation and “cannibalization” of R&D funding for EIDs/neglected diseases. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. Even if the COVID-19 outbreak wanes, opening this new window at CEPI will help to sustain attention to the importance of epidemic vaccine development. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Similarly, CEPI’s existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

► **How would manufacturing and delivery of COVID-19 vaccines be funded?** The fourth and fifth steps in the COV-19 vaccine development process—manufacturing and delivery—would require a separate financing mechanism outside of CEPI. A consortium of public and philanthropic funders is likely to be needed.

► **How would the manufacturing challenges be addressed?** For COVID-19 vaccines under development through CEPI funding, none of the current partners has experience in bulk

manufacturing and they have not previously licensed a vaccine. CEPI is in the process of reviewing additional proposals and anticipates expanding its portfolio with additional vaccine candidates, and it is hoped that some of these will be sponsored by experienced manufacturers. For manufacturing at scale, it is likely that a consortium of manufacturers—including multinational companies (MNCs), contract manufacturing organizations (CMOs), and developing country vaccine manufacturers (DCVMs)—will be needed to produce the large numbers of doses that may be required (e.g., a billion doses 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed.

► **How would regulatory challenges be addressed?** Regulatory agencies and bodies, including the WHO, the US Food and Drug Administration, the European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. There is widespread recognition that a “business as usual” approach is not tenable given the speed at which a pandemic may spread.

► **How would global access to COVID-19 vaccines be ensured?** Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit “first and worst” by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In a pandemic scenario, with multiple waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this scenario, countries would probably need some additional way to prioritize who receives the vaccine. The consortium of manufacturers discussed earlier (MNCs, CMOs, and DCVMs) would ideally provide a “cost plus” contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would then be free at the point of care. If COVID-19 then becomes a globally endemic pathogen, successful vaccines could transition to commercial sales and a tiered pricing model could be adopted.

► **How can we ensure that a COVID-19 vaccine funding push does not siphon off funding needed for other global health priorities?** Additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be *complementary* to other fund-raising processes (e.g., WHO’s mobilization of resources for pandemic response and preparedness as well as the upcoming Gavi replenishment). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.

Abbreviations

AMC	Advanced Market Commitment
APC	Advanced Purchase Commitment
BMGF	Bill & Melinda Gates Foundation
CEPI	Coalition for Epidemic Preparedness Innovations
CFR	Case Fatality Rate
CREDO	Clinical REsearch During Outbreaks
DCVMs	Developing Country Vaccine Manufacturers
EIDs	Emerging Infectious Diseases
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FIF	Financial Intermediary Fund
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
IAVI	International AIDS Vaccine Initiative
IFFIm	International Finance Facility for Immunisation
IP	Intellectual Property
IVI	International Vaccine Institute
MCM	Medical Countermeasure
MICs	Middle-income Countries
MNC	Multinational Company
NOK	Norwegian Crone
NRAs	National Regulatory Authorities
ODA	Official Development Assistance
ODI	Overseas Development Institute
PATH	Program for Appropriate Technology in Health
PEF	Pandemic Emergency Financing Facility
PHEIC	Public Health Emergency of International Concern
R0	Basic Reproductive Number
SAC	Scientific Advisory Committee
SARS	Severe Acute Respiratory Syndrome
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Structure of this background paper

This paper is organized into eight sections. **Section 1** makes the case for why we urgently need a COVID-19 vaccine. **Section 2** argues that new funding for COVID-19 vaccine development is required for all development stages and gives estimates of how much funding is needed. **Section 3** examines ways to mobilize such funding. **Section 4** explores potential funding vehicles. It makes the case that CEPI is well placed to be the vehicle for funding pre-clinical development, clinical development, and “scale out,” but that a different vehicle would be needed for funding manufacturing and delivery. **Section 5** discusses governance of a CEPI funding window for development of COVID-19 vaccines. **Section 6** highlights vaccine manufacturing, IP, global access, and regulatory approval, and **Section 7** highlights issues (including ethical considerations) in conducting trials in the midst of the COVID-19 outbreak. **Section 8** briefly summarizes our main conclusions.

1. Introduction: the urgent need to develop and manufacture COVID-19 vaccines

Key messages: The virus that causes COVID-19, the SARS-CoV-2 virus, has quickly spread worldwide and has the potential to become a pandemic. The WHO has declared COVID-19 to be a Public Health Emergency of International Concern (PHEIC) and has advised all governments to prepare for transmission in their countries. There is uncertainty about what will happen next, e.g., there could be a pandemic, with multiple waves of COVID-19 over 1-3 years and/or SARS-CoV-2 could become a globally endemic virus. We need to prepare for a worst-case scenario, in which the rapid development and scale-up of COVID-19 vaccines is critical to reducing the morbidity, mortality, and economic damage associated with a pandemic. Were SARS-CoV-2 to become endemic, any vaccines developed would likely find sustained global demand for their production. While the costs of development may be high (CEPI estimates the costs of clinical development and “scale-out” alone as up to \$2 billion), the costs of inaction are much larger (the economic costs of COVID-19 in China alone are estimated to be \$62 billion in the first quarter of 2020).

1.1 Current status of COVID-19

As of February 19 2020 at 16.00 (CET), the WHO [reports](#) that there have been 75,285 laboratory-confirmed cases of COVID-19 infection in 26 countries and 2,009 deaths. In comparison, there were [774 reported deaths](#) from the 2003 SARS outbreak. China’s National Health Commission [reports](#) that 1,716 health workers have been infected.

An initial [assessment](#) of the outbreak by Li and colleagues estimated that in the early phase of the COVID-19 outbreak in China, the epidemic doubled in size every 7.4 days and the basic reproductive number (R_0) was 2.2. It has been challenging to accurately track the spread, because of factors such as the lack of rapid diagnostic tests and the mildness of the symptoms in some infected people.

The case fatality rate (CFR) has been the subject of much debate. The CFR for cases outside China is [estimated](#) to be 2.2% (95% confidence interval, 0.6%-5.8%). The [first clinical study](#) of COVID-19 in patients in Wuhan reported a much higher CFR, of about 15%, though this estimate may be [prone to detection bias](#). Hospitalized patients in Wuhan have a high rate of transfer to the intensive care unit: a [study](#) by Wang and colleagues of 138 hospitalized patients found that 36 patients (26.1%) were transferred to the intensive care unit because of complications. There is no specific treatment, though a [large number of treatment trials](#) are now underway; the WHO [estimates](#) that there are 82 trials of various MCMs (including of antiretrovirals and traditional Chinese medicines) being conducted in China.

1.2 Potential future scenarios

The likely pattern of global spread is [debated](#) and is highly uncertain. For example, [modeling](#) by Ira Longini, co-director of the Center for Statistics and Quantitative Infectious Diseases at the University of Florida, an adviser to the WHO, suggests that up to two-thirds of the world could become infected. But other modelers argue this is a worst-case scenario, which even if true would be mitigated by the many people who would be minimally or mildly symptomatic. Models and estimates will be refined as new information becomes available.

A [study](#) by Wu and colleagues using flight data suggested that Beijing, Shanghai, Guangzhou, and Shenzhen are all at risk of substantial numbers of cases, and that “independent self-sustaining

outbreaks in major cities globally could become inevitable because of substantial exportation of pre-symptomatic cases.” Bogoch and colleagues [project](#) a high risk of spread from the Chinese mainland to Taipei, Bangkok, Tokyo, Seoul, Singapore, London, Sydney, Los Angeles, New York, Paris, San Francisco, Moscow, and Cairo. Efforts to contain the virus have clearly slowed its transmission, but at extraordinary cost, and it is unclear how long the quarantines and other measures employed can be maintained. While containment efforts continue for the time being, many experts now doubt that eradication can be achieved.

In addition to the possibility of multiple waves of COVID-19, there is also a [possibility](#) that COVID-19 becomes a globally endemic virus. Given this range of potential scenarios—a global pandemic, independent self-sustaining epidemics, or a globally endemic pathogen—vaccine development has become an urgent priority.

1.3 Economic consequences of inaction

In addition to their major health consequences, previous epidemics and pandemics have also been associated with [large economic losses](#):

- The global economic loss from SARS in 2003 was US\$52.2 billion (more than US\$6 million per case)
- The 2014-2016 Ebola outbreak led to a direct loss of US\$2.8 billion across Guinea, Liberia, and Sierra Leone and an estimated global social and economic burden in excess of US\$53 billion (more than \$1.8 million per case)
- The 2015 MERS epidemic in South Korea was estimated at the time to have resulted in economic losses approaching US\$10 billion (more than \$50 million a case)
- The 2015-2016 Zika outbreak led to an estimated loss of US\$3.5 billion in the Latin American and Caribbean region.

If the COVID-19 outbreak continues on its current trajectory, China is expected to lose up to [\\$62 billion](#) in the first quarter of 2020. The global loss is estimated to be \$280 billion within the same period. Oxford Economics [predicts](#) that China’s economic growth in the first quarter of 2020 will be 4% lower than in the first quarter of 2019. It also expects the global economy to grow by 0.2 percentage points less as a result of COVID-19. The anticipated economic losses are another reason why vaccine development is so urgent.

The Overseas Development Institute (ODI) [developed](#) a “vulnerability index” to estimate which countries are likely to be the most economically vulnerable to COVID-19. Based on countries’ likely exposure to COVID-19 and their poor preparedness to address the economic impacts, the index predicts that the most vulnerable countries in economic terms are Sri Lanka, the Philippines, and Vietnam, followed by Kazakhstan, Kenya, Cambodia, and Nepal.

2. Why funding is needed for the development of COVID-19 vaccines

Key messages: CEPI has proposed three core goals for its vaccine development efforts—*speed*, *scale*, and *access*—goals that will entail large investments in a short time horizon and a high tolerance for risk. CEPI estimates that the costs of developing one or more vaccines, inclusive of clinical and process development with scale-up and potential transfer of manufacturing, are likely to be in the range of \$2 billion. These cost estimates presume development to the point at which the

vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery or administration.

Funding is needed for *all stages* of COVID-19 vaccine development. The first \$100M that CEPI is spending has come from unprogrammed funds already allocated to other projects (CEPI does not have an emergency response lockbox), so this funding also needs to be recouped.

While the urgent need is to develop COVID-19 vaccines, this crisis could potentially also be an opportunity to begin developing a sustained mechanism to mobilize new financing for development and product manufacturing for a broad range of EIDs and neglected diseases.

2.1 The valley of death in funding late stage development for EIDs and neglected diseases

[Research](#) led by the Center for Policy Impact in Global Health at Duke University has illustrated a valley of death in the development of technologies to control both EIDs and neglected diseases. There is a large drop-off in the pipeline of candidates from phase II to III, which partly reflects the very high costs of phase III trials. For example, as of August 31, 2017, just 38 out of the 538 candidates (7%) in the pipeline for neglected diseases were in phase III.

At baseline, there is currently too little funding for late-stage trials, there are too few funders, and the financing is highly fragmented, creating inefficiencies. The result is that for many fatal or disabling conditions, the prospects for developing urgently needed control tools are very poor.

For vaccine development specifically, Rappuoli and colleagues have recently [shown](#) the high costs of late stage trials (Figure 2). While there have been improvements in early stage development, thanks to investments by the Bill & Melinda Gates Foundation, CEPI, PATH, and others, “these improvements in the early development process have revealed a new, and possibly more perilous, Valley of Death in the late vaccine development phase.” Late development is responsible for about 70% of total development costs. There is a major gap in the financing architecture for such late development (Figure 2 shows this gap, which is denoted by “?”). The large costs and time commitments are explained by the need to (a) produce vaccine candidates according to good manufacturing practice (GMP) standards in purpose-built production facilities, (b) conduct large-scale phase III trials, (c) submit data to regulators, and (d) conduct post-marketing surveillance. Although not shown in the figure, phase IV costs can also be [substantial](#).

As described below, there are a number of promising COVID-19 vaccines in early development. However, unless dedicated funding is mobilized to fund this development, and then for late stage trials and manufacturing, these candidates will never be developed and deployed. As mentioned, CEPI has no emergency funds set aside, and so all stages of COVID-19 vaccine development need emergency funding.

While the acute, urgent focus is on funding for COVID-19 vaccine development, the current crisis reveals once again that we need to mobilize new financing, especially for phases III and manufacturing, for a broad range of health technologies for both EIDs and neglected diseases.

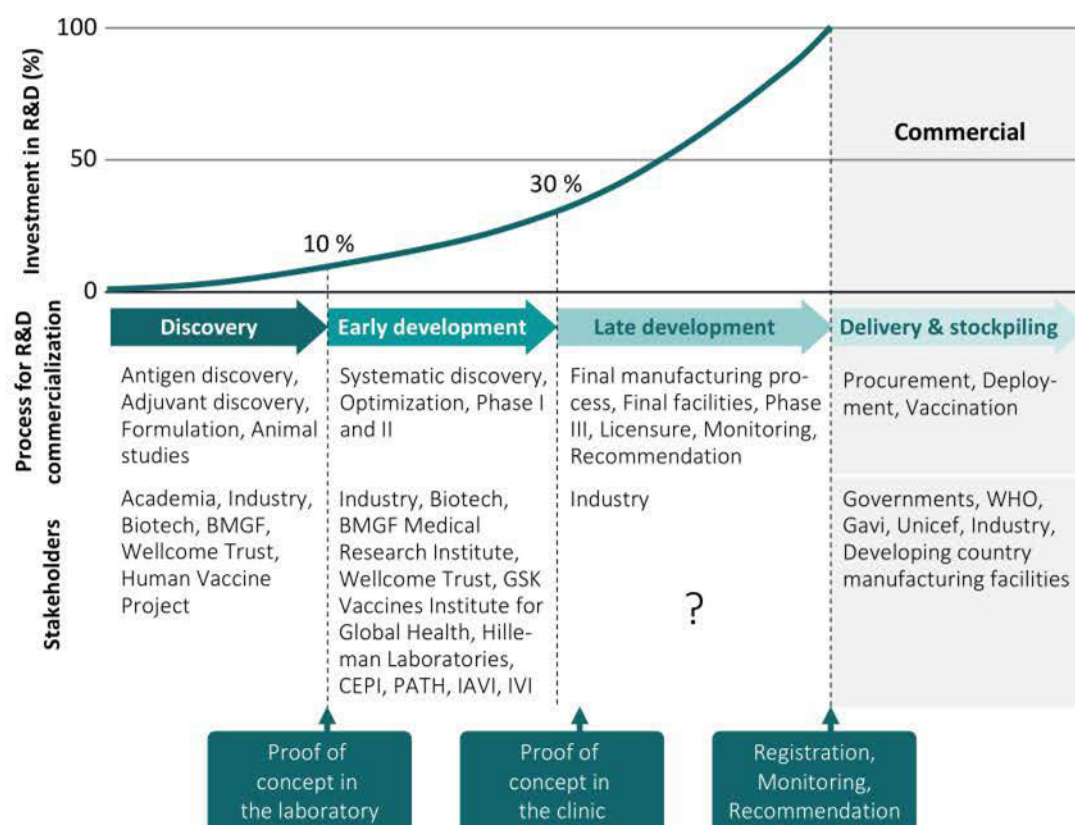


Figure 2. Stages of vaccine development and delivery

The figure shows three stages of vaccine development: discovery (10% of the R&D budget), early development (20% of the budget), and late development (70% of the budget). Under the graph are the funders and stakeholders involved at each step. A major gap can be seen in the financing architecture for late development (denoted by "?"). Figure adapted from a figure in: Rappuoli R, et al. Vaccines and global health: In search of a sustainable model for vaccine development and delivery. *Sci Transl Med.* 2019 Jun 19;11(497).¹

2.2 Status of current COVID-19 vaccines

CEPI is currently funding four candidates through Phase 1, all of which are still in pre-clinical development (Table 1). The platforms supporting these candidates are also being used to develop vaccines for other indications, several of which have reached clinical trials. CEPI recently issued a new call for proposals (the deadline was February 14, 2020), with the aim of expanding the portfolio to a total of 6-8 candidates. The portfolio needs such expansion, given (i) standard attrition rates during development, and (ii) the fact that the current CEPI-funded development efforts involve partners [that](#) do not have the production facilities to make a commercial product in bulk at a scale commensurate with the needs in a pandemic. While all are using innovative techniques to fast track vaccine candidate development, none have licensed a vaccine. Thus, there are substantial barriers ahead with respect to manufacturing and licensure (see below).

¹ **Abbreviations:** BMGF: Bill & Melinda Gates Foundation; CEPI: Coalition for Epidemic Preparedness Innovations; Gavi: Gavi, the Vaccine Alliance; GSK: GlaxoSmithKline; IAVI: International AIDS Vaccine Initiative; IVI: International Vaccine Institute; PATH: Program for Appropriate Technology in Health; UNICEF: United Nations Children's Fund; WHO, World Health Organization

There are [reports](#) of other COVID-19 vaccines being developed, including through a [collaboration](#) between Johnson & Johnson and BARDA, a [collaboration](#) between Sanofi and BARDA, and by Chinese government research organizations through [funding](#) by Jack Ma, Alibaba's founder.

COVID-19 vaccine candidates could potentially be ready for clinical trials in the next few months, and investments in process development and scale up of manufacturing could begin immediately, albeit at risk—hence the urgency to mobilize financing immediately.

Table 1. The four COVID-19 candidate vaccines funded by CEPI as of February 19, 2020

COVID-19 vaccine candidate	Developer	Funding from CEPI for COVID-19 vaccine development
INO-4800	Inovio pharmaceuticals	US\$ 8.9 million
Protein sub-unit (molecular-clamp vaccine platform)	University of Queensland	Up to US\$ 4.5 million
mRNA based vaccine	CureVac	US\$ 8.4 million
mRNA based vaccine (mRNA-1273)	Moderna Inc. in partnership with NIAID	US\$ 0.9 million for manufacturing (clinical trial costs covered by NIAID)

2.3 Costs to develop and deploy a COVID-19 vaccine

Key message: Up to \$2bn is needed to accelerate the development of, scale up, and prepare to roll out vaccines against COVID-19.

On February 14, 2020, CEPI provided a background paper called “Investment Case: Rapid Vaccine Development for COVID-19,” which it shared with us for the development of this paper. CEPI estimates that:

- Up to \$2bn is needed to “accelerate the development of, scale up, and prepare to roll out vaccines against 2019-nCoV [now called COVID-19]
- The best-case scenario would see vaccines that could potentially be deployed, whether as a licensed product or under appropriate ‘emergency use provisions’ within 12-18 months.”

The \$2bn estimate is based on the following:

- “Funding for an initial 8 vaccine candidates from preclinical through phase I, with clinical development cost up to \$10m for each.
- Support for scale up, process development and manufacturing, at risk,² while candidates are in phase I. Such investment will allow for the rapid initiation of phase 2/3 trials. The

² “At risk” in this context means beginning the investment in process development and scale-up without even knowing whether the vaccine candidate works. The process development and scale-up, in theory, are agnostic of the vaccine candidate, so that if a particular candidate failed and a new construct has to be developed, the

assumption is that initial investments would be required in all 8 candidates for an average of close to \$70m for each of those candidates.

- CEPI progresses 6 vaccine candidates through phase II/III, with clinical development costs up to \$150m each including Clinical Trial Material cost.
- If CEPI were to progress 3 vaccine candidates to full licensure there would be additional costs of up to \$100m per candidate.”

CEPI cautions that these are indicative budget estimates based on professional judgment and do not reflect specific budgets from the current set of performers.

These cost estimates presume development to the point at which the vaccines can be licensed or used under emergency use provisions and do not include costs for subsequent manufacturing, delivery or administration.

3. Mobilizing an additional \$2 bn for COVID-19 vaccine development and deployment

Key messages: Closing the US\$2 billion funding gap will require contributions from the public, philanthropic, and private sectors, including from official development assistance (ODA) and domestic health investments. All countries are at risk, and must be prepared, which means there is a strong case for all governments to invest in COVID-19 vaccine development and employment as part of their health systems preparedness investments. There is also an opportunity to use innovative finance mechanisms, such as vaccine bonds, advanced market commitments, as well as instruments within the World Bank’s health portfolio, such as contingent emergency response components. It may be valuable to match different types of financing instruments with different steps in the vaccine development and deployment process.

3.1 Public, philanthropic, and private sources

Given the scale of the threat, and the urgent need for additional financing, an “all of the above” approach is needed to close the funding gap, including new and additional ODA commitments (ODA should not be diverted or “cannibalized” from other key health investments). Many donors have already shown their commitments to the COVID-19 vaccine response, [including](#) to the WHO’s COVID-19 appeal. Norway [pledged](#) NOK 36 million and the United Kingdom [pledged](#) £20m to CEPI for COVID-19 vaccine development

All governments need to prepare for transmission of the SARS-CoV-2 virus in their countries, and investment in the development and deployment of a vaccine against COVID-19 is a critical component of preparedness. Thus alongside *new* ODA, there is a strong rationale for OECD governments to tap into the budgets of their health ministries (as part of their health systems investments aimed at pandemic preparedness) and their ministries of science and technology to fund advanced development and deployment of a COVID-19 vaccine. For those emerging economies with the means to do so, there is a similar rationale for these governments to also support the COVID-19 vaccine funding window.

investment has not gone to waste. It only goes to waste if the particular development program is cancelled altogether (which it might be if the candidate failed while others succeed).

Following the lead of the Bill & Melinda Gates Foundation, which recently [committed](#) US\$100 million in response to the epidemic, and the Wellcome Trust, which [pledged](#) GBP 10 million, philanthropic funding can help close the gap.

There is an important role for the private sector, not just in providing in-kind expertise but also as co-investors—along with the public and philanthropic sectors—in vaccine development and deployment. As the cascading consequences of the COVID-19 epidemic in China demonstrate, private sector companies are increasingly dependent on global supply chains (or on parts of the supply chain located in low-income countries and MICs) and they have a strong economic incentive to invest in the development of vaccines, in addition to any moral compulsion they may feel.

3.2 Innovative financing approaches

Vaccine bonds: The International Finance Facility for Immunisation (IFFIm) was launched in 2006 to rapidly accelerate the availability and predictability of funds for immunization. IFFIm uses the financial markets—through the issuance of bonds—to turn long-term contributions by donor countries into current, or “frontloaded,” cash. IFFIm supports Gavi’s vaccine programs and to date has received legally binding pledges from ten donors totaling about US\$6.6 billion spanning 23 years to 2030. The World Bank is IFFIm’s treasury manager. In June 2019, Norway pledged NOK 600 million (US\$66 million) to IFFIm to support CEPI’s vaccine development efforts. IFFIm bonds are therefore an existing finance model that could be used to help finance the development and deployment of a COVID-19 vaccine. Such IFFIm bonds could be blended with direct contributions from donors.

The Pandemic Emergency Financing Facility (PEF). An alternative bond-based mechanism is the PEF, [launched](#) in July 2017, which includes both a cash window and an insurance window. The PEF is currently undergoing review, including a review of the activation criteria for the insurance window (which have been [criticized](#) for being too narrow). “PEF 2.0” is due to be launched by May 2020. While PEF’s cash window could potentially also be used for funding the development and/or manufacturing and delivery of a pandemic vaccine, this is not an approach that has been fully tried and tested.

Advanced market commitments (AMCs). To de-risk the efforts of manufacturers (described further in Section 6.1), an AMC could be used. Gavi’s AMC for pneumococcal vaccines, for example, guarantees the price of vaccines once they have been developed.³ Funding commitments by donors provide vaccine manufacturers with the incentive they need to expand manufacturing capacity (there is some debate on whether AMCs could potentially also stimulate R&D). In exchange, companies sign a legally binding commitment to provide the vaccines at a price affordable to developing countries in the long term. Another example is the advanced purchase commitment (APC) between Gavi and Merck. Based on a pre-payment made by Gavi, Merck committed to create a stockpile of its Ebola vaccine, which is being used in the DRC today.

World Bank instruments. A number of instruments within the World Bank’s health portfolio, such as contingent emergency response components, could also be leveraged.

³ Though CEPI itself CEPI would not issue an AMC—it would hand off products ready for stockpiling to other partners in the ecosystem, such as Gavi.

3.3 Matching different financing instruments with different steps in vaccine development

Each of the different financing instruments discussed above may be better suited to funding particular stages of COVID-19 vaccine development. An illustrative schematic of this kind of matching is shown in Figure 1 on page 2. How to mix and match funding instruments requires further exploration.

4. CEPI as a venue for funding late stage development of COVID-19 vaccines

Key messages: If provided with sufficient resources, CEPI is an existing platform with scientific expertise and networks that could be leveraged to support and oversee the first three steps in the COVID-19 vaccine development process: pre-clinical development, clinical development, and “scale out.” It would not be the right vehicle for funding manufacturing of vaccine for general use or its delivery, which are outside CEPI’s remit. By using an existing platform as the “add-on” venue for funding advanced development of COVID-19 vaccines, transaction costs would be lower than launching a new mechanism. Additional expertise on funding phase III trials and in tech transfer through CEPI could be quickly incorporated without large investments. Once this expertise and funding window for late stage development is in place, the window would be “ready to go” for future outbreaks. CEPI’s existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond and its existing governance arrangements have flexibility to adapt to the expanded scope of work contemplated by this new financing window. CEPI is already supported by a World Bank financial intermediary fund (FIF), and so using this existing FIF to finance advanced development of COVID-19 vaccines would allow for speed, low transaction costs, flexibility, and global access.

4.1. The advantages of CEPI as a venue for funding late stage development of COVID-19 vaccines

Although CEPI is only three years old (Box 1), it has established expertise in financing the development of a broad suite of epidemic and pandemic vaccines. It has already shown that it can very quickly fund COVID-19 vaccine developers and expand the portfolio of candidates under development. It has strong relationships with key stakeholders in ensuring the late stage development and deployment of a vaccine, including regulators, WHO, Gavi, the Vaccine Alliance, industry, academics, and foundations. CEPI has some experience already with funding phase III trials. Assuming the collaboration of the private sector partner, CEPI can target its investments to complement those of governmental institutions such as BARDA that may also be making substantial investments in COVID-19 vaccine development.

Furthermore, CEPI is supporting rapid response vaccine platform technologies partnerships (e.g. with Imperial College London, CureVac, and University of Queensland) that could potentially shorten the time it takes to develop vaccines from years to weeks.

Using CEPI, as an existing institution, for the first three steps in COVID-19 vaccine development makes strategic sense in terms of speed and keeping transaction costs down. There is existing expertise and institutional capacity within CEPI that could be further strengthened without large investments or substantial amounts of time. Once such a window is established, it could be leveraged for other future outbreaks.

Box 1: About CEPI

- CEPI's mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks.
- CEPI was launched in January 2017 at the World Economic Forum in Davos, Switzerland.
- Its current focus is on early development. However, it can fund phase III trials in certain circumstances where there is a clear need and when it can mobilize funding (e.g., it will fund [late stage trials](#) of two Chikungunya candidate vaccines).
- CEPI's first call for proposals was for the development of vaccines against MERS-CoV, Nipah virus, and Lassa virus, all of which are on the WHO's [R&D Blueprint list for Action to Prevent Epidemics](#). These three pathogens were [prioritized](#) "based on a set of criteria including the risk of an outbreak occurring, transmissibility of the pathogen, burden of disease, and feasibility of vaccine development."
- Its second call was [for](#) "the development of platforms that can be used for rapid vaccine development against unknown pathogens." This call has now been re-opened to invite additional partners to apply. Of the four COVID-19 vaccine candidates under development funded by CEPI (Table 1), one was funded from the first call (Inovio, which had a MERS Co-V vaccine in phase I trials), two were funded from the second call (CureVac and the University of Queensland), and one was from a new call (Moderna Inc.).
- Its [third](#) call was for the development of vaccines against Chikungunya and Rift Valley fever.
- CEPI has received unrestricted multi-year funding from Norway, Germany, Japan, the United Kingdom, Canada, Australia, Ethiopia, the Bill & Melinda Gates Foundation, Wellcome, and the European Commission. It has received restricted multi-year funding from India, a single-year investment from the government of Belgium, and co-funding from EDCTP. It has reached ~US\$ 850 million of its US\$ 1 billion funding target for the period 2017-2021.

4.2. The advantages of using a World Bank financial intermediary fund (FIF)

CEPI is supported by a World Bank FIF. As the beneficiary of a FIF, there would be many advantages to using CEPI as a vehicle for funding both early and late stage development of COVID-19 vaccines. Unlike IDA/IBRD, FIFs allow for contributions from non-government stakeholders, such as private philanthropy or the private sector. FIF recipients are not limited to Bank-eligible countries. The World Bank's role in FIFs is flexible: at a minimum, a FIF is a financial pass-through where use of funds is solely determined by the governing body. The World Bank can also provide program management functions and implementation support. The governance arrangements and design of FIFs are also highly flexible. FIFs can disburse funds rapidly.

Core IBRD/IDA programs can accept contributions only from governments, but FIFs can accept funding from the private sector. FIFs have several other benefits. For example:

- They can channel funding to countries that are not members of the Bank or do not choose to invest in global public goods. For example, from 2006-2013 [the Avian and Human Influenza Facility](#) raised \$126m for avian influenza surveillance and control and allocated some of this funding to “weak link” countries that were not prioritizing influenza control interventions.
- FIFs are usually able to disburse funds more rapidly than core IBRD/IDA funding mechanisms because they sidestep traditional bank administrative and operational processes. For example, unlike in core lending, the bank’s board of executive directors usually are not required to approve FIF proposals. This ability to harness political momentum has been crucial in launching many global health programs targeting infectious diseases.
- The narrowly defined goals and measurability of outcomes of projects funded by FIFs make them attractive to funders.

4.3 A funding vehicle for manufacturing and procurement

CEPI does not have expertise in funding or managing the fourth and fifth steps in vaccine development (Figure 1), which are outside of its remit. A distinct consortium of public and philanthropic funders is likely to be needed.

4.4 Breaking the cycles of panic and neglect: towards a sustained funding approach

Establishing the kind of funding approach for development and deployment of COVID-19 vaccines shown in Figure 1 could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics. Once established, this approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics (antivirals and monoclonals).

The “valley of death” in funding phase III trials and manufacturing of health tools for controlling EIDs also applies to neglected diseases more broadly. This new approach for COVID-19 vaccine financing could be an important step in developing a sustained pooled funding platform for late stage development and deployment of new technologies to control other EIDs and diseases of poverty. In other words, this new approach would set a precedent and it would lay the groundwork to fund late stage development/deployment of technologies to control an array of diseases of poverty.

5. Governance of new COVID-19 vaccine funding channeled through CEPI

Key messages: CEPI’s existing governance arrangements—a Board with 12 voting members that is guided by a Scientific Advisory Committee (SAC) and a Joint Coordination Group— have flexibility to adapt to the expanded scope of work contemplated by this new financing for late stage COVID-19 development.

Since its launch, CEPI has announced three calls for proposals (Box 1), and CEPI’s Board approves all funded projects. The [Board](#) has 12 voting members (“four investors and eight independent members representing competencies including industry, global health, science, resource mobilisation, finance”) and five observers (including WHO and the World Bank). Currently, one third of Board members are based in low- or middle-income countries. There are four Board committees: Executive and Investment, Compensation and Nomination, Audit and Risk, and Equitable Access. The Board receives support and advice from the SAC and a Joint Coordination Group.

Investor Board members are invited to join CEPI's [Investors Council](#), which "nominates Investor representatives to the Board and has some rights including approval of any single investment over \$100 m." The [SAC](#) has 24 voting members and five non-voting members. It provides scientific support and advice, e.g. it provides scientific guidance on CEPI's calls for proposals and it recommends which pathogens should be prioritized for vaccine development. The SAC does not have decision-making authority over CEPI's operations. CEPI's [Joint Coordination Group](#) is a "roundtable of independent institutions with an interest in seeing CEPI's vaccines successfully developed and deployed in an outbreak."

It would be relatively straightforward to modify these arrangements, e.g. by expanding the SAC's expertise to include experts on late stage trials and manufacturing and potentially adding new investors to the Investors Council.⁴ CEPI considers the inclusion of strong representation of LICs and MICs in its development programs essential and such representation should be reflected in any expanded governance and oversight arrangements related to the management of the COVID-19 portfolio.

6. Addressing challenges in manufacturing, intellectual property, access, and regulatory approval

Key messages: For the current set of COVID-19 vaccines supported by CEPI funding, none of the partners has experience in bulk manufacturing and they have not previously licensed a vaccine. For manufacturing at scale, it is likely that a consortium of manufacturers—including MNCs, CMOs, and DCVMs—will be needed to produce the large numbers of doses that may be required (e.g. a billion doses in 12-18 months from now). A new public-private partnership model for bulk manufacturing of COVID-19 vaccines by such a consortium of manufacturers is likely to be needed. CEPI's existing equitable access policy appears to be flexible enough to apply to the expansion of CEPI-funded activities to phase III trials and beyond. Regulatory agencies and bodies recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine. In a pandemic scenario, with waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries.

6.1. Manufacturing the COVID-19 vaccine

In a worst-case scenario, a very large number of COVID-19 vaccine doses will need to be manufactured in a short time period. Establishing large-scale manufacturing capacity for a coronavirus vaccine is a key challenge to be overcome. To produce the needed volumes of vaccine, a large MNC (or several companies) will likely have to be engaged in some way. Yet the large MNCs are wary of being asked to manufacture epidemic and pandemic vaccines because of the high opportunity costs (they have to take a commercially successful product off one of their manufacturing lines); they also fear that tech transfer could lead to them losing commercially

⁴ CEPI's Investors Council has made it clear that only investors making *unrestricted* donations gain full governance privileges (investors who restrict their donations to do gain such privileges). CEPI could adapt, however, to provide appropriate transparency and oversight to investors in the COVID-19 vaccine development effort, perhaps by establishing some kind of "COVID-19 Investors Board," but this would require discussions with the CEPI Board.

valuable IP. Such companies [feel](#) “burned by the string of vaccine pleas,” and are unsure that they can “afford these costly disruptions to their profit-seeking operations.”

However, as discussed below (section 6.2), COVID-19 could end up being an endemic global pathogen, and in this scenario it could be highly profitable for MNCs to manufacture the vaccine and sell it using a tiered pricing model. Thus in comparison to other outbreaks, such as Ebola, we may see MNCs being much more willing to manufacture a vaccine for COVID-19.

There is also vaccine manufacturing capacity in many MICs, such as China and India, and these companies could be highly incentivized to step up their role. CEPI has recently conducted a global survey of such capacity. Rapid tech transfer to these companies in MICs for manufacturing is likely to be part of the solution.

For COVID-19 vaccines under development, CEPI has forged partnerships with biotech companies, a government scientific agency, and a university. CEPI has entered a partnership with one MNC already, GSK, to make its adjuvant technology available. However, to ensure the large-scale production of the vaccine, a new public private partnership model for bulk manufacturing of the COVID-19 vaccine by a consortium of manufacturers (MNCs, CMOs, and MICs) will probably be needed.

6.2 Intellectual property

CEPI outlines its commitment to access in its [equitable access policy](#) (Box 2), which can be applied to ensure global access to a COVID-19 vaccine. CEPI [revised](#) its original equitable access policy last year. The impetus for this change was its desire to provide greater flexibility as to the means of ensuring equitable access to vaccines and to attract more potential industry partners. Although the overarching principles of the original equitable access policy remain intact, the new policy takes a more “principles-based” than “rules-based” approach. This approach allows CEPI to have more flexibility in negotiations with partners, although the shift has attracted [scrutiny](#) from some stakeholders.

In both the new and the old policy, CEPI does not take ownership over IP. However, it can use its [“step-in rights”](#) to move a candidate forward if the awardee is “unable or unwilling to further vaccine development and equitable access.” The triggers that would cause such an action are unique to the negotiated contract for a particular product.

Under the new policy, “stage-gate reviews” are to be used to review compliance with the equitable access mandate (Box 2) at each major stage of development and testing. If a company cannot keep its commitment to making a product available or affordable, CEPI could, according to its negotiated terms, identify a new awardee to which to transfer the IP.

Moving forward, CEPI [intends](#) to adapt the terms of negotiation for each call for proposal round. CEPI’s equitable access policy can probably accommodate the unique elements of funding phase III trials and manufacturing. Based on CEPI’s [existing model](#), a call for phase 3 COVID-19 testing could embed its own unique requirements, different from those for other products. The flexibility of CEPI’s access policy also ensures both CEPI and the awardee are in alignment regarding both the price and the terms that would be used to activate CEPI’s “step-in rights.”

Box 2: CEPI's equitable access policy

Equitable access is at the heart of CEPI's mandate, and was defined in its 2019 revised equitable access [policy](#): *"Equitable access to epidemic vaccines in the context of an outbreak means that appropriate vaccines are first available to populations when and where they are needed to end an outbreak or curtail an epidemic, regardless of ability to pay."* CEPI's approach is grounded in several guiding principles that allow for flexibility in partner agreements and negotiations, all of which must meet agreed upon thresholds for ensuring equitable access.

CEPI aims to facilitate equitable access to epidemic and pandemic vaccines by:

- "(1) Funding the development of vaccines and maintaining investigational stockpiles, to be used free of charge when an outbreak occurs
- (2) Coordinating with others in the global health community to enable licensure of vaccines funded by CEPI, including by securing resources for pivotal clinical trials
- (3) Collaborating with others in the global health community to ensure the procurement, allocation, deployment and administration of licensed vaccines to protect global health, at a price that does not limit equitable access and is sustainable to the manufacturer."

6.3 Ensuring global access

Affordability and accessibility must be the bedrock of any proposal for a new funding push for COVID-19 vaccine development. The poor are hit "first and worst" by outbreaks, and any access model that ends up giving only high-income countries access to the vaccine would clearly be unacceptable. It will be critical to avoid a scenario in which high-income country governments enter into bilateral purchase contracts with manufacturers, thus monopolizing the vaccine.

In a pandemic scenario, with waves of COVID-19 over many years, one global access model would be for the vaccine to be procured with public funding and allocated as close to pro rata as possible to countries. In this scenario, countries would probably need some additional way to prioritize who receives the vaccine. The consortium of manufacturers discussed earlier (MNCs, CMOs, and MICs) would ideally provide a "cost plus" contract (with a small margin) for sales to a global purchasing agent for a time-limited period; the vaccine would be free at the point of care. If COVID-19 then transitions to become a globally endemic pathogen, a tiered pricing model could be adopted.

6.4 Expediting regulatory approval

During the 2014-2016 Ebola epidemic in west Africa, there was widespread agreement that a [new mechanism](#) was needed to rapidly agree on trial designs and to collaborate across borders on fast-track scientific assessment, regulatory approval, and roll-out. For example, the African Vaccine Regulatory Forum [proposed](#) that this mechanism would cover

- "Clear pathways and timelines for expedited ethical and regulatory review of clinical trial applications and approval of products;
- Agreement on timelines and joint safety and efficacy assessments of the new products to fast-track national registration;

- Endorsement of a panel of safety experts for expedited review of safety data of new products with relevant communication to National Regulatory Authorities (NRAs);
- Technical assistance from the World Health Organization (WHO) to facilitate these processes.”

Regulatory agencies and bodies, including the WHO, US Food and Drug Administration, European Medicines Agency, and the International Coalition of Medicines Regulatory Authorities, recognize the urgency of providing a simplified and expedited, joint regulatory review of COVID-19 MCMs. There is widespread recognition that a “business as usual” approach is not tenable.

7. Conducting late stage trials in the midst of the outbreak

Key messages: International experience of conducting phase III trials during epidemics, including Ebola (Box 3), has highlighted several key lessons and principles that should be adopted by the new funding window. These lessons relate to issues such as trial design (including the use of adaptive trials), the ethics of trial conduct, and being sensitive to the needs of communities. In light of the COVID-19 outbreak, on January 20 2020, the Nuffield Council on Bioethics [issued](#) a “Call for Action to research funders, governments, and others involved in health research systems for a more ethical and collaborative approach to conducting research during emergencies such as infectious disease outbreaks.”

Box 3: Conducting trials during outbreaks: what can we learn from the 2014-2016 Ebola epidemic in West Africa?

By the end of the 2014-2016 Ebola epidemic, more than ten therapeutic trials had been designed but none had been fully completed. As of 2019, there were 42 ongoing Ebola vaccine trials. For highly infectious and deadly diseases such as Ebola virus disease and COVID-19, conducting conventional clinical trials is very challenging. The Merck vaccine rVSV-ZEBOV is currently the only approved vaccine against Ebola virus; phase I trials started shortly after WHO declared the West Africa Ebola virus outbreak as a PHEIC. Regulatory approval came five years later. In addition to the common challenges of time and cost, there are ethical challenges in conducting vaccine trials in outbreaks. For example, it is difficult to justify processes such as randomization when only some patients receive a potentially lifesaving intervention. The Ebola trials pointed to the need for adopting new, more efficient clinical trial designs. One of these designs is an alternative platform trial using a “response adaptive randomization strategy” that allows for re-allocation of study participants based on treatment response, as was [proposed](#) during the Ebola epidemic.

7.1 Design of trials conducted during emergencies

There are several challenges in conducting clinical trials during epidemics:

- [Time to enroll and complete a trial](#): The duration of an epidemic is unpredictable, and control efforts are aimed at shortening the duration. Unless trials are started early, these factors make it difficult for trials to reach a conclusion before the epidemic burns out.
- [Enrolling a sufficient number of patients](#): Clinical trials require minimum sample sizes in order to be sufficiently powered to make scientific conclusions. Enrolling enough patients is

often impossible in short-run epidemics. A trial run by Gilead in Wuhan, China, of an antiretroviral to treat COVID-19 is [struggling](#) to recruit patients,

- Capacity for conducting clinical trials: When epidemics occur in low-resource settings, the capacity to conduct a clinical trial may not exist and researchers do not have the luxury of time to build capacity before conducting the trial.
- Resources: Large phase III trials are very costly, which is one rationale for launching a new funding window.
- [Ethical challenges of using investigational new drugs](#): There are often major arguments about compassionate use versus waiting for trial results. A WHO advisory panel [stated](#) that compassionate use is “justified as an exceptional emergency measure” but said that it should not “preclude or delay the initiation of more conclusive investigations of the intervention(s) in properly designed clinical studies.”

Policymakers face a number of important decisions, including (a) choosing the right candidates for inclusion in a trial (limited numbers of patients and resources mean that candidate selection is critical), and (b) choosing the right trial design (some trial designs work better for different situations). A number of solutions and advances have been developed to help meet these challenges, e.g.

- [Adaptive clinical trials](#): Adaptive trials, which use “results accumulating in the trial to modify the trial’s course in accordance with pre-specified rules,” are widely believed to be an important design advance for future outbreaks. Most evidence to date has been based on simulation studies, which show that adaptive trials have a higher potential to reach a decision during the outbreak than regular trials. Nevertheless, adaptive trial designs must take into account a [number of issues](#) (e.g. “whether the adaptation process has led to design, analysis, or conduct flaws that have introduced bias that increases the chance of a false conclusion that the treatment is effective”).
- [Stepped wedge trials](#): in such trials, the intervention is introduced by random allocation at regular intervals to a cluster of participants until all clusters eventually receive the intervention. This design primarily addresses the ethical challenge of enrolling some affected populations in trials while excluding others.
- Non-randomized trials: these remain controversial and hard to interpret, but they could allow trials to be conducted when the capacity to conduct randomized trials is absent.
- Capacity building: An example is the [Clinical REsearch During Outbreaks \(CREDO\) program](#), jointly funded/implemented by TDR, the International Severe Acute Respiratory and Emerging Infections Consortium, and the UK Public Health Rapid Support Team.

7.2 Ethical concerns in conducting trials in an outbreak situation

Too often, the ethical issues involved in conducting trials during epidemics or pandemics—including those related to community consultation and participation—have not been carefully considered *before* trials begin. These issues should not be an “afterthought” but should be front and center of this new vaccine funding window.

In January 2020, after a two-year study conducted by an international working group, the Nuffield Council on Bioethics published its [report](#), “*Research in global health emergencies: ethical issues*.” The report argued that research in emergencies should be guided by an “ethical compass” comprising

three key values: equal respect (treating others as moral equals), helping reduce suffering (acting on duties founded on solidarity and humanity), and fairness (duties of non-discrimination and of “the equitable distribution of benefits and burdens”).

The report makes wide-ranging recommendations to research funders, WHO and other international agencies, governments, researchers, research ethics committees, and other stakeholders. These are summarized in a [Call for Action](#) (Box 4) that has been endorsed by many research organizations and international institutions, including the Wellcome Trust, the African Academy of Sciences, and the International Rescue Committee.

Box 4: Nuffield Council of Bioethics’ [Call for Action](#) on the ethical conduct of health research in emergencies

“We are issuing a call for action to research funders, governments and others to:

- Ensure that research is not supported unless the basic health needs of research participants are being addressed through the response effort. Research funders will need to work in partnerships with humanitarian organisations and ministries of health to ensure this.
- Invest in putting community engagement mechanisms into emergency research to make them a reality. In the longer term, engagement must be a central part of local healthcare systems to ensure sustainability and preparedness.
- Promote fair and equitable collaborations between research organisations, particularly between external research institutions and their local partners in high- and low-income settings.
- Support emergency planning - including securing robust health and health research systems - given the vital importance of properly resourced preparedness between emergencies. ”

8. Conclusions

Given the uncertain trajectory of COVID-19, the global health community must prepare for a worst-case scenario, in which a vaccine will be a critical control tool. While there are several promising vaccine candidates, these could languish in early stage development unless new funding is mobilized to fund all stages of COVID-19 vaccine development and to manufacture the large number of doses that could be needed.

Funding early development through phase 3 trials and “scale-out” under CEPI, an existing platform, offers the advantages of speed, flexibility, and low transaction costs. Additional capacities required to support the later stages of development could be quickly added. CEPI’s existing governance arrangements and equitable access policies could be adapted for phase III/manufacturing without major obstacles. But manufacturing and delivery would require a separate financing mechanism outside of CEPI; a consortium of public and philanthropic funders is likely to be needed. Different financing instruments are likely to be better suited to financing different steps in the COVID-19 vaccine development process.

Ethical conduct of trials, participation of LICs and MICs in governance arrangements, and global access to the vaccine must all be cornerstones of this new funding approach. Innovations in trial designs (e.g. adaptive trials) and manufacturing (e.g. modular approaches) and joined-up approaches to expediting regulatory approval could help to streamline development and deployment of the vaccine.

A new funding approach for late stage trials and manufacturing of a COVID-19 vaccine could be the start of a new, coordinated approach to funding MCMs for epidemic and pandemics, one that helps to break [the cycles of panic and neglect](#). Once established, the approach could be used for future outbreaks—not just for vaccines but also diagnostics and therapeutics. It could also be an important step in developing a sustained and consolidated pooled funding platform for late stage development and deployment of new technologies to control a broad range of diseases, including EIDs and poverty-related and neglected diseases. Due to the lack of a well-resourced funding mechanism for late-stage trials, the prospects for developing urgently need control tools for many fatal or disabling conditions are very poor.

Finally, additional funding is clearly needed for development and deployment of COVID-19 vaccines, but this effort should be *complementary* to other fund-raising processes (e.g. the Gavi replenishment and WHO’s mobilization of resources for pandemic response and preparedness). Using vaccine bonds or an IFFIm mechanism for the COVID-19 effort could be one way to take pressure off these other mobilization efforts. The current crisis is an opportunity for high-level dialogue on ways to reform the overall financing system and to ensure complementarity of funding efforts.

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Consultation on Financing Coronavirus Disease 2019 (COVID-19) Vaccine Development

Thursday, February 20, 2020 | 9:30am – 1:30pm
World Bank Main Complex, Floor C2, Conference Room MC C2-125

AGENDA

- | | |
|-----------------|--|
| 9:30 – 9:45am | Welcome and Opening Remarks <ul style="list-style-type: none">- <i>Muhammad Ali Pate, Global Director, Health, Nutrition & Population, WBG</i>- <i>Richard Hatchett, CEO, CEPI</i> |
| 9:45 – 9:55am | Overview of the Coalition for Epidemic Preparedness Innovations (CEPI) in the Context of COVID-19 <ul style="list-style-type: none">- <i>Richard Hatchett, CEO, CEPI</i> |
| 9:55 – 10:05am | Overview of World Bank's Response to COVID-19 <ul style="list-style-type: none">- <i>Mukesh Chawla, Adviser, Health, Nutrition and Population, WBG</i> |
| 10:05 – 10:35am | Presentation of Background Paper:
<i>"Funding the development and manufacturing of COVID-19 vaccines"</i> <ul style="list-style-type: none">- <i>Gavin Yamey, Public Policy Director, Center for Policy Impact, Duke University</i> |
| 10:35 – 10:50am | <i>Coffee break</i> |
| 10:50 – 12:20pm | Discussion on Background Paper <ul style="list-style-type: none">- <i>Moderated by Feng Zhao, Practice Manager, Health, Nutrition and Population, WBG</i>- <i>All participants</i> |
| 12:20 – 12:30pm | Closing and Next Steps <ul style="list-style-type: none">- <i>Richard Hatchett, CEO, CEPI</i>- <i>Muhammad Ali Pate, Global Director, Health, Nutrition & Population, WBG</i> |
| 12:30 – 1:30pm | Lunch |

Consultation on Financing Coronavirus Disease (COVID-19) Vaccine Development

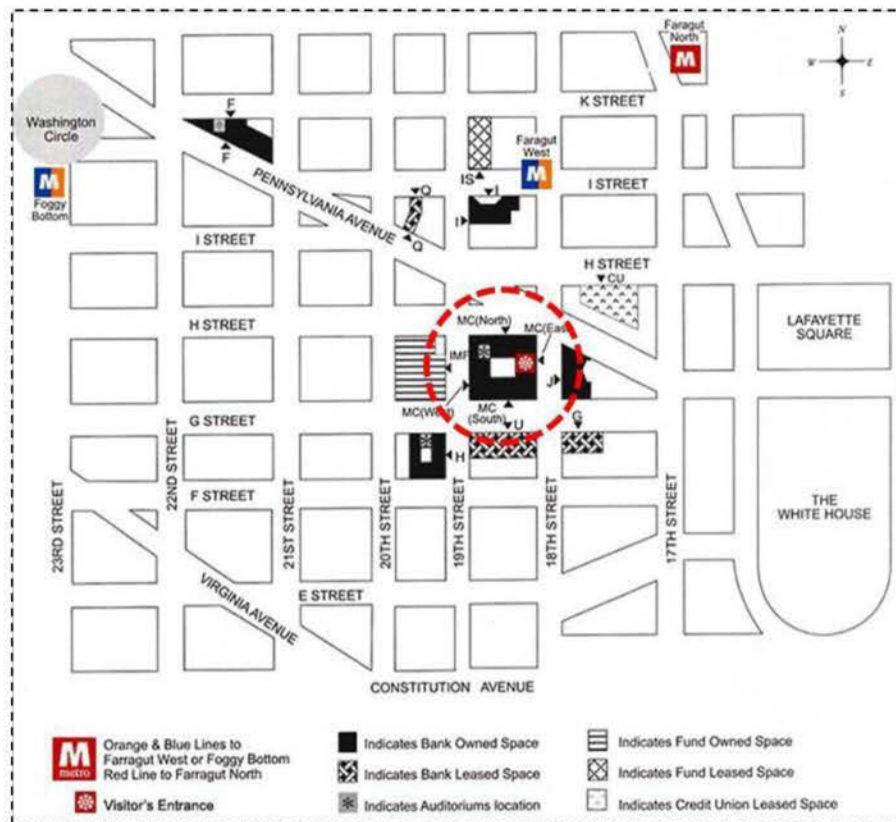
Thursday, February 20, 2020 | 9:30am – 1:30pm

LOGISTICS NOTE

It is our distinct pleasure to host you on the occasion of **Thursday, February 20, 2020 from 9:30am – 1:30pm** at the **World Bank Headquarters in Washington, DC**. Please find in the below pertinent information regarding logistics:

Venue & Location

The meeting will be held at the **World Bank Headquarters (Main Complex) in Washington, DC, USA** (located at 1818 H Street NW, 20433) on the **Floor C2**, in conference room number **MC C2-125**. Please see map below for building location and nearest Metro stations:



Security Clearance & Building Access

Please enter the building through the **WB visitor's entrance located on the 18th street side of the building**. Please **bring a valid form of photo identification**, such as a passport or a Government issued ID. Upon entering, please go through the security checkpoint. A member of our team will be waiting for you to provide you with your building pass and to escort you to the room. Please note that you will need to show your building pass every time you enter or exit the building.

Transportation

Arrival in Washington, DC: A one-way taxi fare from Dulles International Airport (IAD) to downtown Washington, DC costs approximately US\$75. The trip takes about 45 minutes depending on traffic. A one-way taxi fare from Reagan National Airport (DCA) costs approximately US\$25, and the trip takes about 20 minutes.

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Coffee & Lunch

Coffee and tea will be available upon arrival. Lunch will be provided. Vegetarian options will be available.

Connecting Remotely

For those who will be connecting remotely, please find instructions on how to connect via Webex in the below. *Please note that these instructions will also be provided in a calendar invitation for convenience as well.*

To join via computer or electronic device:

- Kindly select the 'join meeting' button below
- Meeting number (access code): (b) (6)
- Meeting password: (b) (6)

[Join meeting](#)

To join via phone, please use the following dial-in and access code:

- Dial in: [1-650-479-3207](#) (Call-in toll number (US/Canada)) or click here for [Global call-in numbers](#)
- Meeting number (access code): (b) (6)

Enquires or questions

If you have any further questions or enquiries regarding the meeting, please do not hesitate to contact the World Bank Health Team directly at Wbhealthevents@worldbank.org.