Overview on SARS-CoV2 & Challenges for COVID-19 Vaccine Development at Pandemic Speed

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R&D Head of Global Health, Partnerships & External Funding

June 3d 2020
## COVID-19 Cases

**June 2d, 2020**

<table>
<thead>
<tr>
<th>#</th>
<th>Country, Other</th>
<th>Total Cases</th>
<th>New Cases</th>
<th>Total Deaths</th>
<th>New Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>1,860,613</td>
<td>+1,290</td>
<td>106,944</td>
<td>+19</td>
</tr>
<tr>
<td>2</td>
<td>Brazil</td>
<td>529,405</td>
<td></td>
<td>30,046</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Russia</td>
<td>423,741</td>
<td>+8,863</td>
<td>5,037</td>
<td>+182</td>
</tr>
<tr>
<td>4</td>
<td>Spain</td>
<td>286,718</td>
<td></td>
<td>27,127</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>UK</td>
<td>276,332</td>
<td></td>
<td>39,045</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Italy</td>
<td>233,197</td>
<td></td>
<td>33,475</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>India</td>
<td>199,785</td>
<td>+1,415</td>
<td>5,612</td>
<td>+4</td>
</tr>
<tr>
<td>8</td>
<td>France</td>
<td>189,220</td>
<td></td>
<td>28,833</td>
<td></td>
</tr>
</tbody>
</table>
SARS 2003-2004
SP summary

Vaccine Development Timeline

- Project Initiation (Week of Aug 29th)
- Notification of Award
- Plaque Purification Amplification Prep of preMSL
- Production of MSV and WSV
- Development of Animal Models
- Development of Reagents/Testing
- QC Release & Stability Evaluation
- First Clinical Lot - Filled - Labeled
- MF(AvP)/IND (NIAID) File Review & Approval
- Phase I Study (NIAID)
- Dec 2004

Worldwide Breakdown of SARS cases.
* 82,445 worldwide
* 730 deaths

SOURCE: World Health Organization, June 12, 2003
Antigenic differences with SARS CoV1

Low / no cross-reactivity of the neutralizing antibodies expected

Legend

- Differences
- Additional loops

Top view of S1

Side view

90°

SARS Spike 3D structure from Li et al., 2005
Beta-Coronaviruses family

SARS CoV-2 closest relative is SARS CoV1 (2003 pandemic)

source: Nextstrain.org
## Comparison between Flu, COVID19, SARS and MERS

<table>
<thead>
<tr>
<th></th>
<th>Flu</th>
<th>Covid19</th>
<th>SARS</th>
<th>MERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R0</strong></td>
<td>1.3</td>
<td>2.4 – 3.5</td>
<td>3</td>
<td>0.3 – 0.8</td>
</tr>
<tr>
<td><strong>CFR</strong></td>
<td>0.05 – 0.1%</td>
<td>3.4% (higher in older age group and people with comorbidities)</td>
<td>9.6 – 11%</td>
<td>34.4%</td>
</tr>
<tr>
<td><strong>Incubation time</strong></td>
<td>1 – 4 days</td>
<td>2 – 14 days</td>
<td>2 – 7 days</td>
<td>6 days</td>
</tr>
<tr>
<td><strong>Hospitalization rate</strong></td>
<td>2%</td>
<td>19 – 20%</td>
<td>Most cases</td>
<td>Most cases</td>
</tr>
<tr>
<td><strong>Annual infected (global)</strong></td>
<td>1 billion</td>
<td>N/A (ongoing)</td>
<td>8,098 in 2003</td>
<td>420 in 2014</td>
</tr>
</tbody>
</table>
WHO Target Research Priorities in Each R Thematic Areas - 2020
( WHO R&D Blueprint -2015)

Scientific Advisory Group

To ensure that those affected are promptly diagnosed and receive optimal care.
To support research priorities in a way that leads to the development.

- animal & environmental
- epidemiological studies
- IPC, including HCWs
- clinical management
- virus: natural history, Dxs
- candidate vaccines
- candidate therapeutics

- Origin of COVID-19
- Role of animal hosts in transmission
- Mathematical Models
- Serological studies
- Containment measures
- Control in healthcare and community settings
- Optimised PPE
- Contamination, aerosol spread
- Ethical considerations
- Prioritization
- Assays and Standardization
- Clinical trials
- Animal models
- Dxs
- Clinical trials
- osOC
- Endpoints
- Clinical trials
- Assays

Integration of social sciences
GLOPID-R an international network of research funding organizations

“facilitate, accelerate and deepen collaboration among research funders on emerging diseases”:
- to strengthen global research preparedness between crises.
- to respond rapidly and effectively to significant infectious disease outbreaks.
REACTing is playing a key role in the coordination and information sharing regarding the COVID-19 outbreak in France.

Visit our dedicated pages on:
- the role of REACTing
- our literature review on COVID-19
- funding opportunites on COVID-19
The overall objectives of this topic are described in the following subtopics:

1. Accelerating the development of treatment agents (single products and their combinations) against coronaviruses:
   1.1. Focusing on re-purposing of drugs
   1.2. Identity novel chemical or biological antiviral treatment agents

2. Advancing the development of point of care diagnostics

- This current programme will be launched in 2020 with a provisional total budget of about € 90 million (Half EFPIA Companies).
- Given the level of urgency and type of activity, the call will be set up as an emergency single stage procedure. The indicative duration of the action is 72 months
- Vaccines are not included in this call

- Another Research H2020 call was launched worth of € 47.5 million (2-3 MM / applicant) for Academic Consortia
Bill & Melinda Gates Foundation COVID 19 Grants

SEATTLE, February 5, 2020 – The Bill & Melinda Gates Foundation today announced that it will immediately commit up to $100 million for the global response to the 2019 novel coronavirus (2019-nCoV). The funding will help strengthen detection, isolation and treatment efforts; protect at-risk populations; and develop vaccines, treatments and diagnostics. The new funding is inclusive of $10 million the foundation committed to the outbreak in late January.

SEATTLE, March 10, 2020 – The Bill & Melinda Gates Foundation, Wellcome, and Mastercard today committed up to $125 million in seed funding to speed-up the response to the COVID-19 epidemic by identifying, assessing, developing, and scaling-up treatments. The partners are committed to equitable access, including making products available and affordable in low-resource settings. The COVID-19 Therapeutics Accelerator will play a catalytic role by accelerating and evaluating new and repurposed drugs and biologics to treat patients with COVID-19 in the immediate term, and other viral pathogens in the longer-term. Currently there are no broad-spectrum antivirals or immunotherapies available for the fight against emerging pathogens, and none approved for use on COVID-19. The Gates Foundation and Wellcome are each contributing up to $50 million, and the Mastercard Impact Fund has committed up to $25 million to catalyze the initial work of the accelerator.
# Vision, mission, and strategic objectives

## Vision

A world in which epidemics are no longer a threat to humanity

## Mission

CEPI accelerates the development of vaccines against emerging infectious diseases and enables equitable access to these vaccines for affected populations during outbreaks

## Strategic objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Preparedness</strong></td>
<td>Advance access to safe and effective vaccines against emerging infectious diseases</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Accelerate the research, development and use of vaccines during outbreaks</td>
</tr>
<tr>
<td><strong>Sustainability</strong></td>
<td>Create durable and equitable solutions for outbreak response capacity</td>
</tr>
</tbody>
</table>
CEPI’s vaccine development so far

31st Dec 2019
WHO notified of pneumonia-like case cluster in Wuhan, China

14th Feb
First cases reported in Africa

11th Feb
SARS-CoV-2 included disease named COVID-19 by WHO

11th March
WHO declares SARS-CoV-2 a global pandemic

10th March
GPMB calls for scaled-up global response (US$8 billion)

12th April
Wellcome Trust launch COVID-Zero resource mobilisation

24th April
Global launch of ACT Accelerator

Jan 2020
Jan 31st
CEPI announces 4th development partnership
Jan 8th
CEPI contacted awardees
Jan 7th
CEPI activated response

Feb 3rd
CEPI launches Call for Proposals for COVID-19 vaccines
Feb 23rd
CEPI announces 3 COVID-19 vaccine development programmes
Feb 23rd
CEPI announces 3 COVID-19 vaccine development programmes
Feb 10th-20th
4 new (8 total) CEPI COVID-19 vaccine development partnerships

Mar 3rd
GSK/CEPI collaboration on adjuvant technology
Mar 17th
CEPI partner Moderna enters first in human clinical trial
Mar 11th

Apr 6th
CEPI partner Inovio starts first in human clinical trial
Apr 10th
CEPI partner w/IVI and KNIIH for Phil/ill trial in South Korea
Apr 16th
CEPI announces 9th vaccine development partnership
Apr 23rd
Phi clinical trial starts for CEPI partner Oxford University
Apr 23rd

May 4th
CEPI announces second Call for Proposals to expand portfolio
May 4th
European Commission pledging marathon to raise US$8.3 billion
Sanofi Pasteur: Two Approaches For A COVID-19 Vaccine
(February 18th, April 14th and March 27th 2020)

1 - Baculovirus recombinant vaccine approach

- Cell Culture → Protein Antigens + Adjuvants → Human

- Licensed platform
- Safety experience
- BARDA collaboration
- Existing large scale manufacturing capacity

AF03 SP/ASO3 GSK

2 - Translate Bio mRNA vaccine approach

- In Vitro Transcription → mRNA → Delivery System → mRNA Formulation → Human

- Different MoA
- Adds manufacturing capacity
- Building on current collaboration
- R&D synergies
Recombinant Influenza Vaccine

First recombinant hemagglutinin (rHA) containing influenza vaccine

- Baculovirus expression vector system used instead of eggs to produce rHA
- Developed by Protein Sciences (*acquired by Sanofi in 2017*)

- Baculovirus engineered with the gene of interest (e.g., hemagglutinin [HA] for influenza vaccine)
- Baculoviruses are highly specific to *Spodoptera frugiperda* [fall armyworm]-positive cells (SF+)
- SF+ cells infected with engineered virus
- Incubated for ~48 to 72 hours
- High yield of protein of interest generated (in this case, HA) – extracted and purified

The recombinant technology developed for influenza vaccines will also be used in efforts to combat COVID-19 disease

Reference:
Benefits of Recombinant Vaccine Platform

Unique circumstances make this an attractive option for a vaccine

- The experience with the SARS vaccine can be leveraged to expedite COVID-19 vaccine development

- There is a US licensed recombinant influenza vaccine based on the platform
  - Research and Clinical material could be produced relatively quickly
    - Assuming a similar purification process a vaccine candidate against the novel coronavirus could be produced with the expectation that the candidate would be immunogenic and have an acceptable safety profile
  - The manufacturing platform is approved by the FDA and under consideration of other global regulatory authorities
  - Existing infrastructure to facilitate production of large quantities of vaccine
    - Could be produced at our existing facilities (Pearl River, NY and Unigen, Akita, Japan)

- The technology provides a rapid relatively low risk path to large scale supply
  - Assuming the SARS experience proves applicable to development of a vaccine candidate.
BARDA Sanofi Pandemic Preparedness Partnership

US-based adjuvant and antigen manufacturing of pandemic flu vaccine

Secure domestic rHA production by retrofitting a manufacturing facility

Establish MF59 adjuvant production in existing building in Swiftwater

“End to end” Pandemic response capability in Swiftwater

Develop and license an MF59 adjuvanted pandemic rHA

Ensuring adequate fill finish capacity in the event of a pandemic

BARDA provides

Funding

BARDA wants

US-based manufacturing of MF59 adjuvant and 100 million doses of pandemic recombinant (7.5mcg)

Facilities to remain operational ten years after contract ends
Sanofi’s collaboration on mRNA vaccine platform

Existing agreement to develop mRNA vaccines for five infectious diseases

Rodent and non-human primate studies complete on other vaccine programs

Opportunity to scale-up to commercial volumes

Lead mRNA and LNP candidates tested across disease targets

Large scale process development in progress for lead mRNA constructs
Probability of success at each phase of research
(37% + 69% + 42% + 15%: less than 10 percent of drug trials are ultimately approved)
Biotechnology Innovation Organization 2006 – 2015

Overview of Potential SARS-CoV2 Vaccine Platforms

Immunity 52, April 14, 2020
Perspective SARS-CoV-2 Vaccines: Status Report
https://doi.org/10.1016/j.immuni.2020.03.007
PUBLIC AND PRIVATE DEVELOPMENT LANDSCAPE

North America

China

Europe

Australia and other Asia

Number of developers (by leading group only)

Public and non-profit  Academic  Private and industrial

doi: 10.1038/d41586-020-01221-y
Vaccine Time to licensure benchmarks

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Time to licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>28 years</td>
</tr>
<tr>
<td>FluMist</td>
<td>28 years</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>15 years</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>15 years</td>
</tr>
<tr>
<td>Pediatric combination</td>
<td>11 months</td>
</tr>
<tr>
<td>Covid-19 goal</td>
<td>18 months</td>
</tr>
</tbody>
</table>

Note: Rotavirus and HPV vaccines include time from filing of the first investigational new drug to approval.
Source: “Plotkin’s Vaccines” (7th edition)

Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm

Traditional Paradigm — Multiple Years

- Target ID, development partner selection, and preclinical trial
- Small-scale clinical trial material
- Manufacturing scale-up, commercial scale, validation of process
- Large-scale manufacturing
- Go or no-go decision to invest in candidate
- Phase 1
- Phase 2a
- Phase 3
- Licensure
- First trial in humans
- Efficacy trial in humans
- Evaluation trial in humans

Outbreak Paradigm — Overlapping Phases Shorten Development Time

- Target ID, development partner selection, and preclinical trial
- Clinical development
  - Safety/dose selection
  - Safety/efficacy
  - First in humans (safety)
  - Efficacy trial
  - Regulatory pathway for emergency authorization
- Manufacturing development, scale-up, clinical trial material, commercial scale, validation of process
- Large-scale manufacturing
- Go or no-go decision to invest in candidate
- Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

How to move to pandemic paradigm?

Assume We Already Understand the Coronavirus
Start trials early
Rely on work from studying SARS and MERS to shorten preparations before clinical trials

Don’t wait for academic research
Skip to clinical phases using what we know about the coronavirus so far

Move at ‘Pandemic Speed’ Through Trials
Use ‘pandemic speed’ timeline
Start subsequent steps before previous phases are completed

Push to large-scale tests sooner
Move more swiftly to Phase 3 trials by combining phases

Use emergency provision
Vaccinate front-line and essential workers early

Start Preparing Factories Now
Make vaccines early
Build and manufacture early, anticipating that factories will be useful for a future vaccine and that the product will clear regulatory hurdles

Speed Up Regulatory Approvals
Take a bet on a successful Technology
The experimental may be faster to produce/leverage existing facility

Fast-track federal approvals
Shorten approval window from a year to six months
How artificial intelligence and machine learning can help healthcare systems respond to COVID-19

Mihaela van der Schaar, John Humphrey Plummer et al.

Cambridge Centre for AI in Medicine

March, 27th, 2020
Summary I: COVID-19: partnerships will be essential to success

The United States Government
- FDA
- BARDA
- NIH
- Trump’s “Operation warp speed”

European governing bodies
- EU Commission
- EMA
- ECDC
- EU countries’ national governments (France, Germany…)

National scientific networks
- French COREVAC
- REACTING
- INSERM

Act-Accelerator
Global organizations targeting an end-to-end access solution
- Bill & Melinda Gates Foundation
- Wellcome Trust
- WHO
- CEPI
- GAVI
Summary II: Two complementary vaccine approaches with unparalleled pandemic capacity

1. Baculovirus recombinant vaccine approach
   - Licensed recombinant platform (1)
   - Existing large scale capacity
   - BARDA collaboration
   - Collaboration with gsk for proven AS03 adjuvant

2. mRNA vaccine approach
   - Innovative approach (2)
   - Potential for accelerated development
   - Significant existing investment in mRNA capacity to be applied towards vaccine

Platform:
- Protein Antigen
- Adjuvant

Advantage:
- Existing capacity for 100-600 million doses
- Goal to extend to >1 billion doses in 12 months (3)

Expected timelines:
- FIH study start: Q4 2020
- Earliest approval: H2 2021

Capacity:
- Capacity for 90-360 million doses by H1 2021
- Investigating to extend capacity significantly (3)

BARDA: Biomedical Advanced Research & Development Authority; gsk: GlaxoSmithKline; FIH: first in human

(1) Flublok® is manufactured with this platform and licensed in the U.S.
(2) In collaboration with Translate Bio
(3) Estimates pending clinical doses and industrial yields outcome
Thank You!

- Interdependence: Trust based Sharing of Interests