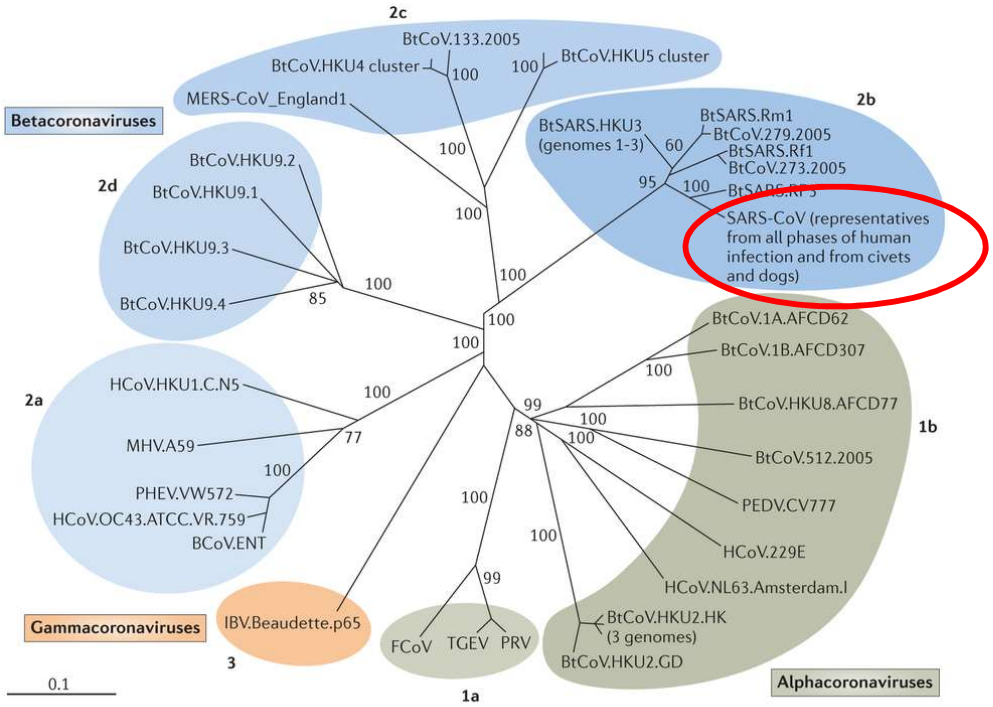
- Test, track, isolate and treat in South Korea (and COVID-19 vaccine development)

Jerome H. Kim, MD
International Vaccine Institute
24 April 2020

International Vaccine Institute

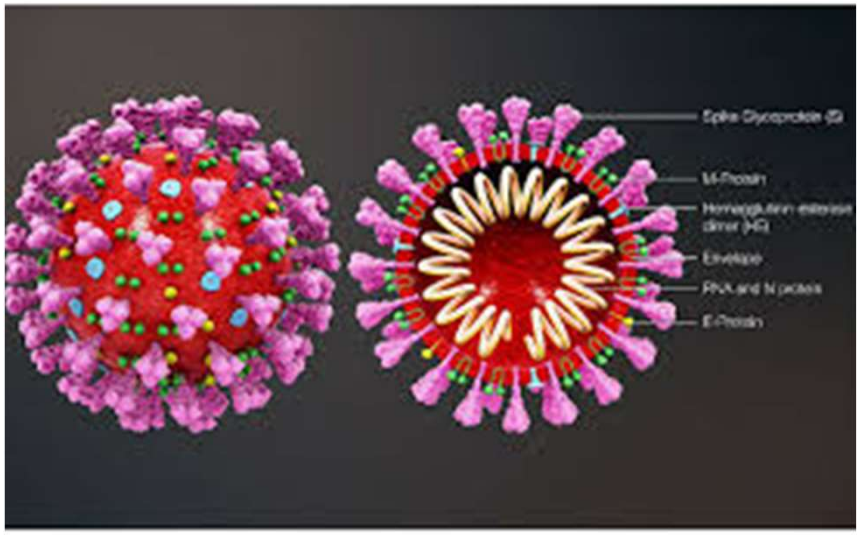
COVID-19: the latest pandemic, not the last

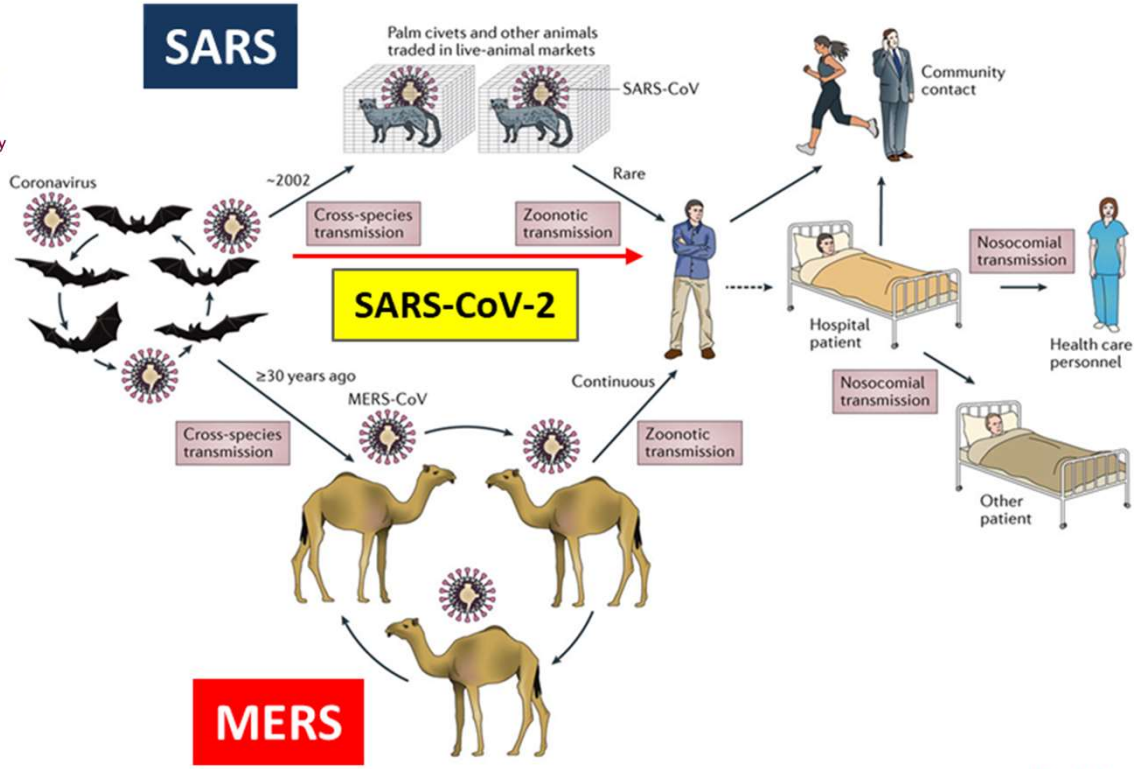
Coronavirus taxonomy and host range



Nature Reviews | Microbiology

- Coronaviruses are a promiscuous family of mammalian RNA viruses
- SARS-CoV and SARS-CoV-2 share 79% sequence homology, 72% in the S1 gene
- SARS-CoV-2 has 8 circulating strains containing 11 (?30) mutations in a 30,000 kB genome, mutation rate is 8-10x lower than influenza





Nature Reviews | Microbiology

Flattening the curve in South Korea

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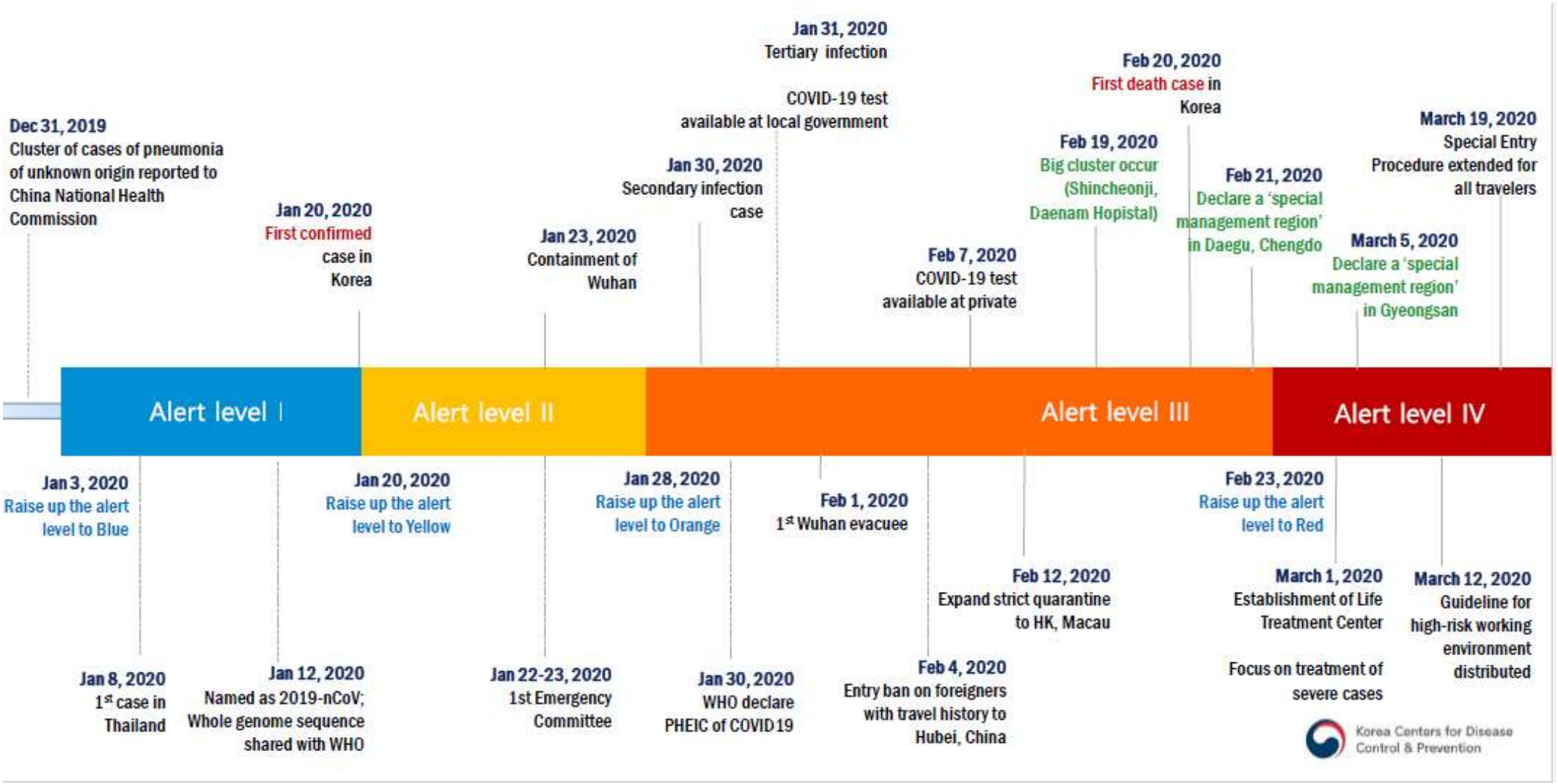
South Korean model

- **Preparation (MERS, 2015)**
- **Command Control Communications**
  - Clear command from PM to districts
  - Transparent, decisive, data-driven decisions
  - Clear messages reinforced frequently
  - No lockdown – voluntary compliance – use of information, tracking etc
- **Test-isolate-track-treat**

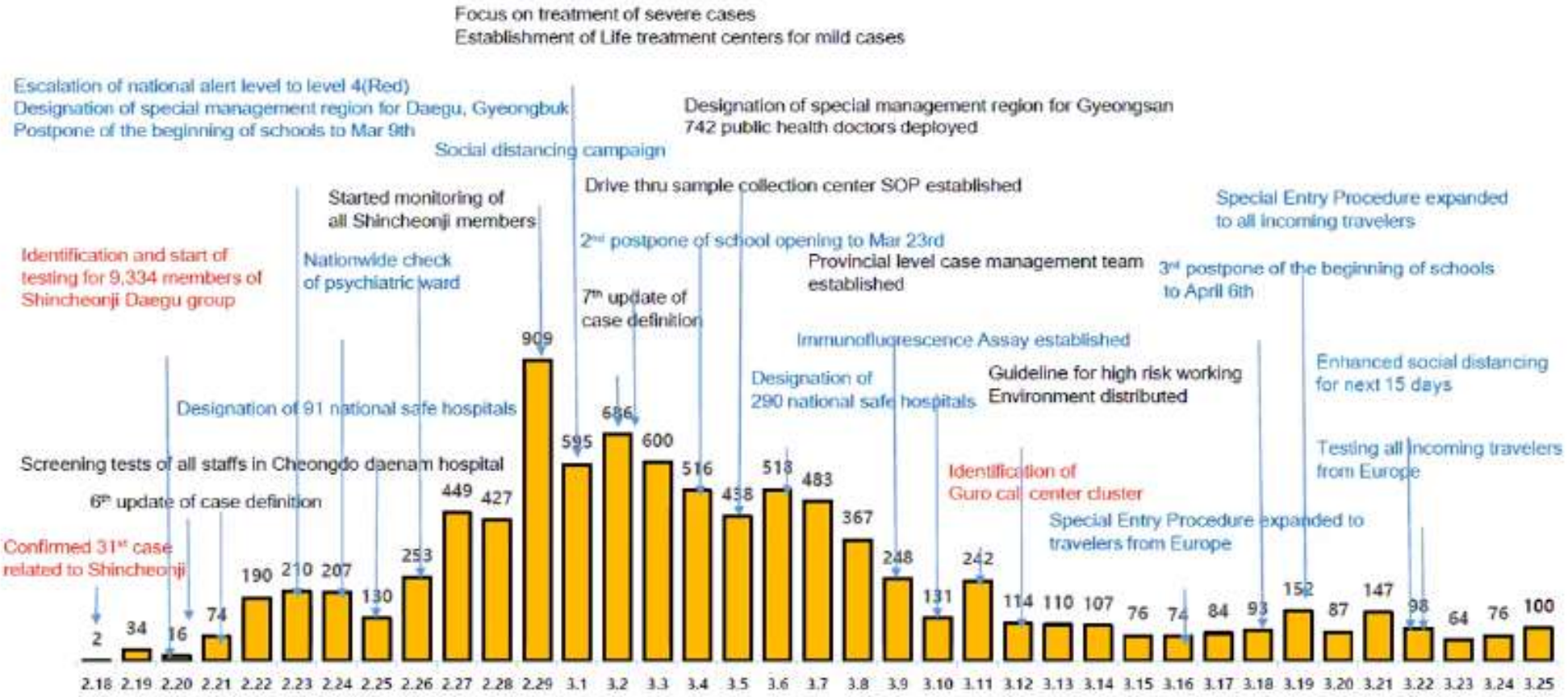
Preparation for release

- 14-21 days at negative slope or "threshold" of ?deaths, cases
- Hospital capacity
- Supplies, personnel, test kits & surveillance for test, isolate, track and treat
- Piloting?
- CCC→ TITT

Evolution of the S. Korean response to Level IV



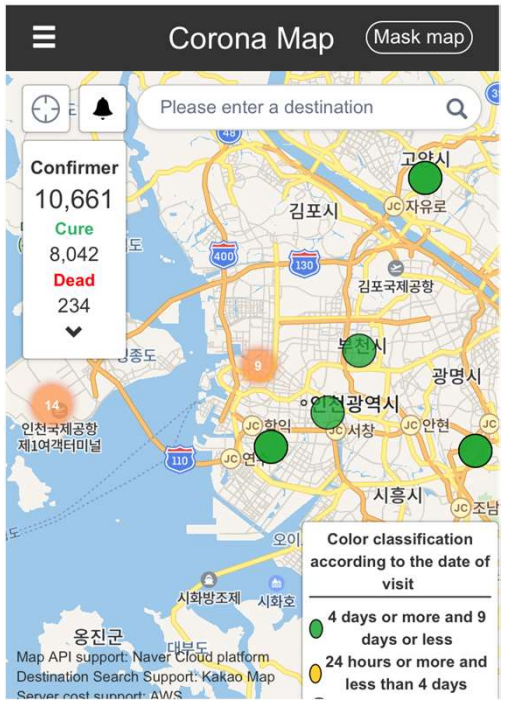
Timeline of the Korean COVID-19 Outbreak: Round 1

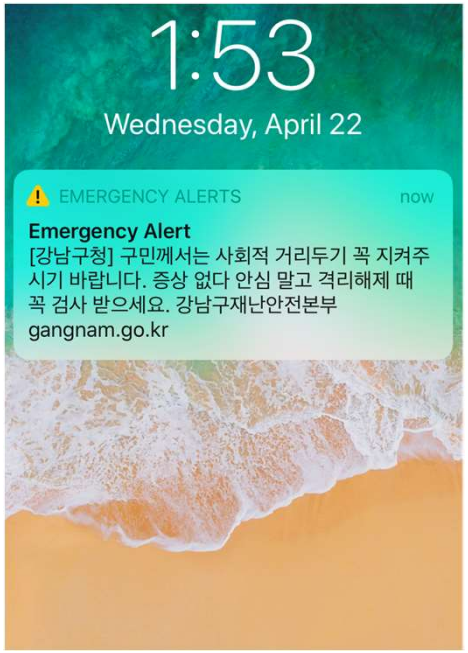


The use of information technology was key

Government provided free apps for mobile phones

- **Emergency information**
- **Social distancing reminders**
- **Latest information on testing, identification of hotspots and location of cases**
- **Referral to national and local government websites for additional information**





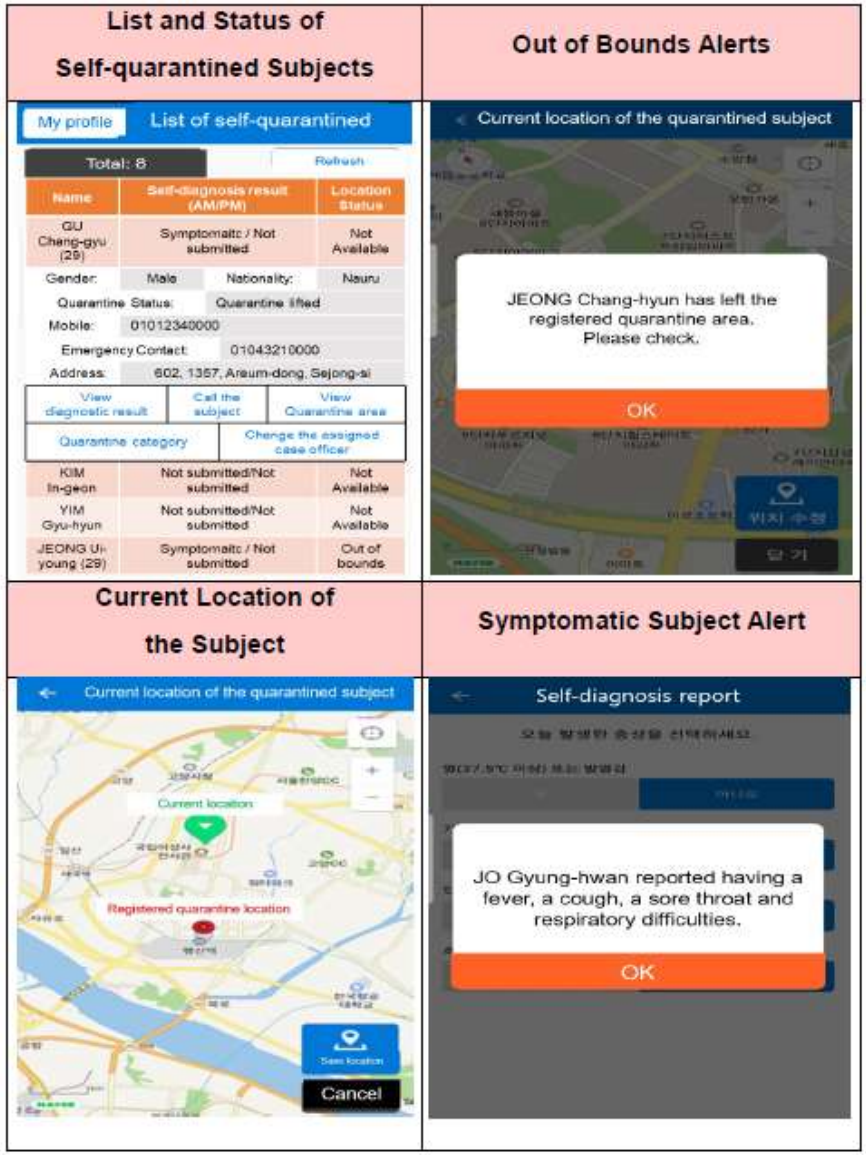
Other government measures included

- **Temporary approval of telemedicine**
- **Wireless base for low income families**
- **Educational content on TV**
- **Self diagnosis & tracking app for travelers (in-bound)**
  - URL / QR codes at airport
  - If you don't respond you are called, if you don't respond you are visited
  - If you are caught violating quarantine there are penalties that include a fine, expulsion from Korea (non residents), and/or mandatory quarantine

Daily self diagnosis

Self-quarantine safety app

- From 7 March for people who were under quarantine
- Monitors symptoms and location
- Government case officers had a complementary app to track the people under their watch
- The government officer calls periodically and does home visits at random



Infectious Diseases Prevention and Control Act, 2010

Amended 2015, 2017 after MERS outbreak

- Blue – interest, Yellow – case in Korea, Orange – local spread, Red – national spread
- Certain powers and responsibilities of the state, local governments and medical personnel, in addition to the rights and duties of the people
- When an infectious disease harmful to citizens' health is spreading, the Minister of Health and Welfare shall promptly disclose information with which citizens are required to be acquainted for preventing the infectious disease, such as the movement paths (GPS data), transportation means, credit card transactions, medical treatment institutions, and contacts of patients of the infectious disease without a warrant

Park M, Epidemiol Health 2017

Central control, defined roles and responsibilities

Red alert

- **Central disaster and safety countermeasures HQ**
- **At highest level of alert, responsibility shifts to Prime Minister**
- **Government can send extra resources to an area**
- **Can forcibly close schools and other organizations**

Information that can be collected

Collection item*	Purpose and use	Advantages	Limitations	Related branch and institution
History of using medical facilities	(Purpose) Identify the clinical symptoms and date of initial onset of symptoms of the patient Obtain medical records and evaluate the date of onset of symptoms	Obtain objective data about the clinical symptoms of the patient Specify medical facilities that were visited during the time of exposure	Long time needed to review the medical records If there are no related symptoms because the medical facilities were visited for a different illness, it is impossible to obtain related information	National Health Insurance Corporation Health Insurance Review and Assessment Service
GPS (cell phone location)	(Purpose) Identify the route of the patient Verify the consistency of the patient claims Additionally check the previous route Use phone GPS (latitude and longitude) data	Evaluate the consistency of the patient route identified via interview Obtain additional information about the route that the patient does not remember	There are limitations to specify accurate location information because mobile phone locations are used Errors if the name on the phone and location of purchase (overseas) are different Long time needed to view the information if there is a large difference between the time of patient confirmation and date of symptom onset	National Police Agency
Card transaction log	(Purpose) Identify the route of the patient Verify the consistency with the patient claims Specify a location for defense against infectious diseases	Specify the visited location, and use it to select the scope of contact investigation Monitor detailed route within a location	If a card with the patient's name is not used, the transactions of another person are mixed and need reclassification	Financial Services Commission
CCTV	(Purpose) Identify the route of the patient Identify patient's clinical symptoms Evaluate the exposure risks of contacts	Check whether the patient was wearing protective gear (e.g., mask) and the patient's clinical condition at the corresponding location Help evaluate the risk of exposure if there is a large unspecified number of contacts	Long time needed to check the CCTV There are limitations to clearly identify if there is no internal CCTV or blind spots are present	National Police Agency

*Related basis (Infectious Disease Control and Prevention Act Article 76 Section 2 (request to provide information), Infectious Disease Control and Prevention Act Article 32 Section 2 (information that can be requested to be provided).
GPS = global positioning system; CCTV = closed-circuit television.

But practically

Taking exams, 1620 Joseon dynasty

Line for polling station 66% turnout for National Assembly

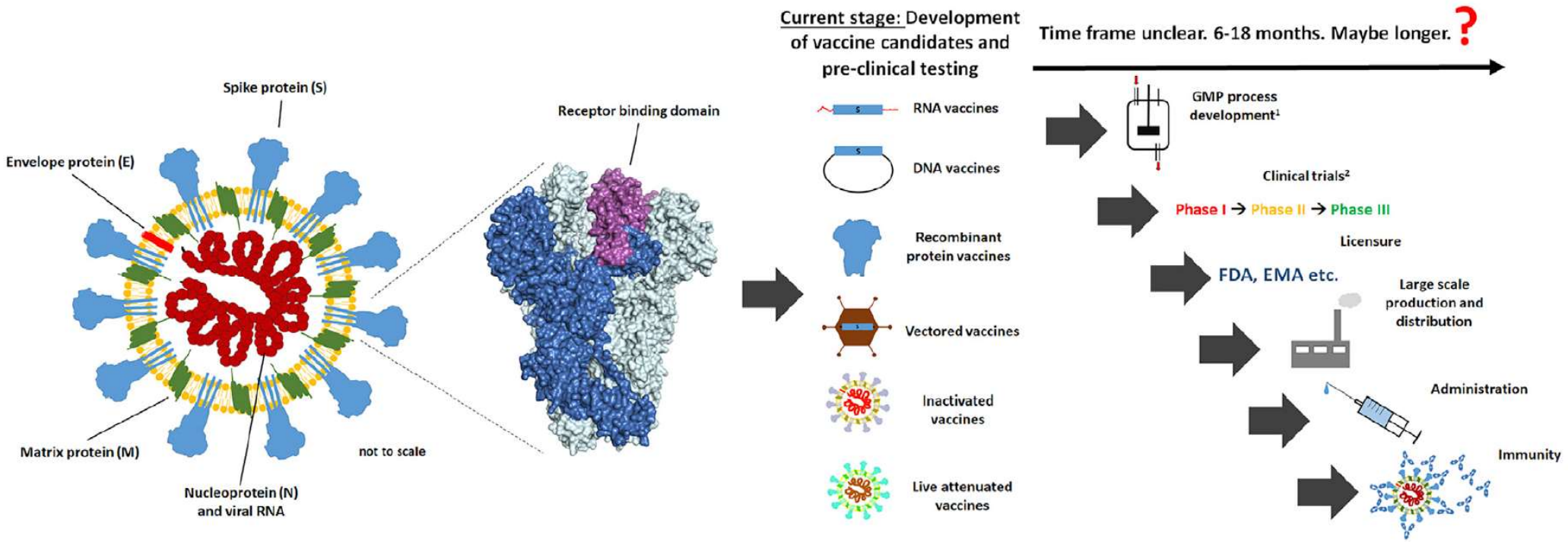
Even the quarantined voted

Masks, gloves & sanitizer

SARS-CoV-2 Vaccine Development

International Vaccine Institute

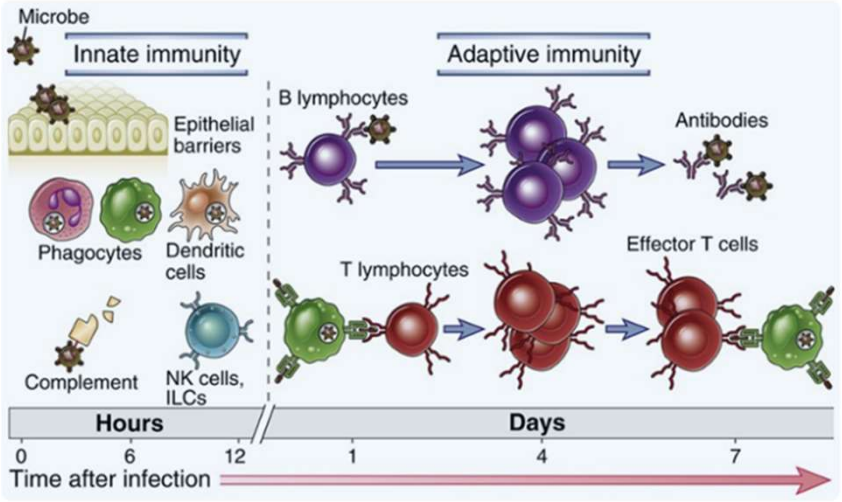
Vaccine development approaches: SARS-CoV-2



Amnat et al, Immunity 2020

Known unknowns [1]

- **Does infection provide immunity?**
  - Classic vaccine – disease model (e.g. Hepatitis A, polio)
    - Variable courses and sequelae but almost all recover completely (polio, rubella, influenza)
    - Vaccine induced immune response or natural immune response clear virus completely
    - Lifelong immunity from reinfection (or after booster immunization)
    - Or is this like EBV, cytomegalovirus, HIV, or TB?
  - If it does provide immunity how long does it last?



Abbas AK, et al (eds), Cellular and Molecular Immunology, 8e, 2015

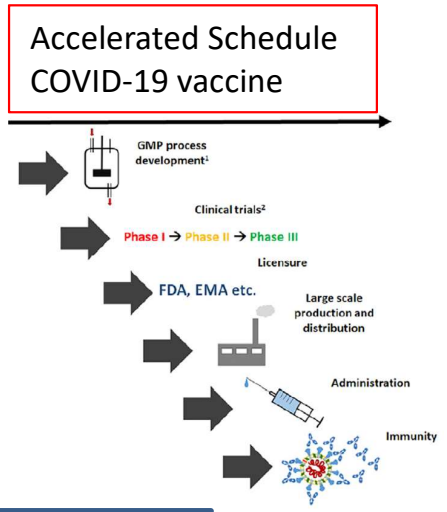
- **What immune responses are important in clearing infection >> and which immune responses protect?**

Known unknowns [2]

- **What is the appropriate animal model?**

- **Are there any safety issues?**

Under normal circumstances it takes 5-10 years to make a vaccine



5-10 years

Technology

Assay & Process Development

Disease burden
Public health need

Basic

Translational

Clinical Development

Discovery & Exploratory Stage

Preclinical Stage

Phase I

Phase II

Phase III

Regulatory approval

Production & launch
Phase IV

Only 1 in 10 vaccines make it here

- Pathogenesis
- Immune responses
- Antigen discovery
- Animal model

- Vaccine design
- Formulation
- Adjuvant
- Toxicity
- Proof of concept in animals

Scaling up manufacture
Quality controls

Management
Funding

Market

PUSH

PULL

Vaccine development is costly, and risky

Cost to develop a vaccine

- Serbodova et al, Am J of Public Health 2006; $200-500M.
- Young et al, Gates open res 2018; $400M – 1.0B
- Sir Andrew Witty, CEO GSK, billion dollar estimates are “one of the great myths of the industry.”

Failure rate

- Only 7% of vaccines reaching preclinical development are licensed

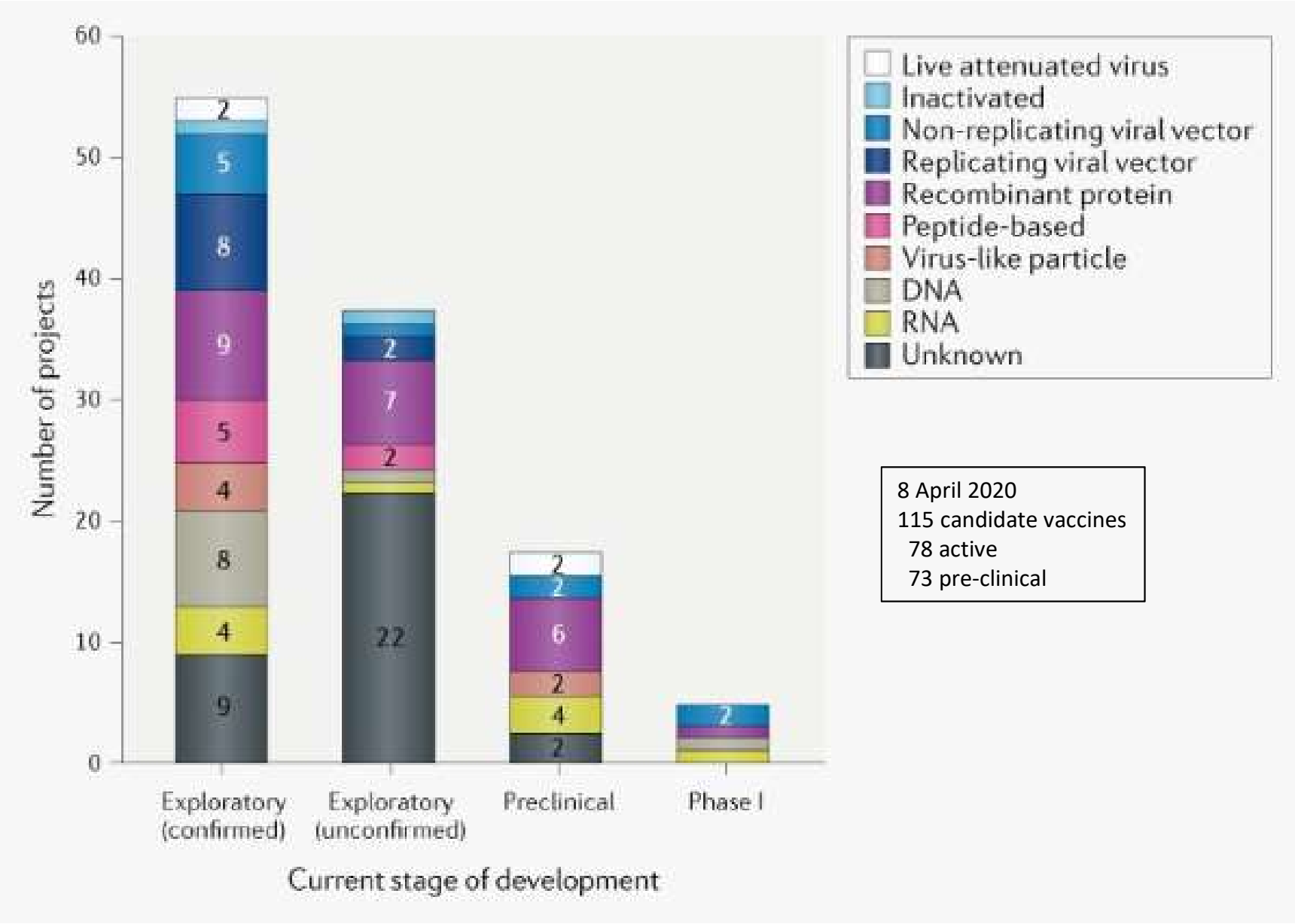
Hi cost, hi risk, lo incentive

- Why spend $1 B with a high risk of failure and a low ROI?

Vaccine	Developer	Status	Cost to BMGF on PQ
MenAfriVac	Serum Institiute/PATH	PQ	$50 million
OCV	Shantha/EuBiologics/IVI	PQ	$28 million
ViDT	SK Chemicals/BioFarma/IVI*	Phase II	$34 million*

**projected*

SARS-CoV-2 vaccine pipeline



8 April 2020
115 candidate vaccines
78 active
73 pre-clinical

Le et al, Nat Rev Drug Discovery, 2020

COVID-19 prophylactic vaccines in Phase I testing

- **Moderna**
  - NCT04283461, N = 45, safety and immunogenicity, dose-ranging
  - LNP-encapsulated mRNA (mRNA 1273)
- **Inovio**
  - NCT04336410, N=40, safety, tolerability, dose-ranging
  - INO-4800 DNA by electroporation
- **Jenner Institute (Oxford)**
  - NCT04324606, N = 510, Ph I/II
  - ChAdOx1 non replicating simian adenovirus
- **CanSino,**
  - NCT04313127, Phase I, N=108 enrolled
  - Ad5-nCoV
  - Phase II starting 10 Apr 20
- **Beijing Institute of Biological Products**
  - ChiCTR2000031809
  - Whole inactivated / alum

DRAFT Phase I/II clinical trial in S. Korea

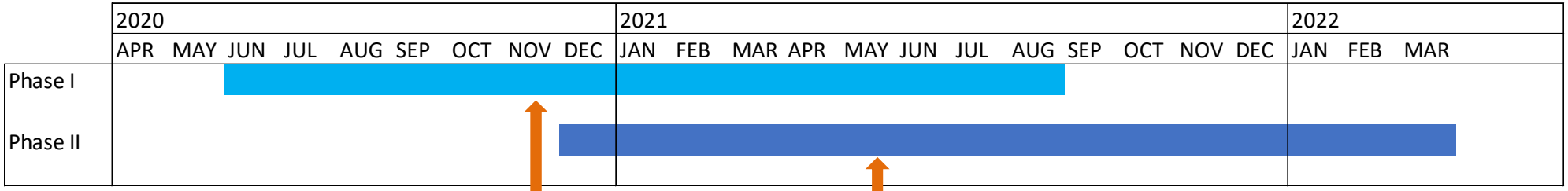


Figure 2: CELLECTRA® 2000 Pulse Generator

Dose decision for Phase II

Ph II week 8 data review

- N = 160
- Part A, N = 40, 1 mg & 2 mg, 0, 4 wk
- Part B, N = 120, 1 or 2 mg, @ 0, 4 wk
- Electroporation by Cellectra 2000 with 3P-ID device

PART A (N=40)

1. Low Dose (N=20) 1mg INO4800 + EP at D0 /W4
2. High Dose (N=20) 2mg INO4800 + EP at D0 /W4

- **Open-label**
- **Dose-ranging**

PART B (N=120)

3. IP Arm (N=90) Confirmed dose* (either 1 or 2mg) INO4800 + EP at D0 /W4
   Control Arm (N=30) Confirmed dose* (either 1 or 2mg) placebo + EP at D0 /W4

- **Randomized**
- **Placebo-controlled**
- **Double-blinded**

CELLECTRA® 3P-ID Applicator with Sheath and Array Installed

Will this end up like SARS(1) and MERS? No vaccine?

- **SARS and MERS were different diseases with different pathogen specific features that make them different from COVID-19 with a higher transmissibility than SARS, 10 fold greater mortality than flu, and that turns 80% of the infected into mildly symptomatic spreaders**
- **The World Bank estimates that the cost of outbreaks in the 21st century is 6 trillion dollars.**
  - MERS cost $10 billion
  - SARS $40 billion
  - Ebola $6 billion
  - COVID-19 $2-4 trillion

CEPI | New vaccines for a safer world

Does a safety concern with SARS-CoV => a safety issue for SARS-CoV-2 / COVID-19?

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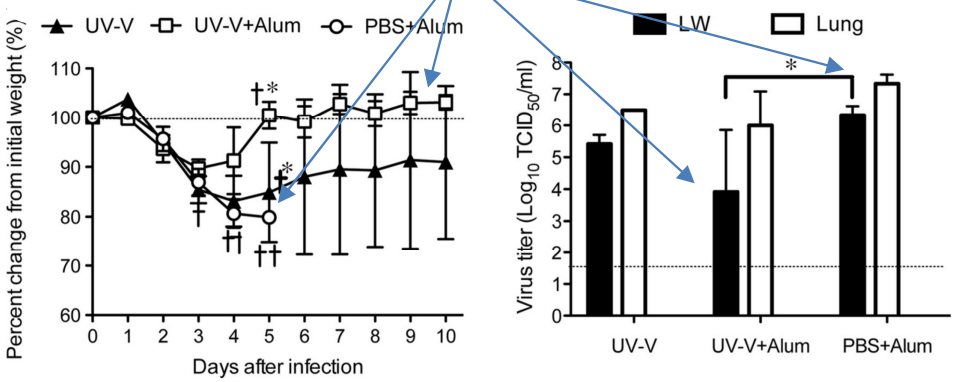
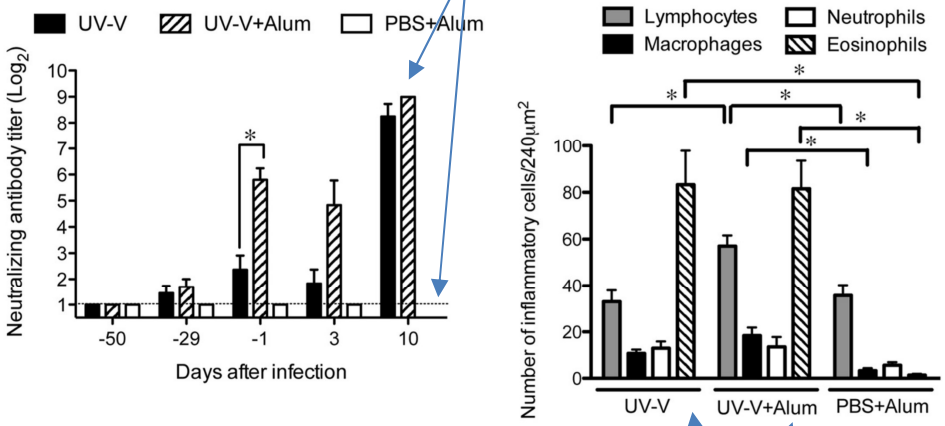
Eosinophilic pulmonary disease after vaccination with UV-V virus and challenge with WT SARS-CoV-(1)

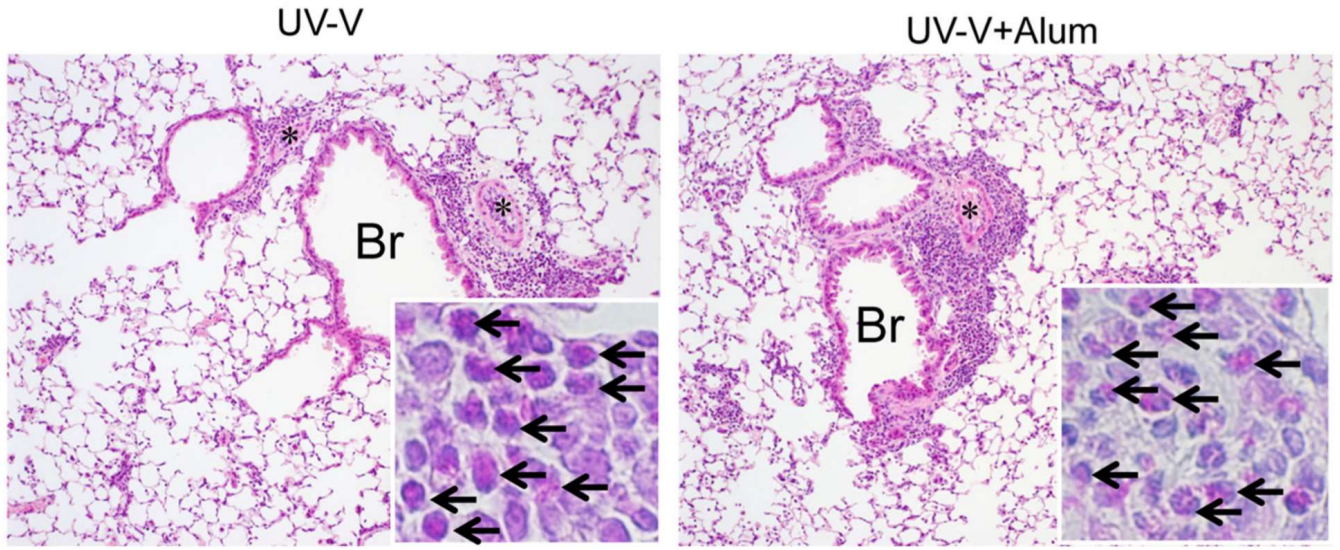
Mice do well with lower VL



Mice UV-V plus alum: higher Nab but eos



Female Balb/c mice vaccinated with SARS-CoV UV irradiated virus then challenged with SARS-CoV



Eosinophilic infiltrates in mice receiving WIV with or without alum

Iwata-Yoshikawa et al, JVI 2015

Enhanced disease after SARS-1 challenge of vaccinated animals

Type of vaccine	Virus	Antigen	Adjuvant	Animal	Protection [1]	Lung pathology [2]
Inactivated	MERS-CoV	Whole virus	-	Mouse	Yes	Yes
Inactivated	MERS-CoV	Whole virus	Alum	Mouse	Yes	Yes
Inactivated	MERS-CoV	Whole virus	MF59	Mouse	Yes	Yes
Inactivated	SARS-CoV	Whole virus	-	Mouse	Yes	Yes
Inactivated	SARS-CoV	Whole virus	Alum	Mouse	Yes	Yes
Inactivated	SARS-CoV	Whole virus	Delta inulin	Mouse	Yes	No
Inactivated	SARS-CoV	Whole virus	TLR-ligation	Mouse	Yes	Some
Inactivated	SARS-CoV	Whole virus	-	Ferret	Yes	No
Inactivated	SARS-CoV	Whole virus	Alum	Ferret	Yes	No
Inactivated	SARS-CoV	Whole virus	-	Hamster	Yes	No
Inactivated	SARS-CoV	Whole virus	ASO1B	Hamster	Yes	No
Virus Like Particle	SARS-CoV	S	-	Mouse	Yes	Yes
Virus Like Particle	SARS-CoV	S	Alum	Mouse	Yes	Yes
Subunit	SARS-CoV	S	-	Mouse	Yes	Yes
Subunit	SARS-CoV	S	Alum	Mouse	Yes	Yes
Subunit	SARS-CoV	S	Delta inulin	Mouse	Yes	No
Subunit	SARS-CoV	S trimer	Alum	Hamster	Yes	No
Adeno vector	MERS-CoV	S1	-	Mouse	Yes	Yes [3]
Adeno vector	MERS-CoV	S1	CD40-L	Mouse	Yes	No
Adeno vector	SARS-CoV	S + N	-	Ferret	Yes	No
VV or VEE vector	SARS-CoV	S	-	Mouse	Yes	No
VV or VEE vector	SARS-CoV	N	-	Mouse	No	Yes
VV vector	SARS-CoV	S	-	NHP	Yes	Yes
Live attenuated	SARS-CoV	Whole virus	-	Hamster	Yes	No

Zellweger R, et al, unpublished

Is there any pattern to enhanced disease in vaccinated animals after challenge?

- **Viruses: SARS-CoV > MERS || SARS-CoV-2 unknown**
- **Antibody dependent enhancement different from pulmonary disease, but what about when Ab decreases**
- **Animal model?**
  - Mice
  - Hamsters
  - Ferrets
  - Monkeys
- **Vaccine types WIV > vectored > subunit?**
- **Adjuvants $T_h2 > T_h1$**

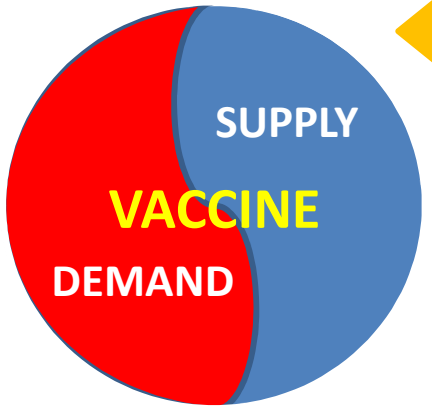
The road to “normalcy”

- Natural history of multiyear COVID-19 outbreaks will lead to herd immunity, creating “immunological distance”, at a cost of 70% mortality in the elderly and 14% rates of hospitalization in the average person
- Vaccines should protect and when enough people are vaccinated, we will also achieve herd immunity
- We could establish a better “new normal” with effective medication, prophylactic antibodies, or prophylactic medication – not normal, but better
- The disease might simply disappear, or it might become chronic and seasonal with multiple circulating strains that periodically change

Begin with the end in mind: *Saving Lives, Building a Stronger, Healthier World*

Impact
- Lives saved
- ↓ DALYs
- Healthier families
  - ↓ poverty
  - ↑ cognitive and physical development
  - ↑ education
- ↑ Economic growth

New global health vaccines



Developing Country Vaccine Manufacturer

VACCINATION PROGRAMS

DELIVERY

WHO/SAGE
Gavi
UNICEF
NITAGs

Manufacturing
Clinical Development
NRA approval
WHO PQ

DEVELOPMENT AGENCIES
- KOICA, SIDA, DFID, USAID

FOUNDATIONS / TRUSTS
DONORS

- Burden data
- Cost Effectiveness
- Investment Cases
- Full Public Value of Vaccines Analyses
- Support for NRA / NITAGs

- Clinical Development and Regulatory
- Biostatistics
- Data Management
- Support for PQ

Technology Transfer & Mfr Support

PRODUCT DEVELOPMENT PARTNERSHIPS

ACADEMIC LABORATORY

New vaccines


International Vaccine Institute
20 Years Advancing Global Health
Thank You!
IVI website
www.ivi.int
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