Vaccines for Emerging Infectious Diseases: MERS-CoV

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International Vaccine Institute
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International Vaccine Institute

Emerging infectious diseases

- Emerging infectious diseases (EIDs)
  - Not previously recognized in man
  - Examples: Ebola, SARS, MERS, Nipah, drug resistant organisms, etc.

- Re-emerging infectious diseases
  - Existed in past, now increasing in host or geographic range
  - Examples: Dengue, Zika, Chikungunya, West Nile virus, etc.

EIDs and “transitions of civilization”

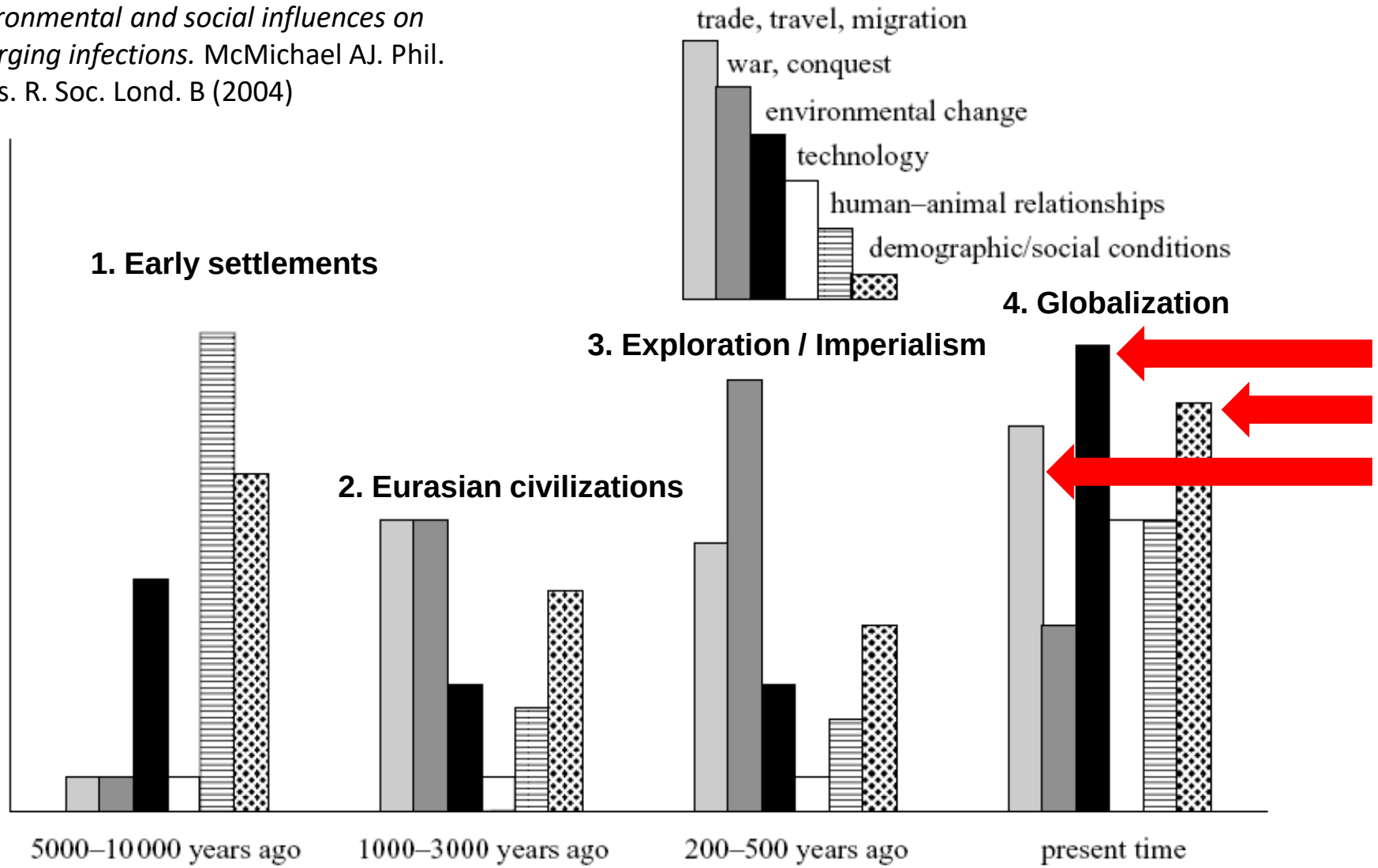
- Domestication of livestock (10,000-15,000 years ago)
  - Facilitates cross-species transmission (zoonotic diseases)
  - Conditions supporting pathogen survival

- Settlements becoming cities
  - Densely packed susceptible hosts
  - Sanitation and pest control problems
  - Multi-use services (e.g., water well)

- Migration, trade, exploration, conquest
  - Infections migrate
  - Pathogens find new susceptible hosts

Period-specific drivers of EIDs during transitions

Environmental and social influences on emerging infections. McMichael AJ. Phil. Trans. R. Soc. Lond. B (2004)



We are currently experiencing a "transition of civilization"

Current global drivers are just increasing

- Population growth with uncontrolled urbanization
  - Massing of susceptible hosts
- Human mobility
  - Local, regional and global mobility
- Changing ecology
  - Climate change
  - Animal-human interface

❖ Ongoing pathogen evolution

➢ We can expect more EIDs

Vaccination prevents deaths and saves money

- Vaccination programs have prevented >3 billion infections worldwide
  - >500 million deaths prevented
- Vaccines will save lives from 2011-2020:
  - 25 million deaths prevented

US CDC estimate

From 1994-2013 in USA

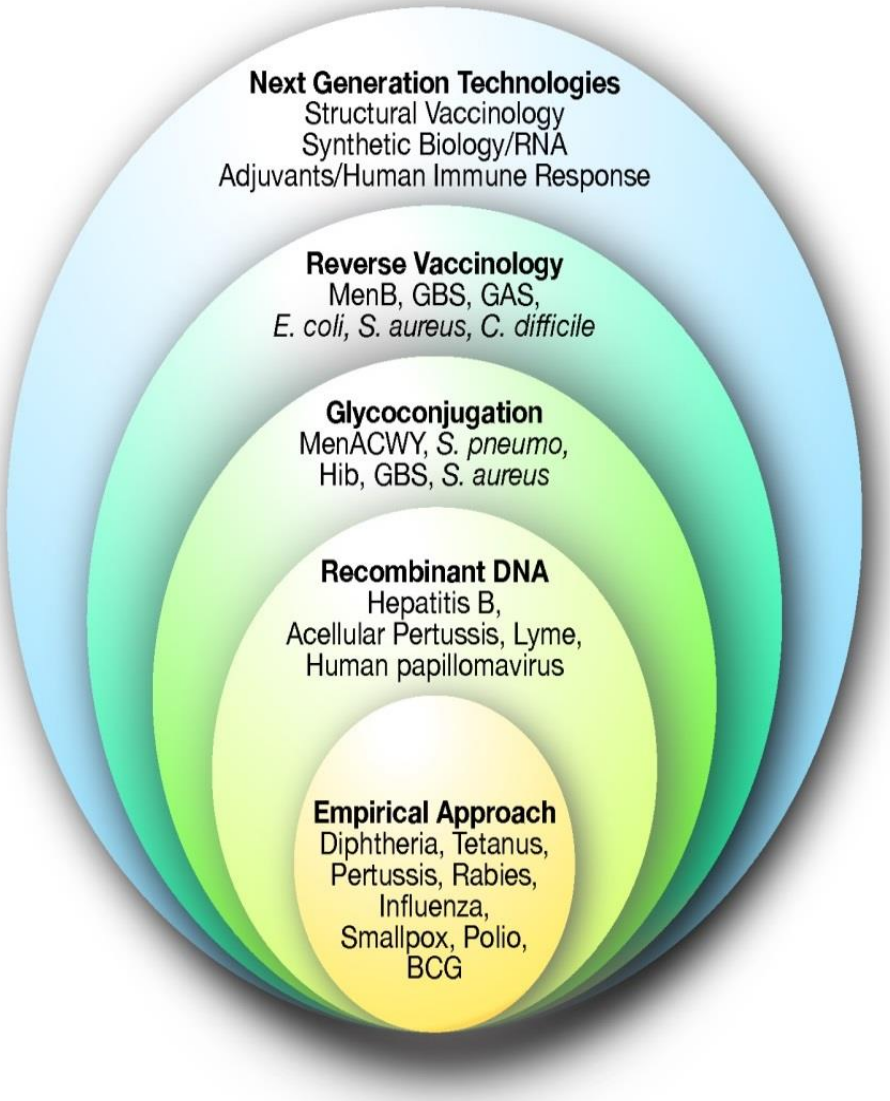
Vaccines prevented:
- 322 million illnesses
- 21 million hospitalizations
- 732,000 deaths

Vaccines saved:
- $295 billion direct costs
- $1.38 trillion in total societal costs

For every $1 spent on vaccines, $16 are saved in future healthcare costs, lost income, and lost productivity. If all indirect costs are included, the ROI is 44:1.

WHO Global Action Plan
http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/index.html)

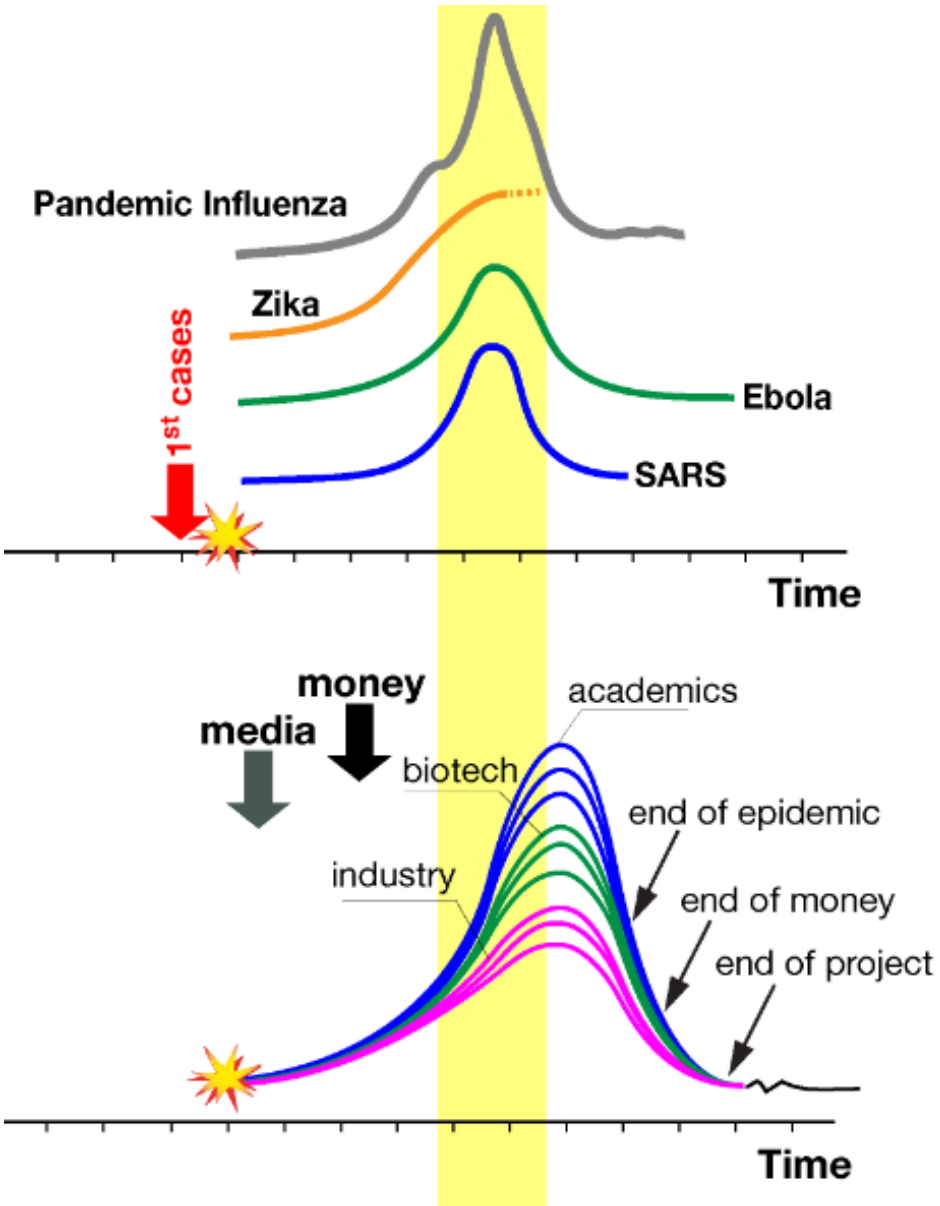
New vaccine approaches are available



Emerging Infectious Diseases

From R. Rappuoli

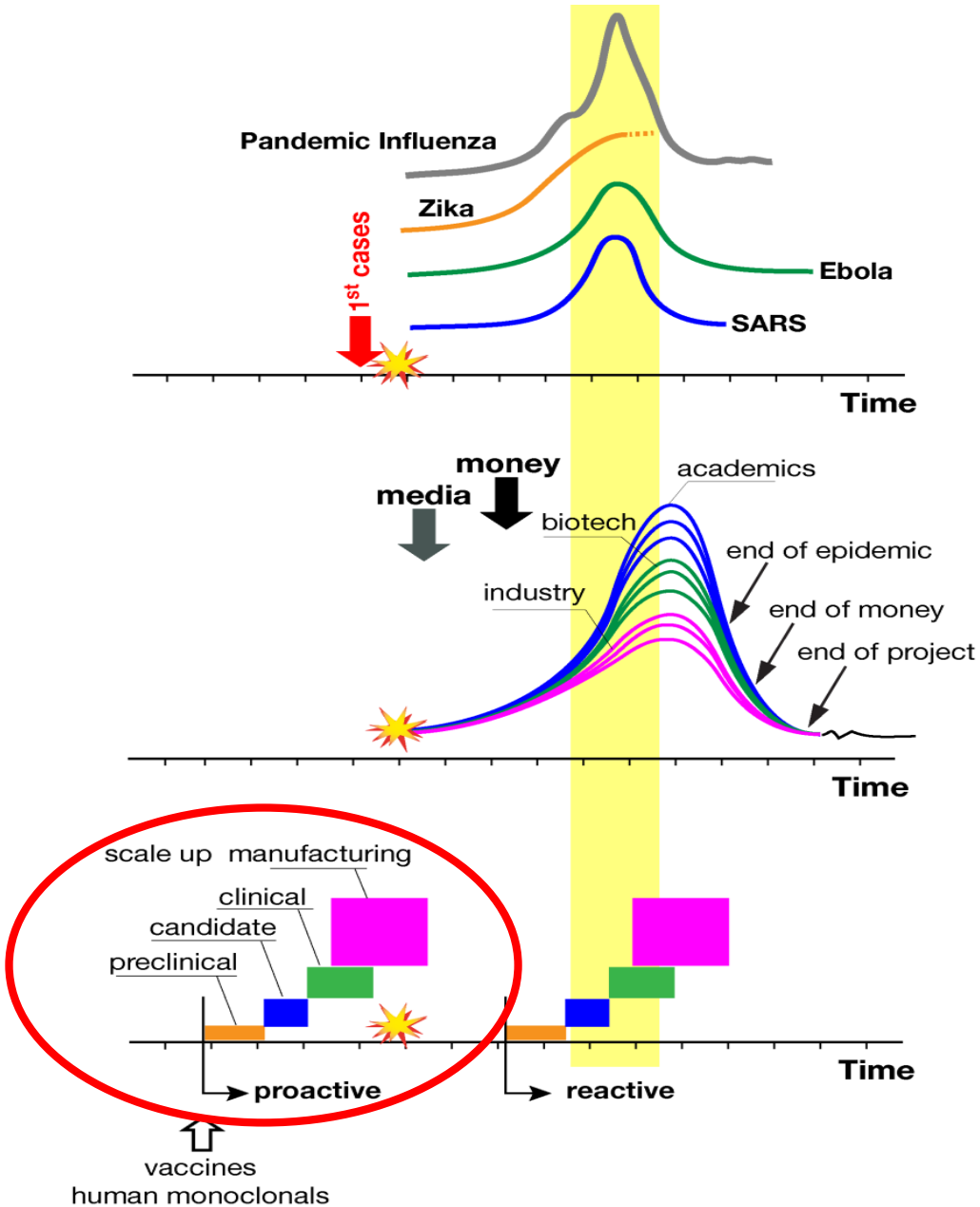
Response to EIDs inadequate



- **Reactive**: Start after outbreak has already spread
- **Ineffective**: Possible tools available only after emergency is over
- **Un-sustained**: Industry diverts resources which cannot be sustained without ROI
- **Minimal lessons learned**: Start over with each new EID

Bloom DE, Black S, Rappuoli R. PNAS 2017.

Proactive strategy for responding to EIDs

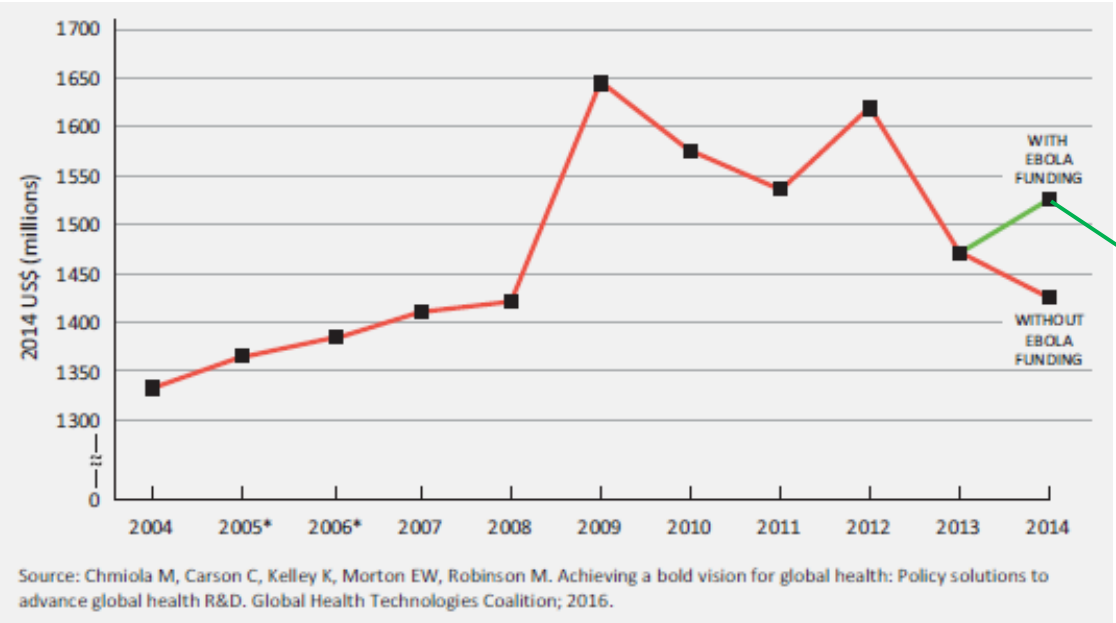


Bloom DE, Black S, Rappuoli R. PNAS 2017.

Incentivizing vaccines for EIDs

Millions in Ebola funding, a casualty of Zika virus, may not be replenished

By DYLAN SCOTT / JUNE 1, 2016



Source: Chmiola M, Carson C, Kelley K, Morton EW, Robinson M. Achieving a bold vision for global health: Policy solutions to advance global health R&D. Global Health Technologies Coalition; 2016.

Funding for neglected "tropical" diseases with and without Ebola, GHTC 2016

A Global Vaccine Development Fund?

"CEPI":
Proposed cost: $2 billion

The cost of failure?
- Ebola: est. $6 billion
- Deaths: 20,000

COALITON FOR EPIDEMIC PREPAREDNESS INNOVATIONS

Comparison of Existing Global Health Funds and Proposed Vaccine-Development Fund.*

Variable	Global Fund to Fight AIDS, Tuberculosis and Malaria	GAVI	UNITAID Airline Tax	Proposed Vaccine Development Fund
Focus	HIV, tuberculosis, and malaria prevention, treatment, care, and support	Purchase and delivery of childhood vaccines	Purchase of HIV, tuberculosis, and malaria drugs	Accelerating discovery and development of new vaccines
Source of funds	Donor governments (95%); private foundations, corporate donors, and individuals (5%)	Donor governments (80%); private foundations (17%); International Finance Facility for Immunization (2%)	Airline solidarity levy	Donor governments (50%); private foundations and industry (50%) Options: financial transactions tax, tax breaks for industry donors
Eligibility	Middle- and low-income countries	Low-income countries	85% of funds must go to low-income countries	Scientists, institutions, and biotechnology companies engaged in vaccine discovery and development
Application process	Competitive country proposal	Facilitative country proposal	Funds distributed to implementing agencies and NGOs on a discretionary basis	Competitive proposal
Proposal review	Country proposals reviewed by independent technical review panel; board usually follows panel's recommendations	Country proposals facilitated by GAVI, reviewed by independent reviewers appointed by GAVI; decisions made by board	No proposals required	Proposals subject to rigorous scientific review by independent panel; board makes funding decision on the basis of scientific merit and available funds
Features	Performance-based model emphasizing results, transparency, accountability; hands-on monitoring by local fund agents and independent auditors; does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; hands-off monitoring; does not implement or fund research	Does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; independent auditors will monitor and assess performance; will not finance phase 3 clinical trials or conduct research
Governance	27-member international board representing donor and recipient countries, foundations, NGOs, industry, other stakeholders; 5 members are nonvoting representatives of WHO, U.N. agencies, and World Bank	28-member international board representing donor and recipient countries, private individuals, U.N. agencies, vaccine industry, foundations, other stakeholders	12-member executive board; 1 member is nonvoting WHO representative	Streamlined structure; medium-sized board whose majority of voting members represent donors; rest of composition to be determined
Funds disbursed through December 31, 2014	$25.8 billion	$7.8 billion	Approximately $2 billion	Goal: raise $2 billion initially

* Information is from the Foundation for Vaccine Research. GAVI denotes Global Alliance for Vaccines and Immunization, NGO nongovernmental organization, WHO World Health Organization, U.N. United Nations, and UNITAID Unity and AID.

Perspective
JULY 23, 2015

Establishing a Global Vaccine-Development Fund

Stanley A. Plotkin, M.D., Adel A.F. Mahmoud, M.D., Ph.D., and Jeremy Farrar, M.D., Ph.D.

NEW ENGLAND JOURNAL OF MEDICINE 1812 1823 1828 1928

Challenges for EID vaccines

1. The pipeline is weak for most emerging infectious diseases characterized by lack of market incentives

2. Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks

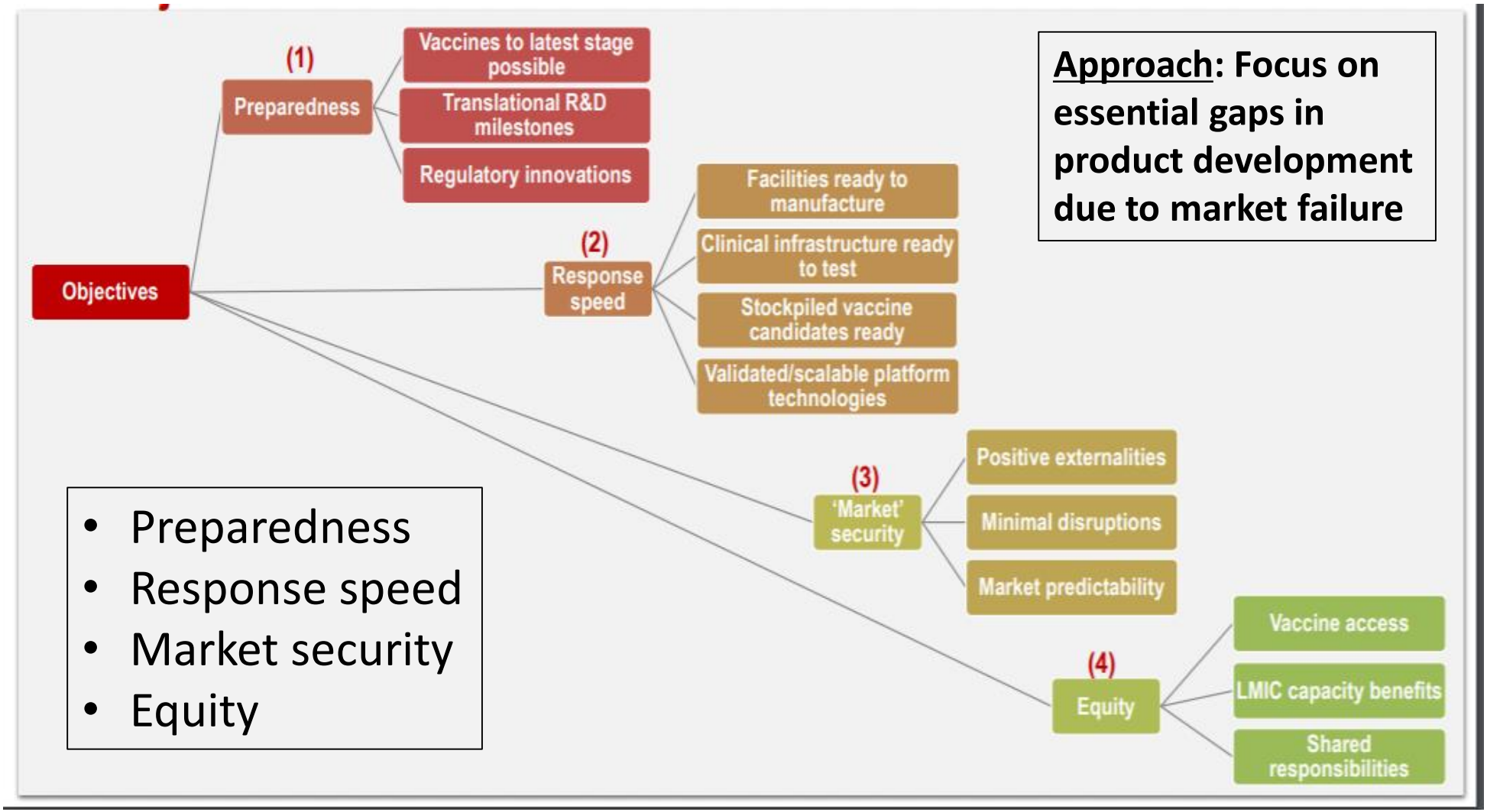
3. Clinical & regulatory pathways are not easily adaptable to epidemic contexts

4. Incentives are lacking to motivate greater industry engagement

CEPI fundamentals

Vision	Vaccines can **prevent outbreaks from becoming health, economic** and **humanitarian** crises.
Mission	**Prioritize, stimulate, finance and coordinate** vaccine development against EIDs with epidemic potential, especially in cases where market incentives alone do not achieve this.
Scope	End-to-end approach to vaccine development 1. **Advance EID vaccines** through late preclinical studies to proof of concept and safety in humans, and 2. Develop **platforms** that can be rapidly deployed against known and unknown pathogens.

CEPI objectives and end-to-end approach



Priority pathogens

CEPI Initial List

Group 1: first choice for funding

- Chikungunya
- Coronaviruses (MERS)
- Filoviruses
- Rift Valley fever
- West Nile

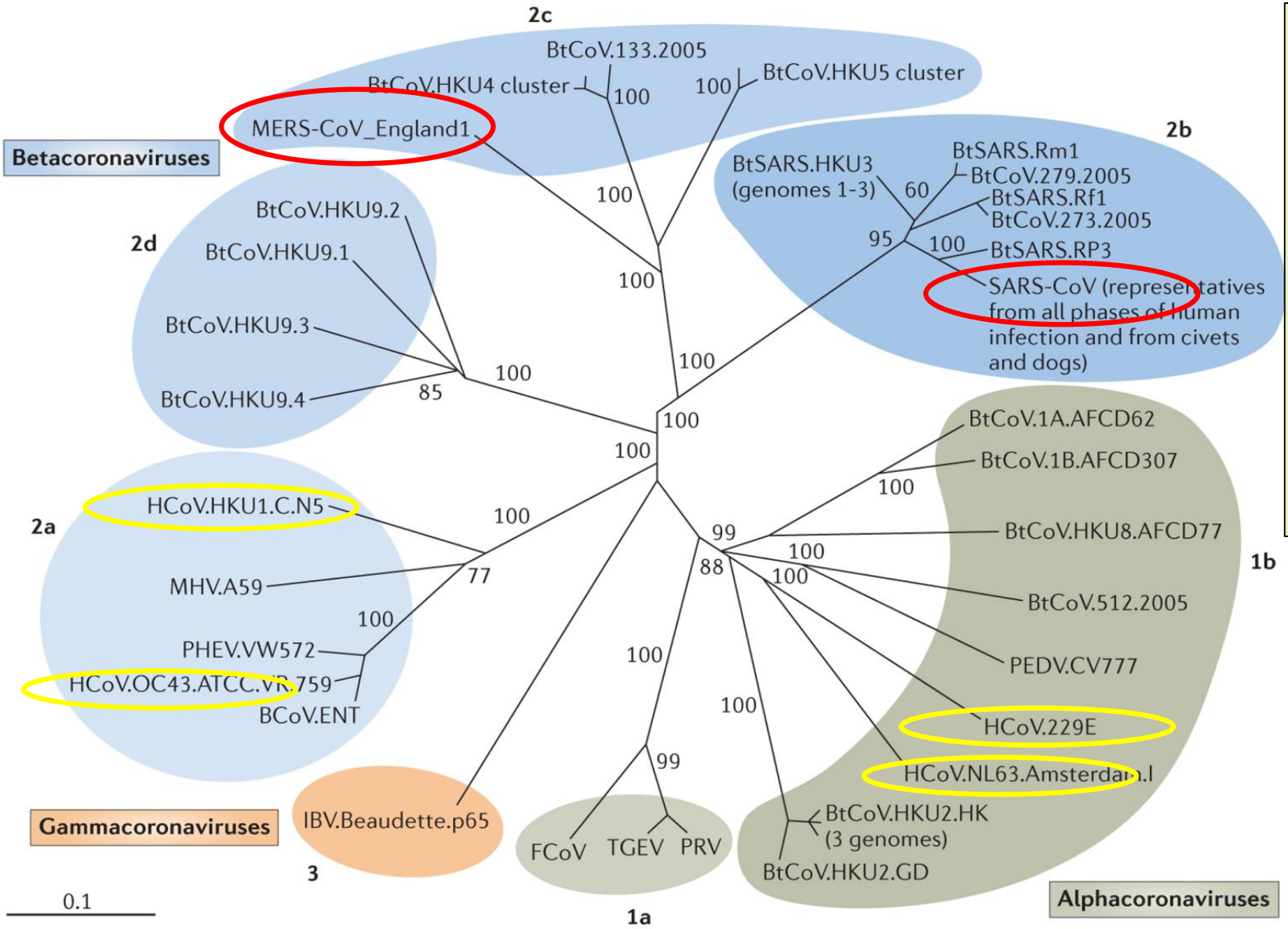
Group 2: Additional choice for funding: Lassa, Nipah, Paratyphoid A, Plague

Group 3: Targets without candidate vaccines: Congo-Crimean hemorrhagic fever, severe fever with thrombocytopenia, Zika

WHO List

- Arenavirus hemorrhagic fevers (Lassa)
- Congo-Crimean hemorrhagic fever
- Filovirus diseases (Ebola, Marburg)
- MERS
- Other pathogenic coronaviruses (SARS)
- Nipah
- Rift valley fever
- Severe fever with thrombocytopenia syndrome
- Zika
- Disease X

MERS-CoV as a target EID vaccine



MERS-CoV:
- **Coronavirus family**
- **Betacoronavirus genus**
- **Lineage c**

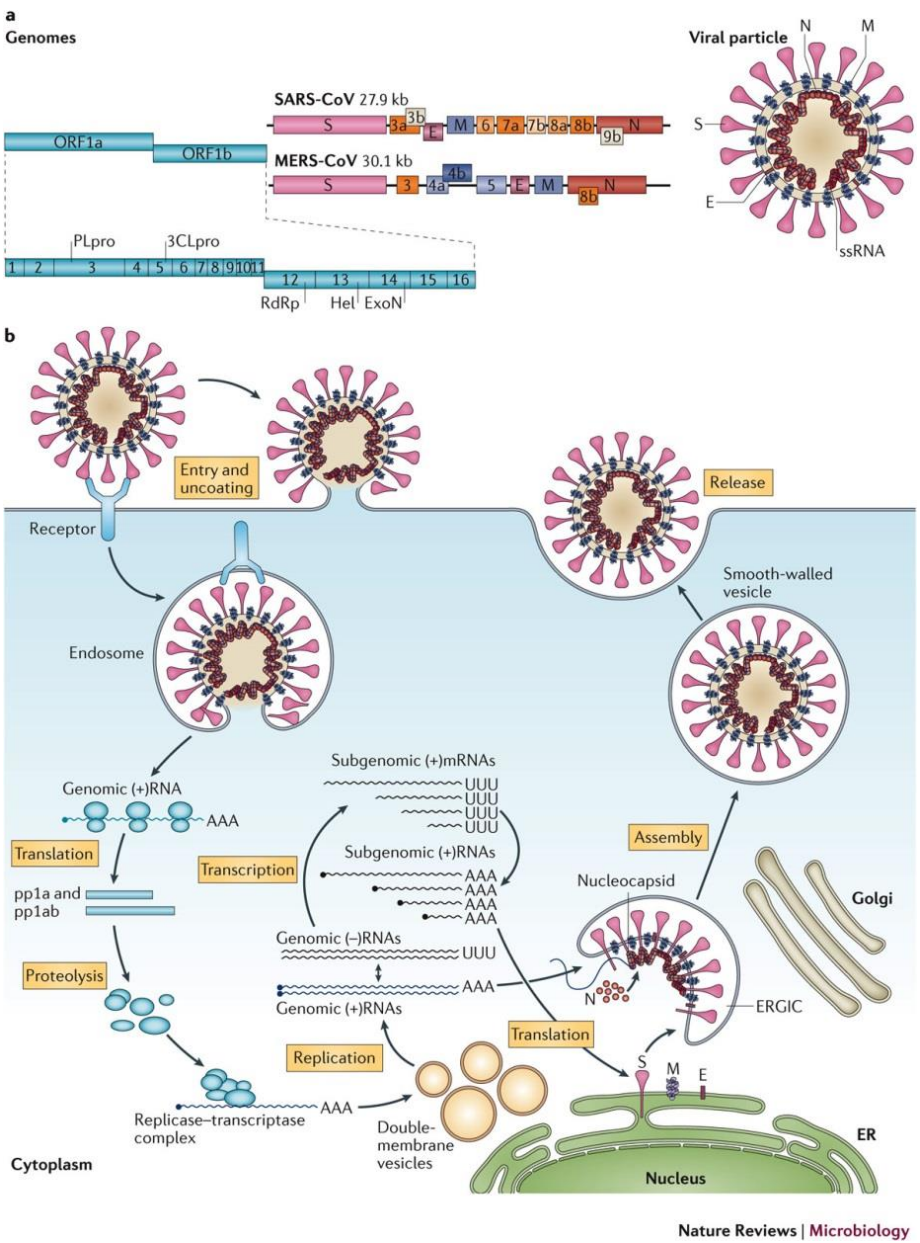
SARS-CoV is lineage b

Other CoVs cause mild respiratory illnesses in humans

Graham RL, Donaldson EF, Baric RS. Nat Rev Microbiol. 2013 Dec;11(12):836-48.

Nature Reviews | Microbiology

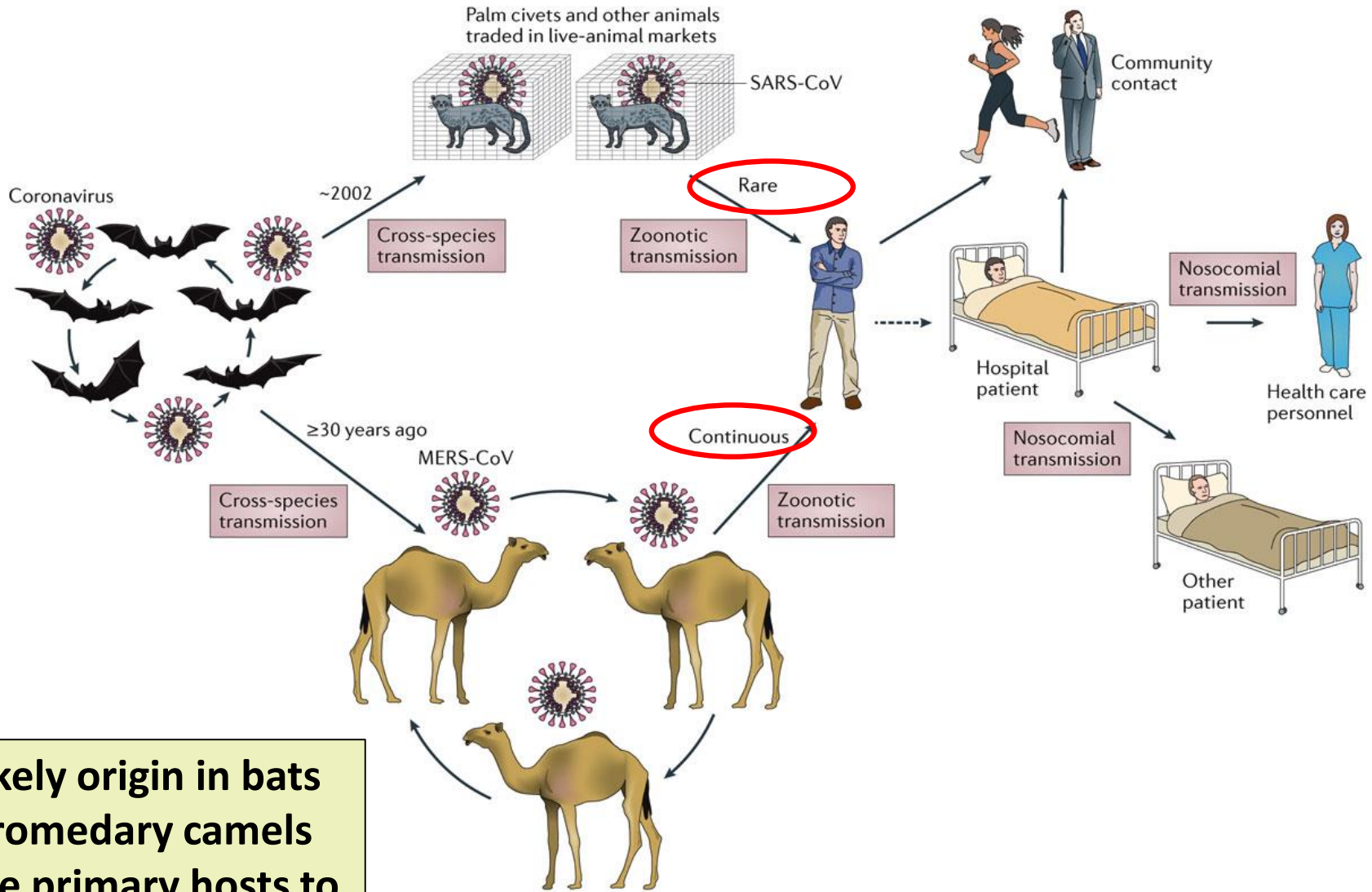
MERS-CoV background



- 30 kb enveloped, single-stranded, positive-sense RNA virus
- 4 structural proteins: spike (S), envelope(E) matrix (M), nucleocapsid (N)
- S protein is primary target for neutralizing Abs during natural MERS-CoV infection
- S1 subunit contains **receptor-binding domain (RBD)**
- Host cell receptor for RBD is **dipeptidyl peptidase 4 (DPP4 or CD26)**

de Wit E et al. Nat Rev Microbiol. 2016 Aug;14(8):523-34.

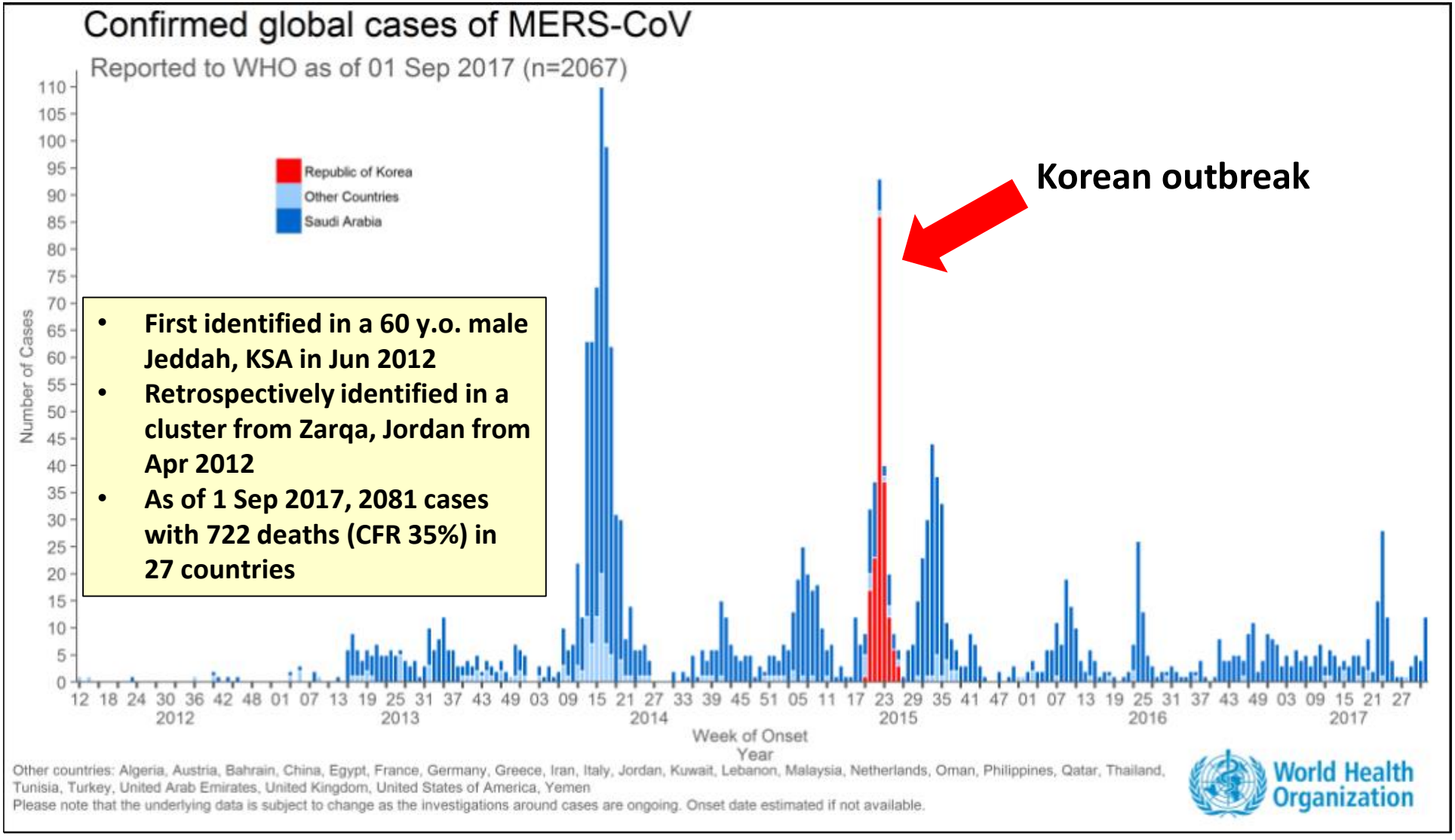
MERS-CoV transmission



- **Likely origin in bats**
- **Dromedary camels are primary hosts to humans**

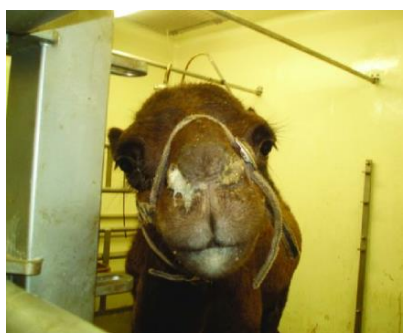
de Wit E et al. Nat Rev Microbiol. 2016 Aug;14(8):523-34.

MERS-CoV epidemiology



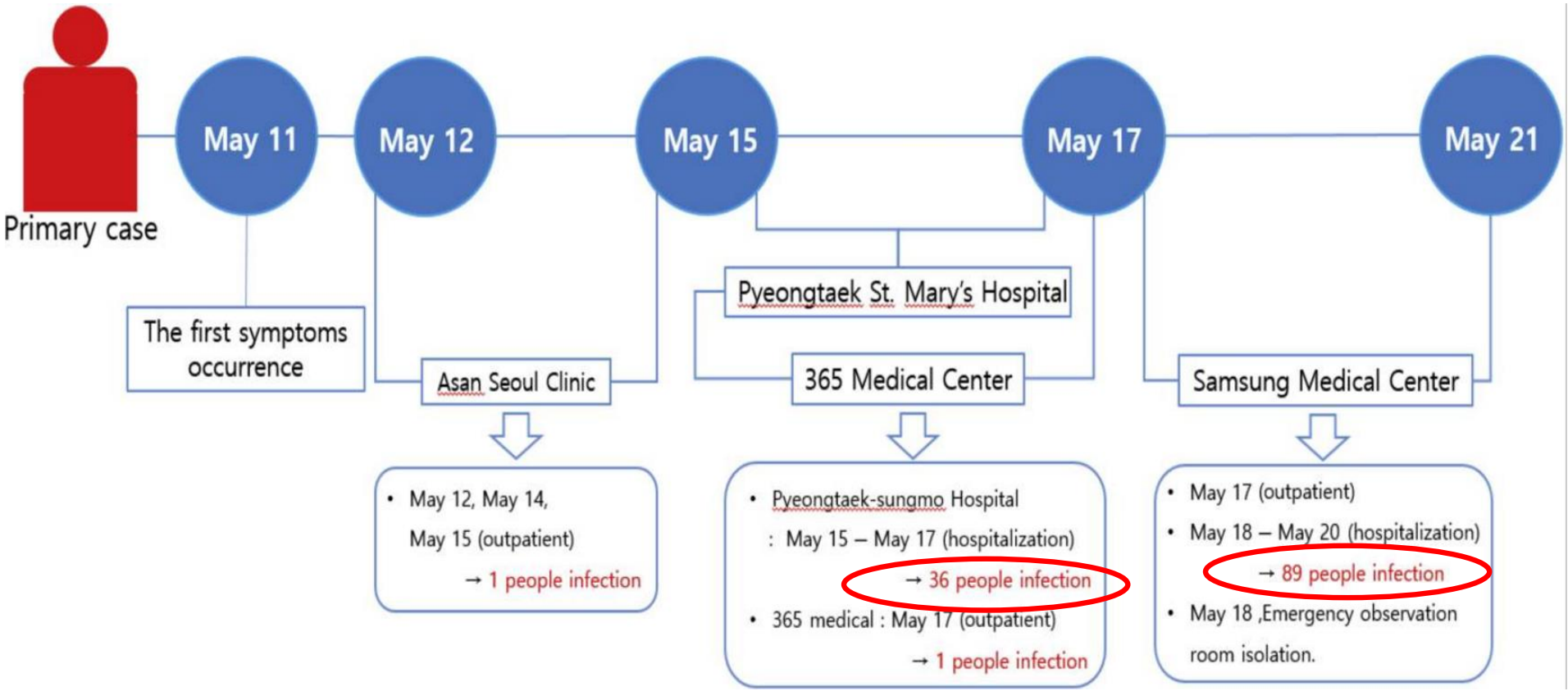
Dromedary camel reservoir

- Ongoing transmission from camels to humans is likely to continue, with consequent continuous epidemic risk
  - Transmission in camels is widespread
    - Seroprevalence in camels is high
  - Transmission in camels has been occurring for a long time
    - Retrospective serological testing indicates dromedaries in Saudi Arabia have had MERS-CoV for at least 30 years
  - Camels have only mild symptoms
    - Due to upper respiratory tract distribution of DPP4
  - Human cases are underreported
    - Subclinical or mild infections in humans



❖ Ongoing mutations in camels and humans

MERS-CoV epidemic potential: Korean outbreak



- **One 68 year old male traveler returning to Korea from Middle East in Apr 2015**
- **Became sick on 11 May 2015 with visits to 3 different Korean hospitals**
- **MERS-CoV confirmed on 20 May 2015**
- **186 confirmed cases; 39 deaths (CFR 21%)**

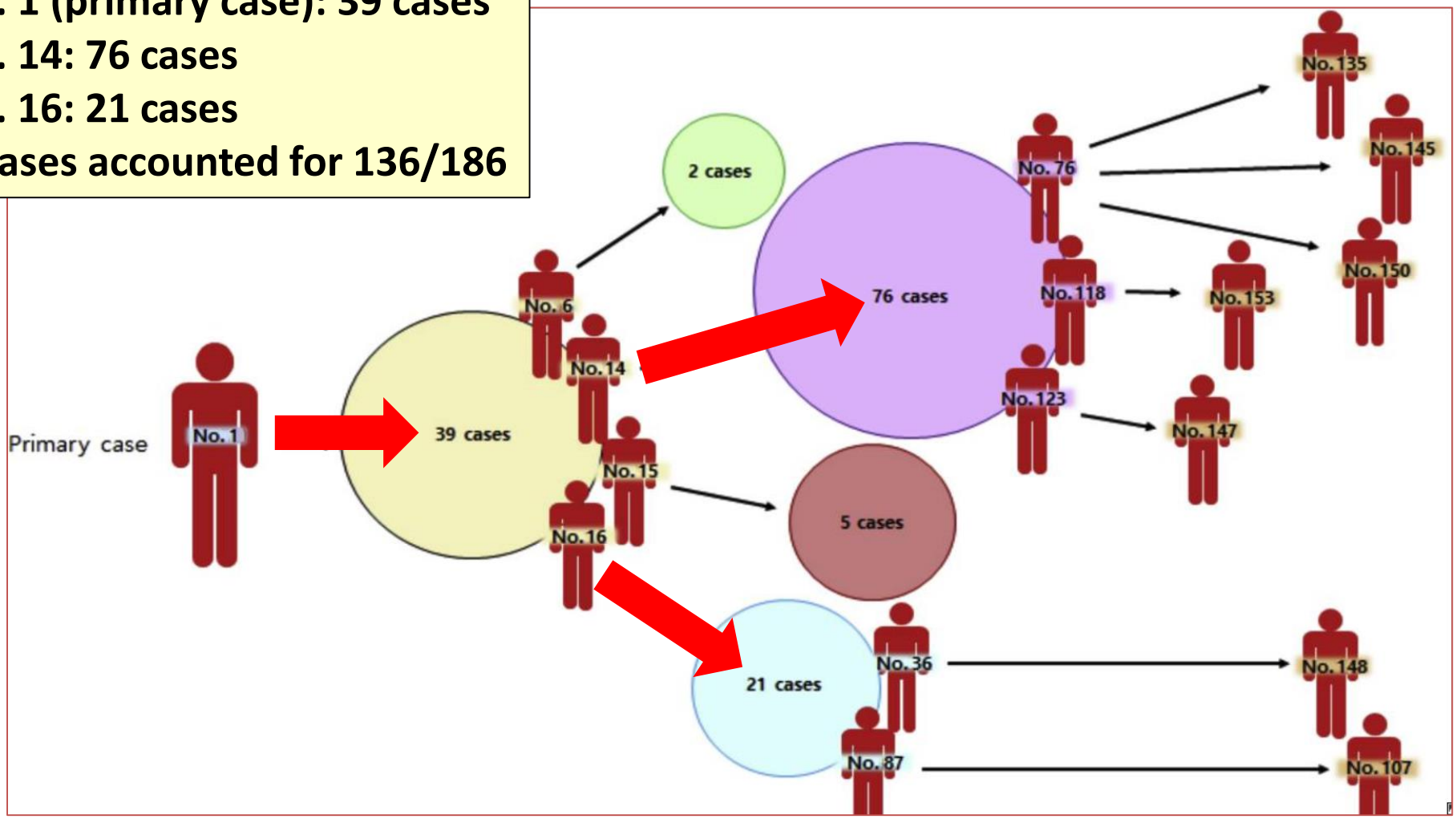
Kim Y et al. Osong Public Health Res Perspect. 2016 Feb;7(1):49-55.

Super-spreading in Korean outbreak

Super-spreading events:

- **No. 1 (primary case): 39 cases**
- **No. 14: 76 cases**
- **No. 16: 21 cases**

So 3 cases accounted for 136/186



Kim Y et al. Osong Public Health Res Perspect. 2016 Feb;7(1):49-55.

MERS in Korea

- About 17,000 people quarantined
- Massive disruption
- Huge economic impact

WHO MERS R&D roadmap and TPP

- Develop and license vaccine suitable for reactive use in outbreak settings with rapid onset of immunity

- Develop and license vaccine with long-term protection for administration to those at high ongoing risk of MERS-CoV such as healthcare workers and those working with potentially infected animals

- Dromedary camel vaccine: Develop and license a vaccine suitable for administration to camels to prevent transmission of MERS-CoV from animal reservoir to humans

Modjarrad et al, Nat Med 2016; 22:70
1

WHO R&D Blueprint http://www.who.int/csr/research-and-development/en/

MERS-CoV vaccine pipeline (1)

Vaccine type	Vaccine name	Design	Animal immunogenicity	Animal protection	Stage of development	Sponsor/ Developer
DNA	GLS-5300	Plasmid DNA encoding full-length S; with electroporation	C57BL/6 mice, rhesus, camels	Rhesus	Phase I ongoing in the US	GeneOne/Inovio
Protein subunit	MERS-S	Nanoparticles of full-length S trimers; with Matrix-M adjuvant	BALB/c mice	Transduced mice	Preclinical; SAB-301 polyclonal Abs from transgenic cows in Phase I	Novavax
	MERS-CoV VLP	VLP of S, E, M in baculovirus/Sf9; with alum	Rhesus	-	Preclinical	Jiangsu Center, China
	S-RBD-Fc	S1-RBD subunit fused with human Fc; with various adjuvants	BALB/c mice, rabbits	Transduced mice	Preclinical	New York Blood Center; Fudan Univ; Central South Univ
	MERS-CoV rRBD	Truncated S1-RBD subunit; with alum	BALB/c mice, rhesus	Rhesus	Preclinical	China CDC
Heterologous prime-boost	S-DNA/S1 Protein	Plasmid DNA encoding full-length S (prime) + S1 subunit (boost)	BALB/c mice, rhesus	Rhesus	Preclinical	US NIH/VRC

MERS-CoV vaccine pipeline (2)

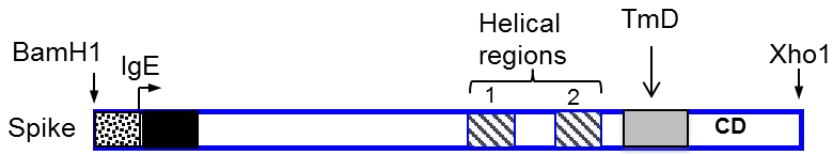
Vaccine type	Vaccine name	Design	Animal immunogenicity	Animal protection	Stage of development	Sponsor/ Developer
Vector	MVA-S	MVA vector with full-length S	BALB/c mice, camels	Transduced mice, camels	Preclinical; Phase I planned in Germany	DZIF consortium
	ChAdOx1-MERS-S	Chimp adenovirus 3 with full-length S	Mice	Mice	Preclinical; Phase I planned in UK	Jenner Institute, UK
	MERS-S/MERS-solS	Measles vector with full-length S/solS	IFNAR -/- mice	Transduced mice	Preclinical	Paul Ehrlich Insitut; German Cent for Inf Res
	Ad5-S & Ad41-S	Human adenovirus vector with full-length S	BALB/c mice	-	Preclinical	China CDC
	GreMERSfi	Human adenovirus 5 vector with full-length S	Mice	-	Preclinical	Greffex
Live recombinant	rMERS-CoV-ΔE	Recombinant without E	-	-	Preclinical	Universidad Autonoma de Madrid

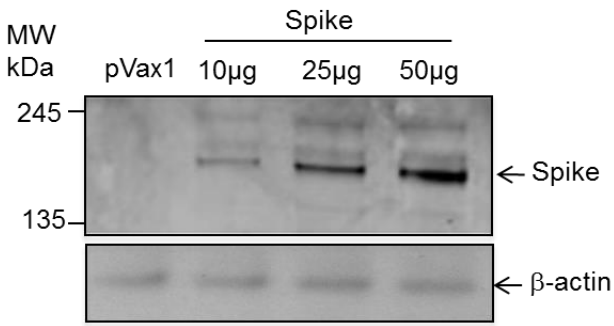
GeneOne/Inovio DNA vaccine

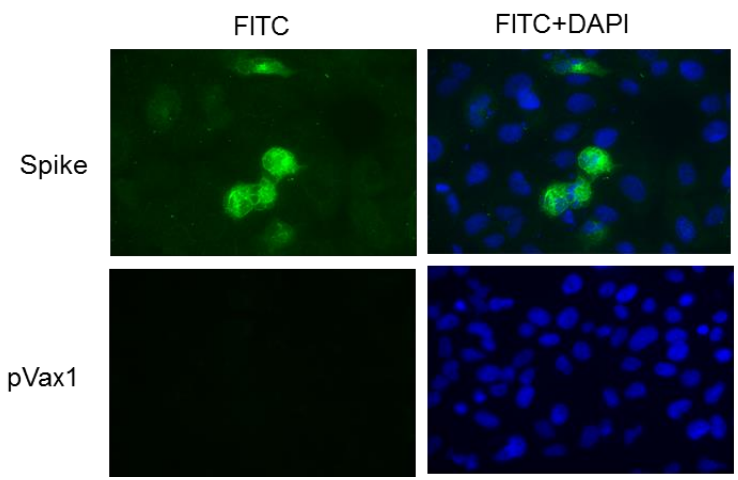
Most advanced candidate in development

pVax1 plasmid DNA coding full-length S glycoprotein using consensus sequence

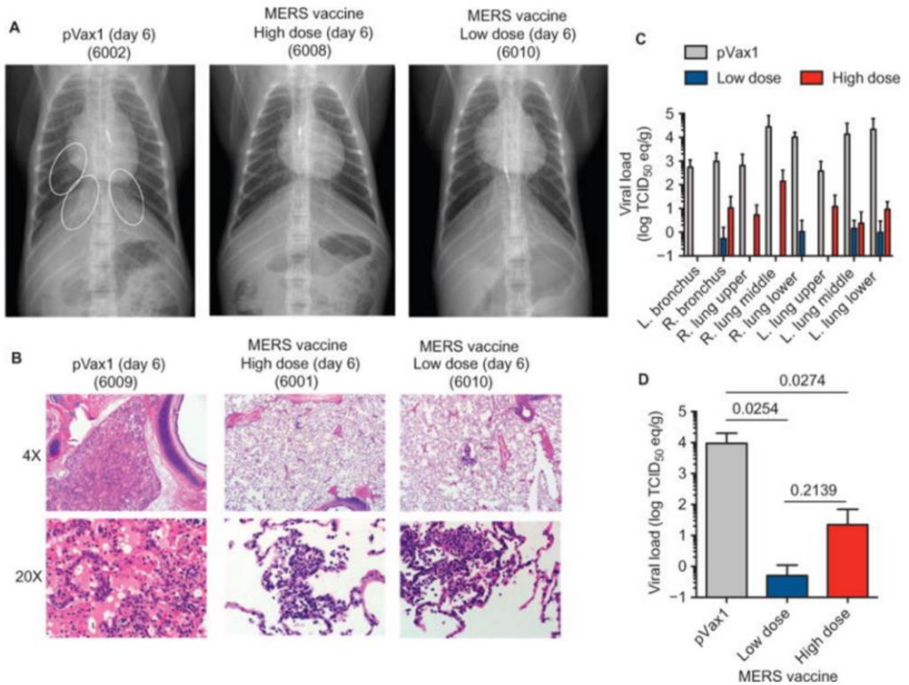
Given with electroporation







Rhesus immunogenicity and protection



- 12 rhesus macaques at control, low and high dose at 0, 3, 6 wks
- Challenged at 11 wks (4 wks after 3rd dose)
- Full protection by radiography

- Binding & neutralizing antibodies
  - *Seroconversion and induction of strong MERS-CoV Spike specific bAb responses after single immunization*
  - *bAb titers: 10^4 - 10^5*
  - *nAb titers: 1:80-240 post dose 3*
- Cellular immune responses
  - *Induction of strong T-cell immune responses*
  - *Antigen specific CD4+ and CD8+*
  - *Multiple epitopes recognized across length of S protein*

Muthumani K et al. Sci Transl Med. 2015 Aug 19;7(301):301ra132.

Phase I first-in-human MERS vaccine trial

- Randomized, open-label trial of GeneOne MERS DNA vaccine (GLS-5300)
  - 75 healthy adults in 3 dose groups (0.67 mg, 2 mg, 6 mg)
  - Vaccinations at 0, 4 and 12 weeks administered by electroporation
- Primary objective
  - Safety up to 60 wks
- Secondary objectives
  - Immunogenicity
    - 1, 2, 3 and 4 wks after 1st dose
    - 2 wks after 2nd dose (i.e., at 6 wks)
    - 2 wks after 3rd dose (i.e., at 14 wks)
    - 3, 6 and 12 mos after 3rd dose (i.e., at 24, 36 and 60 wks)

Study update

- Fully enrolled
- All study visits completed
- Vaccine has been safe & well tolerated
- No Serious Adverse Events reported

Sponsor: GeneOne Life Science Inc.
PI: Kayvon Modjarrad MD
Clinical Trials Gov: NCT02670187

CEPI investment

- MERS-CoV vaccine landscape will change dramatically in near future
- CEPI grant results to be announced by end of 2017
- Accelerate pace of clinical development
- However, inherent challenges to EID vaccines

Challenges for MERS-CoV human vaccines

- Animal models not ideal
  - Transduced mice, transgenic mice, rhesus, marmosets, camels
- No immune correlate of protection in humans
- Protective immune response unclear
  - Broad immune responses may be needed (high mutation rate of CoVs)
  - Cross-neutralizing Abs; T cells to multiple S epitopes
- Scientific risks
  - E.g., theoretical risk of enhancement
- Difficulty in demonstrating efficacy in field
  - Regulatory innovations

Conclusions

- Global risk from EIDs with epidemic potential will likely continue or increase
- Despite known impact of vaccines, it has been difficult to develop vaccines for EIDs
- Proactive strategies are needed
- CEPI represents an approach to incentivizing EID vaccine development
- Even with substantial investment, EID vaccines face considerable challenges
- However, technical and procedural innovations are promising

IVI is an International Organization dedicated to Global Health

Global Vaccine Research Institute

- **HQ and labs at Seoul National University**
- **Field programs in 29 countries: Asia, Africa, Latin America**
- **12 nationalities in workforce of ~130**

OECD-recognized International Organization (not for profit)

- **UNDP initiative**
- **First international organization in Korea (1997)**
- **35 countries and WHO as state parties**

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