Vaccines for Emerging Infectious Diseases: MERS-CoV

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International Vaccine Institute
17 Oct 2017
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

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
New vaccine approaches are available

From R. Rappuoli

Next Generation Technologies
- Structural Vaccinology
- Synthetic Biology/RNA
- Adjuvants/Human Immune Response

Reverse Vaccinology
- MenB, GBS, GAS,
- E. coli, S. aureus, C. difficile

Glycoconjugation
- MenACWY, S. pneumo,
- Hib, GBS, S. aureus

Recombinant DNA
- Hepatitis B,
- Acellular Pertussis, Lyme,
- Human papillomavirus

Empirical Approach
- Diphtheria, Tetanus,
- Pertussis, Rabies,
- Influenza,
- Smallpox, Polio,
- BCG

Emerging Infectious Diseases
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

Proactive strategy for responding to EIDs

Incentivizing vaccines for EIDs

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

By DYLAN SCOTT / JUNE 1, 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

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

*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.*

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### 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.
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

<table>
<thead>
<tr>
<th>Vision</th>
<th>Vaccines can <strong>prevent outbreaks from becoming health, economic</strong> and <strong>humanitarian</strong> crises.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mission</td>
<td><strong>Prioritize, stimulate, finance and coordinate</strong> vaccine development against EIDs with epidemic potential, especially in cases where market incentives alone do not achieve this.</td>
</tr>
</tbody>
</table>
| 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

- Preparedness
- Response speed
- Market security
- Equity
## 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

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)

MERS-CoV transmission

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

MERS-CoV epidemiology

- First identified in a 60 y.o. male, Jeddah, KSA in Jun 2012
- Retrospectively identified in a cluster from Zarqa, Jordan from Apr 2012
- As of 1 Sep 2017, 2081 cases with 722 deaths (CFR 35%) in 27 countries

Confirmed global cases of MERS-CoV

Reported to WHO as of 01 Sep 2017 (n=2067)

- **Republic of Korea**
- **Other Countries**
- **Saudi Arabia**

Korean outbreak

Other countries: Algeria, Austria, Bahrain, China, Egypt, France, Germany, Greece, Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, Netherlands, Oman, Philippines, Qatar, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, United States of America, Yemen

Please note that the underlying data is subject to change as the investigations around cases are ongoing. Onset date estimated if not available.
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%)

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

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*

### MERS-CoV vaccine pipeline (1)

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Vaccine name</th>
<th>Design</th>
<th>Animal immunogenicity</th>
<th>Animal protection</th>
<th>Stage of development</th>
<th>Sponsor/Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>GLS-5300</td>
<td>Plasmid DNA encoding full-length S; with electroporation</td>
<td>C57BL/6 mice, rhesus, camels</td>
<td>Rhesus</td>
<td>Phase I ongoing in the US</td>
<td>GeneOne/Inovio</td>
</tr>
<tr>
<td>Protein subunit</td>
<td>MERS-S</td>
<td>Nanoparticles of full-length S trimers; with Matrix-M adjuvant</td>
<td>BALB/c mice</td>
<td>Transduced mice</td>
<td>Preclinical; SAB-301 polyclonal Abs from transgenic cows in Phase I</td>
<td>Novavax</td>
</tr>
<tr>
<td>MERS-CoV VLP</td>
<td></td>
<td>VLP of S, E, M in baculovirus/Sf9; with alum</td>
<td>Rhesus</td>
<td></td>
<td>Preclinical</td>
<td>Jiangsu Center, China</td>
</tr>
<tr>
<td>S-RBD-Fc</td>
<td></td>
<td>S1-RBD subunit fused with human Fc; with various adjuvants</td>
<td>BALB/c mice, rabbits</td>
<td>Transduced mice</td>
<td>Preclinical</td>
<td>New York Blood Center; Fudan Univ; Central South Univ</td>
</tr>
<tr>
<td>MERS-CoV rRBD</td>
<td></td>
<td>Truncated S1-RBD subunit; with alum</td>
<td>BALB/c mice, rhesus</td>
<td>Rhesus</td>
<td>Preclinical</td>
<td>China CDC</td>
</tr>
<tr>
<td>Heterologous prime-boost</td>
<td>S-DNA/S1 Protein</td>
<td>Plasmid DNA encoding full-length S (prime) + S1 subunit (boost)</td>
<td>BALB/c mice, rhesus</td>
<td>Rhesus</td>
<td>Preclinical</td>
<td>US NIH/VRC</td>
</tr>
</tbody>
</table>
## MERS-CoV vaccine pipeline (2)

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Vaccine name</th>
<th>Design</th>
<th>Animal immunogenicity</th>
<th>Animal protection</th>
<th>Stage of development</th>
<th>Sponsor/Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector</td>
<td>MVA-S</td>
<td>MVA vector with full-length S</td>
<td>BALB/c mice, camels</td>
<td>Transduced mice, camels</td>
<td>Preclinical; Phase I planned in Germany</td>
<td>DZIF consortium</td>
</tr>
<tr>
<td></td>
<td>ChAdOx1-MERS-S</td>
<td>Chimp adenovirus 3 with full-length S</td>
<td>Mice</td>
<td>Mice</td>
<td>Preclinical; Phase I planned in UK</td>
<td>Jenner Institute, UK</td>
</tr>
<tr>
<td></td>
<td>MERS-S/MERS-solS</td>
<td>Measles vector with full-length S/solS</td>
<td>IFNAR -/- mice</td>
<td>Transduced mice</td>
<td>Preclinical</td>
<td>Paul Ehrlich Insitut; German Cent for Inf Res</td>
</tr>
<tr>
<td></td>
<td>Ad5-S &amp; Ad41-S</td>
<td>Human adenovirus vector with full-length S</td>
<td>BALB/c mice</td>
<td>-</td>
<td>Preclinical</td>
<td>China CDC</td>
</tr>
<tr>
<td></td>
<td>GreMERSfi</td>
<td>Human adenovirus 5 vector with full-length S</td>
<td>Mice</td>
<td>-</td>
<td>Preclinical</td>
<td>Greffex</td>
</tr>
<tr>
<td>Live recombinant</td>
<td>rMERS-CoV-ΔE</td>
<td>Recombinant without E</td>
<td>-</td>
<td>-</td>
<td>Preclinical</td>
<td>Universidad Autonoma de Madrid</td>
</tr>
</tbody>
</table>
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 1\textsuperscript{st} dose
    - 2 wks after 2\textsuperscript{nd} dose (i.e., at 6 wks)
    - 2 wks after 3\textsuperscript{rd} dose (i.e., at 14 wks)
    - 3, 6 and 12 mos after 3\textsuperscript{rd} 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

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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