

A photograph of a desert landscape at sunset. The sky is a deep orange, and the sand dunes are illuminated with a warm, golden light. In the foreground, a caravan of camels is walking across the dunes, with two people in white robes walking alongside them. The shadows of the camels and people are cast long and dark on the sand. The overall scene is serene and evocative of a traditional desert caravan.

Update on MERS-CoV

Rick Bright, PhD
Director Division of Influenza

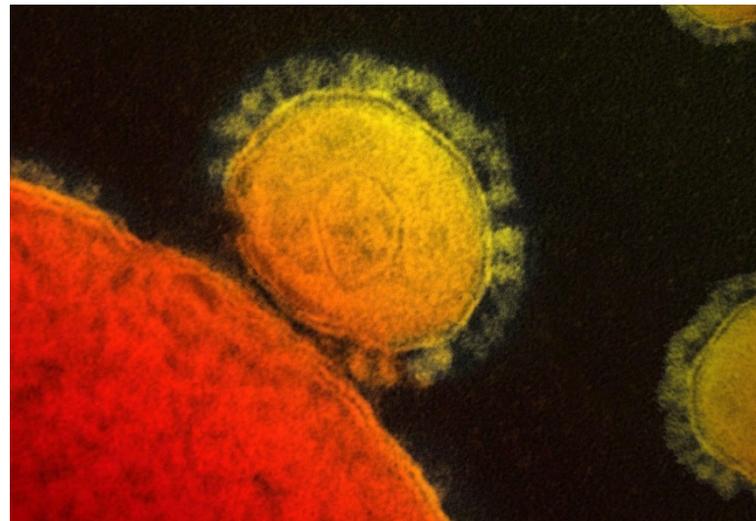
BARDA Industry Day
October 15, 2015



Middle East respiratory syndrome coronavirus (MERS-CoV)

- MERS-CoV belongs to the family *Coronaviridae*
- Other coronaviruses include:
 - SARS-CoV
 - Human coronavirus 229E & OC43
 - Feline coronavirus
- Enveloped viruses containing nonsegmented, positive-strand RNA genome
- Two outbreaks of novel coronaviruses (SARS and MERS) causing acute respiratory distress syndrome and high death rates this century
- **There are currently no licensed/approved vaccines or treatments for Coronaviruses**

MERS-CoV

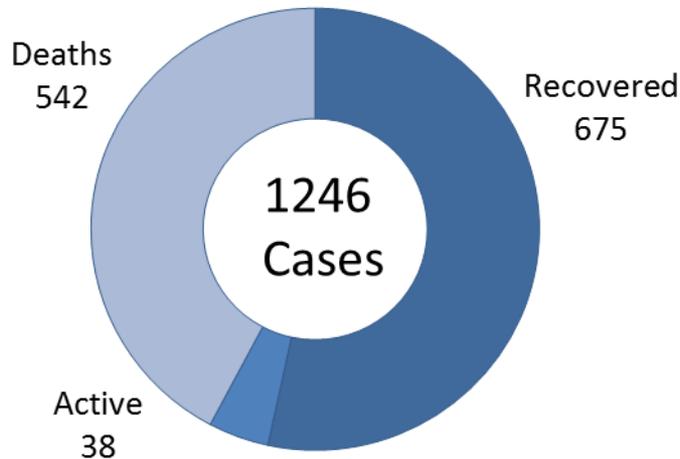


South Korea Wedding during the MERS outbreak

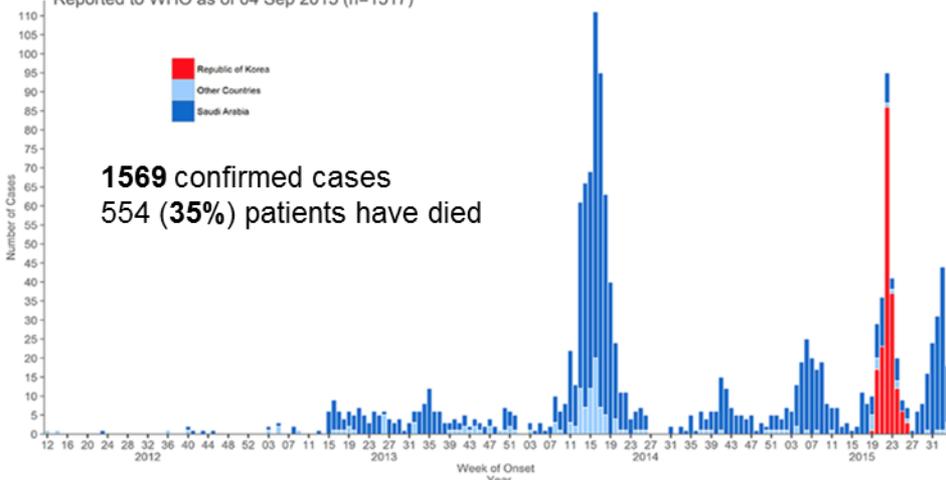


MERS-CoV outbreaks in Saudi Arabia and South Korea

Saudi Arabia since 2012

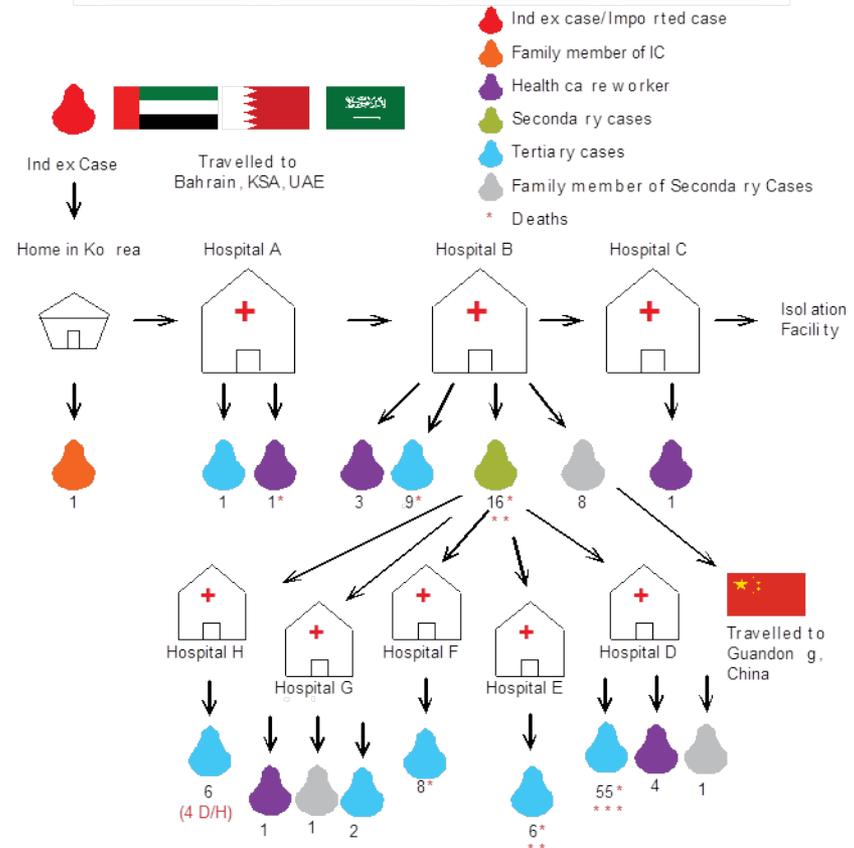


Confirmed global cases of MERS-CoV Reported to WHO as of 04 Sep 2015 (n=1517)

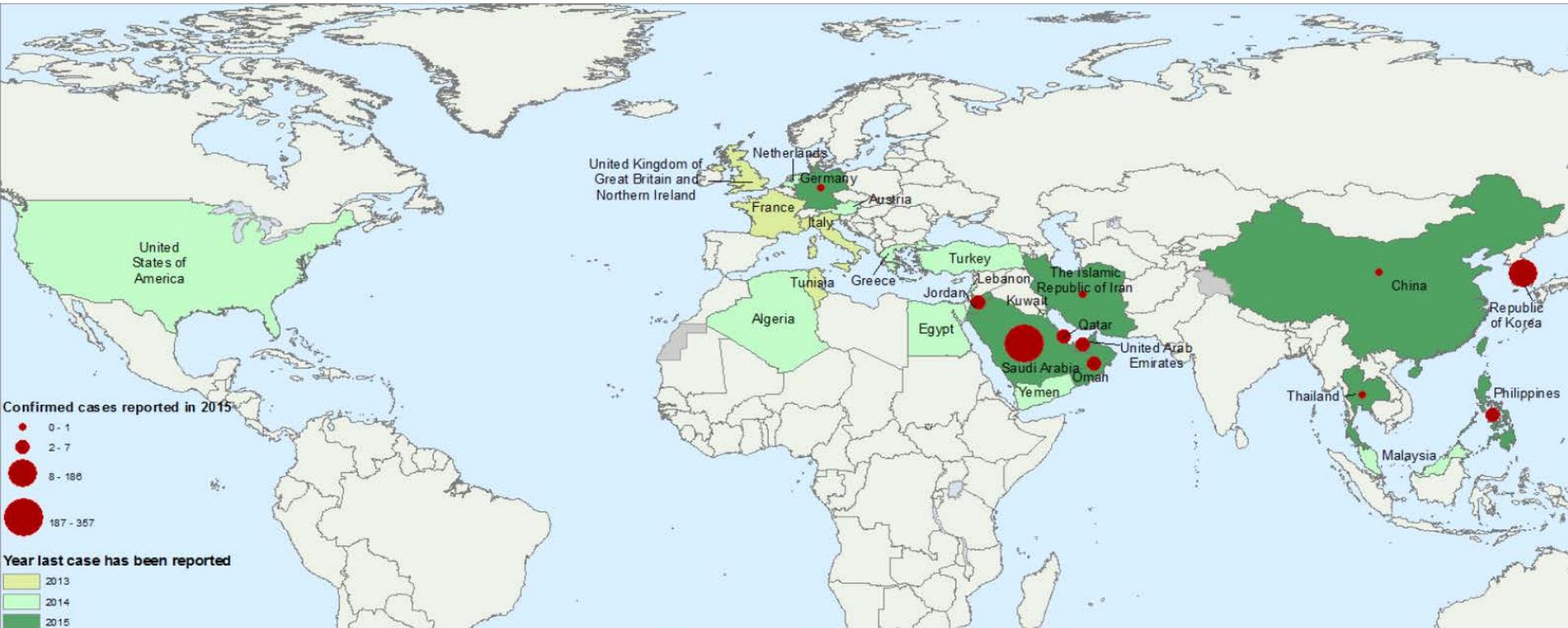


South Korea, 2015

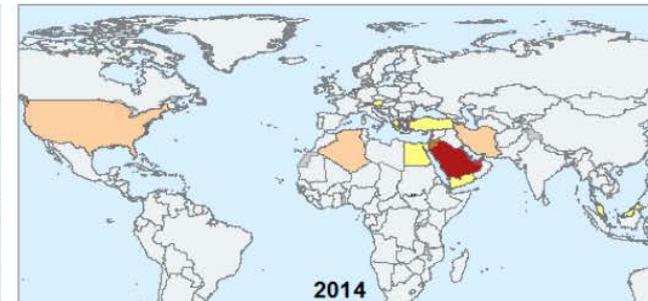
| TOTAL CONFIRMED | Republic of Korea | China | DEATHS |
|-----------------|-------------------|----------|-----------|
| 186 | 185 | 1 | 36 |



Geographical Spread of MERS-CoV 2012 – 2015



Number of cases reported in previous years





Clinical Observations

- **Symptom Onset median 5 (2-19) days after exposure. Range from asymptomatic to severely ill.**
- **Initial Illness**
 - Fever, cough, bloody sputum, chest pain, hypoxia
 - Upper respiratory illness progresses quickly to:
 - Lower respiratory illness including pneumonia, Acute Respiratory Syndrome (ARDS), and Respiratory Failure
 - Septic Shock
 - Multi-organ failure, (high rate of renal failure)
 - Death
 - Older patients and those with pre-existing co-morbidities are most at risk
- **High rate of advanced medical utilization: series of 70 consecutively identified MERS CoV infections:**
 - **91% Hosp, 70% ICU, 66% Mechanical Ventilation, 60% Death**



Findings and Updates from the ASPR MERS-CoV Stakeholder Workshop

April 3, 2015



- Multiple RT-PCR tests have been described
 - Two have FDA EUAs
 - Others are used in global referral centers
- Several serology tests for prior infection are described with reagents available
- Lower respiratory tract samples are optimal
 - Upper respiratory samples are not reliable for identifying infected patients



Animal Models



- Mice are not naturally susceptible due to lack of receptor for MERS-CoV (DPP4 receptor)
- Mice transduced with adenovirus expressing DPP4 are susceptible
- Transgenic mice expressing DPP4 are susceptible and have more severe disease/death
- Non-Human primates
 - Some NHPs are naturally susceptible to MERS-CoV
- Rhesus macaques have mild and transient disease
- Marmosets have more severe and protracted disease with some lethality

All models require further development and standardization



MERS-CoV Immunotherapeutic Landscape



in vitro studies

Pre-Clinical

Clinical

Juntendo University
順天堂大学

DANA-FARBER
CANCER INSTITUTE

REGENERON
science to medicine[®]
Fully human antibodies
from transgenic mice,
Tested in Transgenic
Mouse & NHP

وزارة الصحة
Ministry of Health
Convalescent serum
Clinical trial ongoing

The University of Hong Kong

NATIONAL
CANCER
INSTITUTE

SAB
BIOTHERAPEUTICS
Fully human antibodies
from transgenic bovine,
Tested in Ad5-Mouse

CERUS
Convalescent serum

UNIVERSITY OF MINNESOTA

HUMABS BioMed
mAb from human,
Tested in Ad-5 mouse



MERS-CoV Small Molecules Landscape



in vitro studies

Pre-Clinical

Clinical



Alferon N
(Host-directed)



Helicase Inhibitor



Nitazoxanide
In vitro-MERS
(Host-directed)



FDA-Approved
Drug Screen
(2 hits)



Ribavirin
(polymerase)



Soluble DPP4
Decoy
(binding inhibitor)



DPP4-peptide
Micelle



BCX4430
(polymerase)



Lopinavir
SARS Drug Screen
(protease inhibitor)



PEG Interferon
Alpha
(Host-directed)



Protease Inhibitor



T-705
(polymerase)



Interferon B1b
(Host-directed)



Peptide Inhibitor
(fusion inhibitor)



CSW-1

Clinically approved drugs for a different indication. Not in clinical trials for MERS-CoV, but have been used for therapy.

MERS-CoV Vaccine Landscape

in vitro studies

Pre-Clinical

Clinical Trials

S Subunit

Live attenuated

Ad5 S and S1

Purified S Protein Trimer

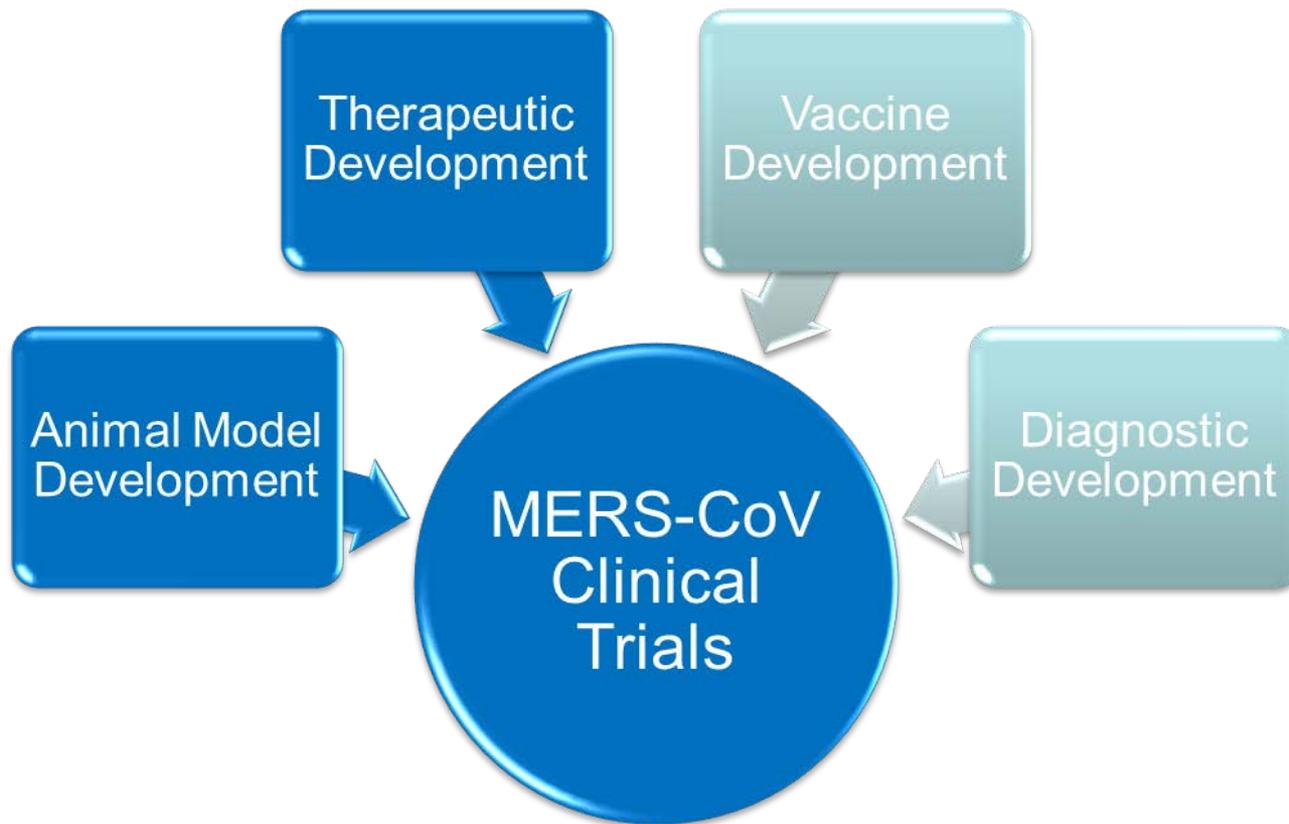
Fully-deleted Adenovirus vector expression S Protein

DNA Prime+Boost or DNA Prime+ S protein boost

Adeno vector, Recombinant Spike, live attenuated

DNA expressing S protein+ Electroporation

Priorities

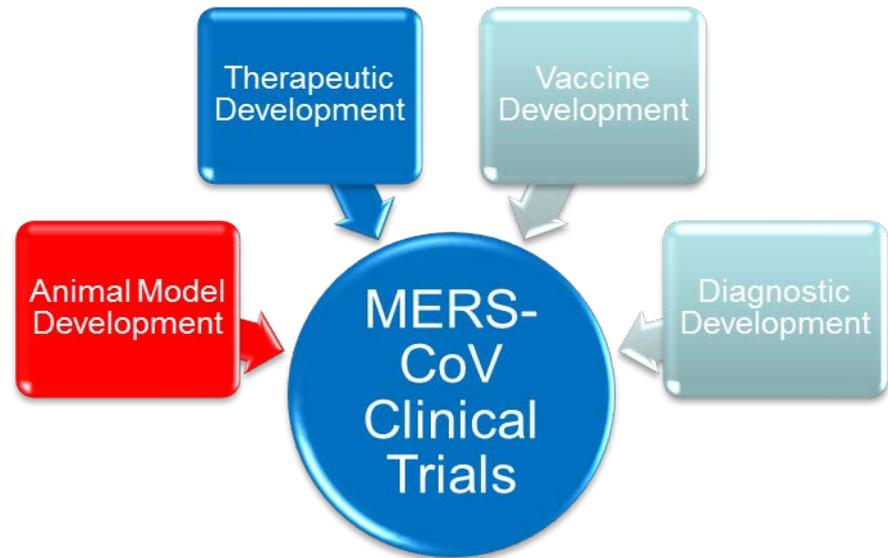




Priorities: Animal Model Development

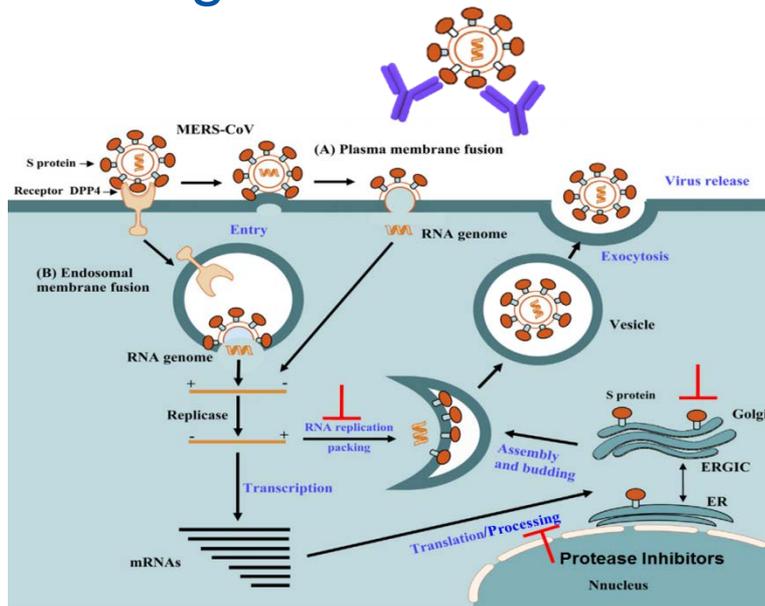
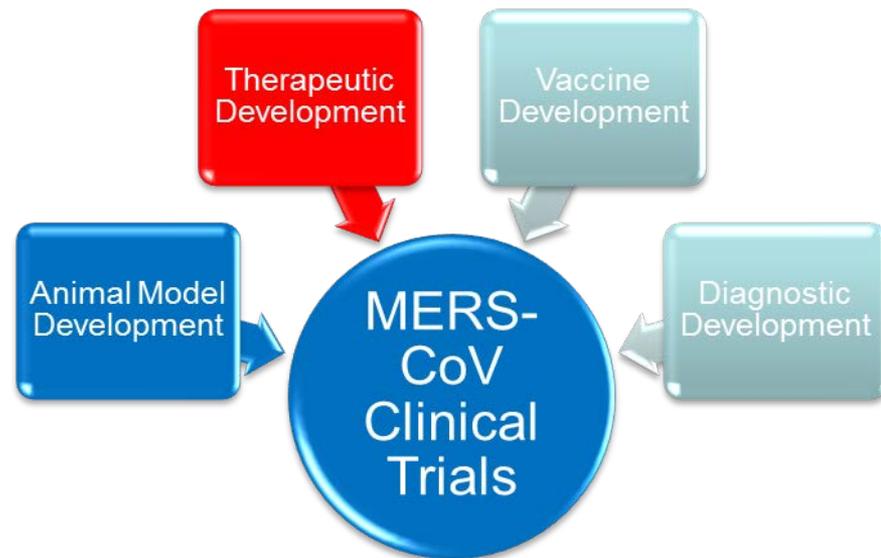


- Mouse studies at University of Maryland School of Medicine
- NHP studies at NIAID Rocky Mountain Laboratories
- Utilize the BARDA Nonclinical Development Network to standardize models
- NIH MERS Animal Model Standardization Workshop



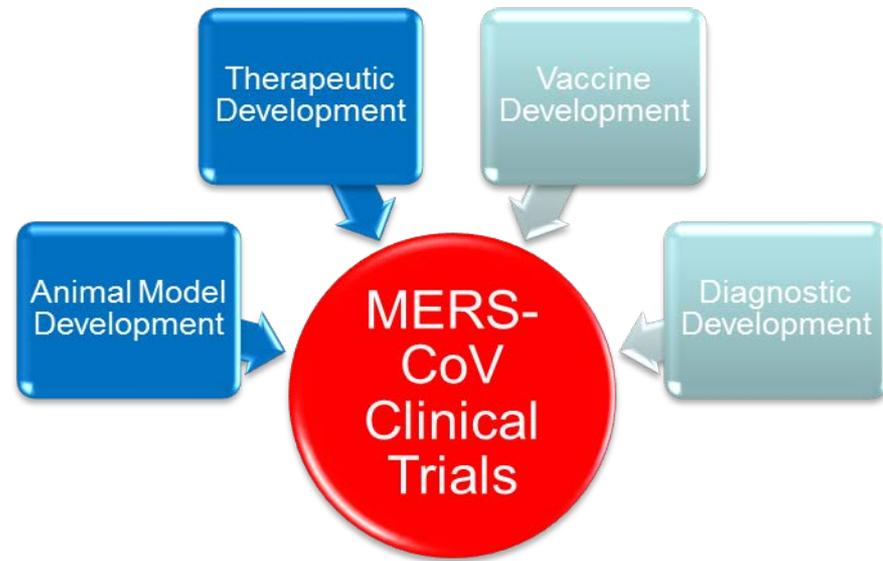
Priorities: Therapeutic Development

- Work with university and government partners, industry, and affected countries to obtain necessary data to begin human clinical trials
- From preclinical efficacy data to planning clinical trials



Priorities: MERS-CoV Clinical Trials

- Meeting in KSA Sept 9 – 10, 2015
- Objectives:
 - Establish a collaborative approach with national and international authorities and agencies
 - Present and discuss research options/priorities
 - Discuss logistics and requirements for early phase clinical trials
- Outcomes:
 - International collaboration
 - Prioritization of therapeutic candidates
 - Pathway towards a common adaptive clinical trial protocol



- Coronaviruses are a continuing and emerging treat
 - Two novel coronavirus have caused large outbreaks since 2002
 - Potential for MERS-CoV spread globally and cause significant morbidity and mortality
 - Research on potential MERS-CoV MCMs remains preliminary
 - International collaboration is needed to better understand the virus, disease and to develop/evaluate MCMs
- BARDA's experience in national and international preparedness and response can accelerate global preparedness for this emerging infectious disease

Ballerinas during the SARS outbreak

