The MERS Vaccine Initiative

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Outline

- **Middle East Respiratory Syndrome CoV**
  - Virology
  - Clinical
  - Epidemiology
  - MERS in S. Korea
- **MERS vaccine candidates**
- **IVI MERS program**
- **Summary**

MERS CoV
Biology, Clinical Features, Epidemiology, and MERS in S. Korea

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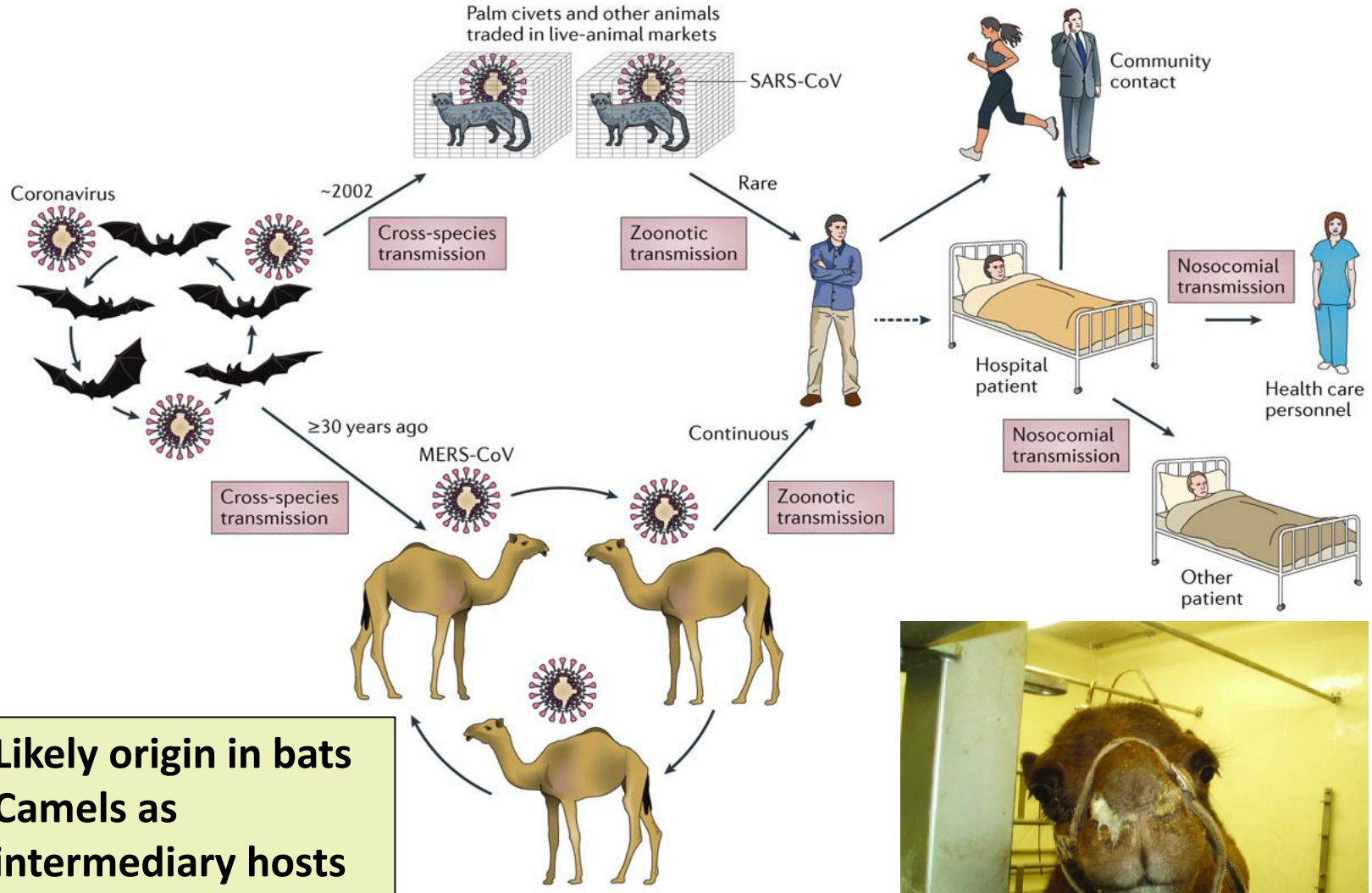
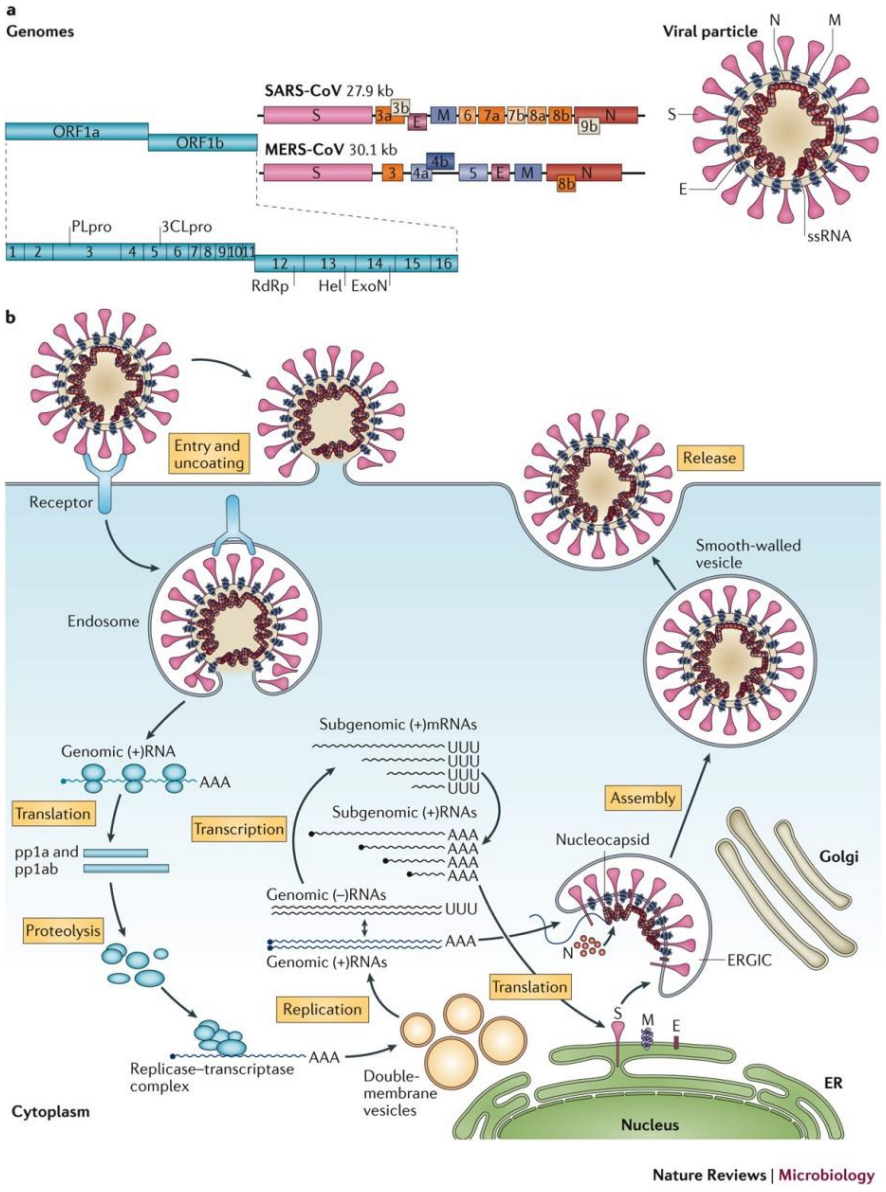
Emergence of new viruses - MERS coronavirus



- **Likely origin in bats**
- **Camels as intermediary hosts to humans**

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

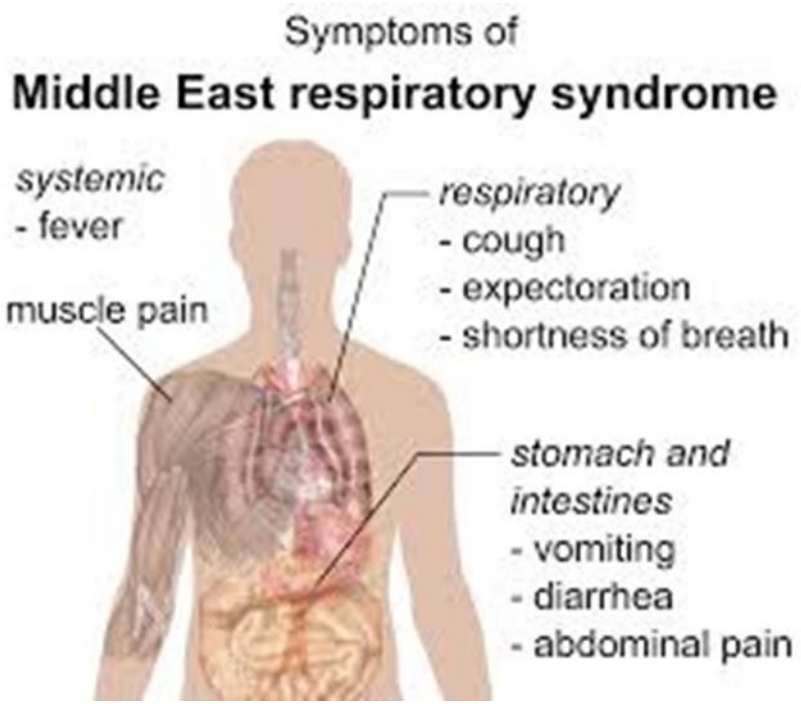
MERS-CoV background



- 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)**
- Dromedary camels are intermediary reservoir for transmission to humans

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

MERS-CoV in humans

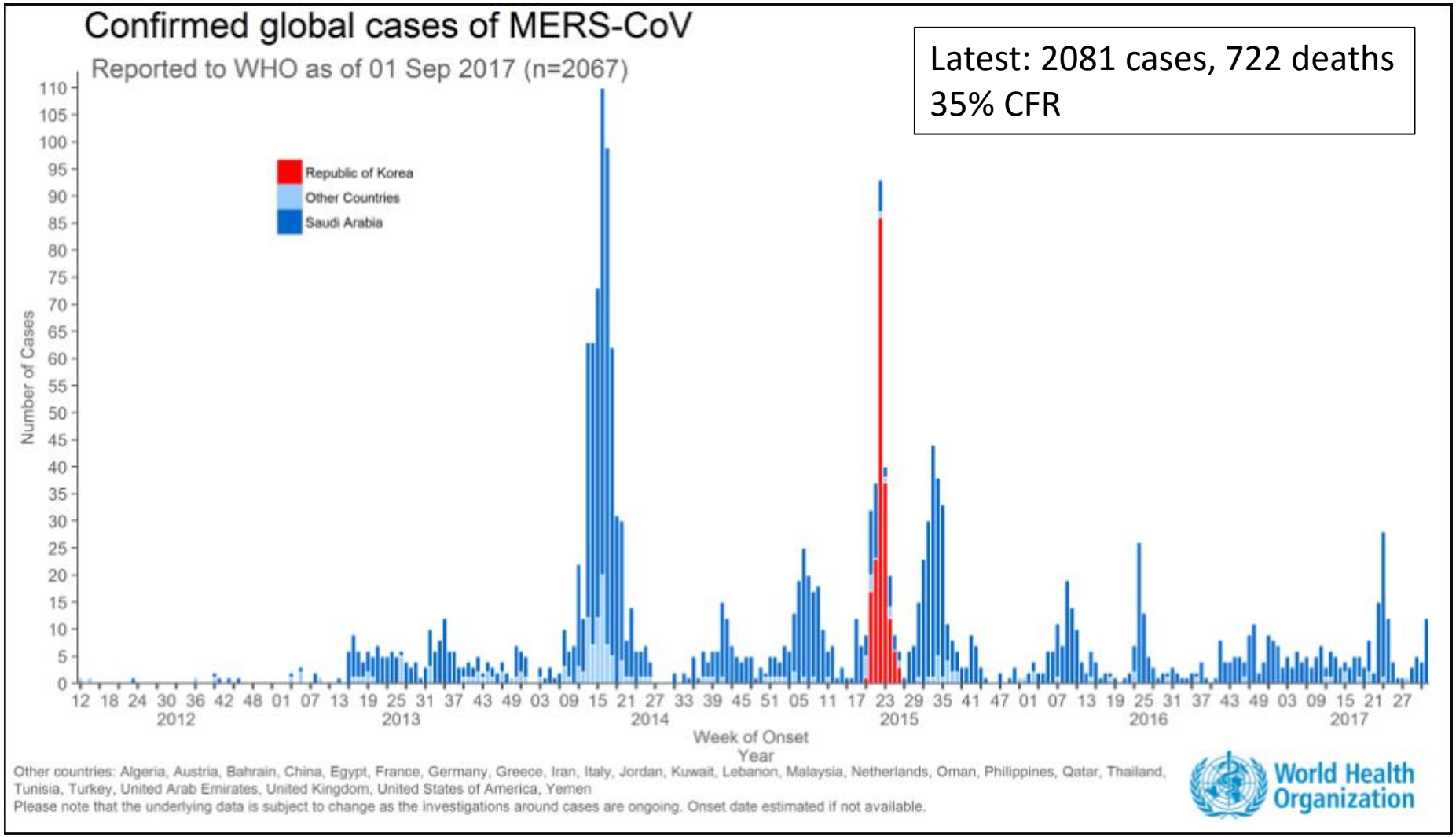


- From asymptomatic to mild to severe
- Comorbidities and age (obesity, hypertension, diabetes and cardiac disease) associated with a fatal outcome of MERS-CoV infection
- Incubation period ~ 5 days
- Rapid progression from hospital into ICU and intubation
- Extensive nosocomial transmission and superspreader potential

Human-to-human transmission

- No sustained human-to-human transmission
  - Basic reproductive number $R_0 < 1$
  - Can vary depending on situation
- Majority of outbreaks in nosocomial or household clusters
- Global risk
  - Hajj/Umrah pilgrimage (2 million)
  - Migrant workers
    - 9 million in KSA
    - Pakistan, India, Egypt, Yemen, Bangladesh

MERS-CoV epidemiology



Latest: 2081 cases, 722 deaths
35% CFR

MERS in Korea

Summary

- 186 cases MERS-CoV infection
- 36 deaths (19%)
- 16,693 in placed in quarantine

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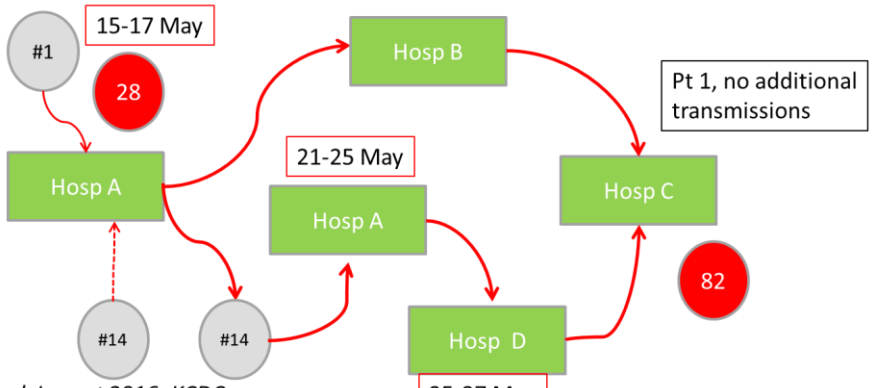
Korean MERS Outbreak (2015)

- Pt 1: 28 secondary infections (including Pt 14)
- Pt 14: 82 secondary infections (33 pt, 8 hcw, 41 visitors)



Cho et al, Lancet 2016; KCDC

- Time from exposure to onset (2-16 days), median 6.5 days
- Time from symptoms to diagnosis (0-17 days), median 5 days

For Pt 14

- Persons within same zone: incubation 5 days
- Persons outside of same zone: incubation 11 days
- Staying in same zone as index case: attack rate 20% (47/239)
- Passage in same zone/same time: attack rate 5% (6/116)
- Always in different zone: attack rate 2% (15/2003)
- HCW: 5/218 (2%)

Cho et al, Lancet 2016

- Only outbreak driven by human-to-human transmission outside of Middle East
- 68 year old Korean male traveled in Middle East in Apr 2015, and returned to Korea
- Became sick on 11 May 2015 with visits to 3 different Korean hospitals
- MERS-CoV confirmed on 20 May 2015
- 186 confirmed cases; 38 deaths (CFR 20%); 16,993 people quarantined

MERS Vaccine candidates

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MERS vaccine development: Considerations

- Animal models not ideal
  - Transduced mice, transgenic mice, rhesus, marmosets, camels
- No immune correlate of protection in humans
- Broad immune responses may be needed (high mutation rate of CoVs)
  - Cross-neutralizing Abs; T cells to multiple S epitopes
- Theoretical risk of enhancement
- May be difficult to demonstrate efficacy in field

Will one the viruses circulating now be the virus that causes a true epidemic?

Will it be important for at least one platform to be “rapid” (in terms of response to new strains)?

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	DZIF consortium
	ChAdOx1-MERS-S	Chimp adenovirus 3 with full-length S	Mice	Mice	Preclinical; Phase I planned in UK in mid 2017	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

MERS Vaccine Pipeline

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Overall IVI MERS program goal

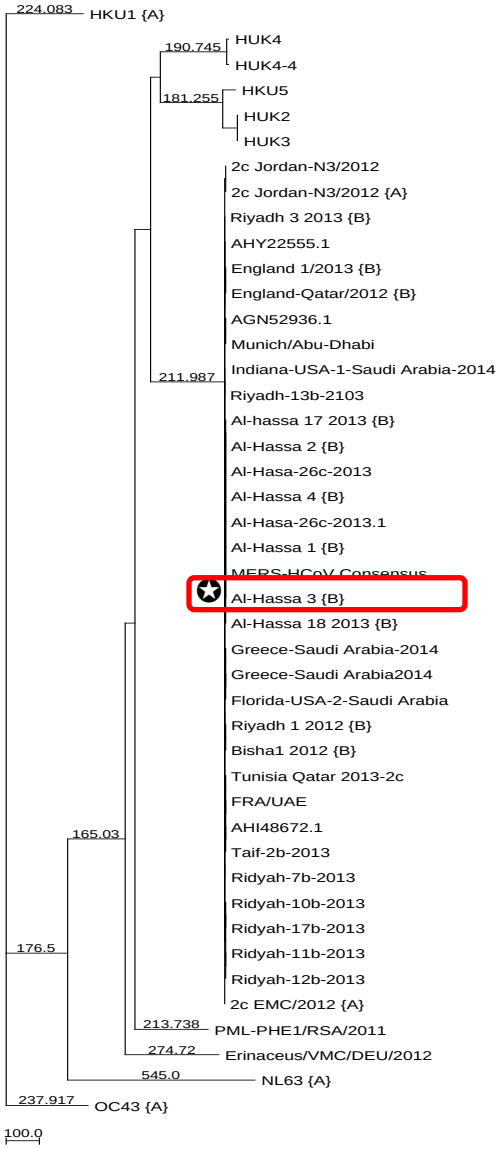
- IVI MERS program initiated with funding by Samsung Life Public Welfare Foundation
  - Samsung Medical Center impacted by Korean MERS outbreak
- Overall MERS program goal: Make MERS vaccine available for use in emergency response to potential outbreak in Korea
  - Select two MERS vaccine candidates to support preclinical and early clinical development
- Supportive activities
  - Certify and maintain IVI BSL-3 laboratory
  - Establish IVI biobank system

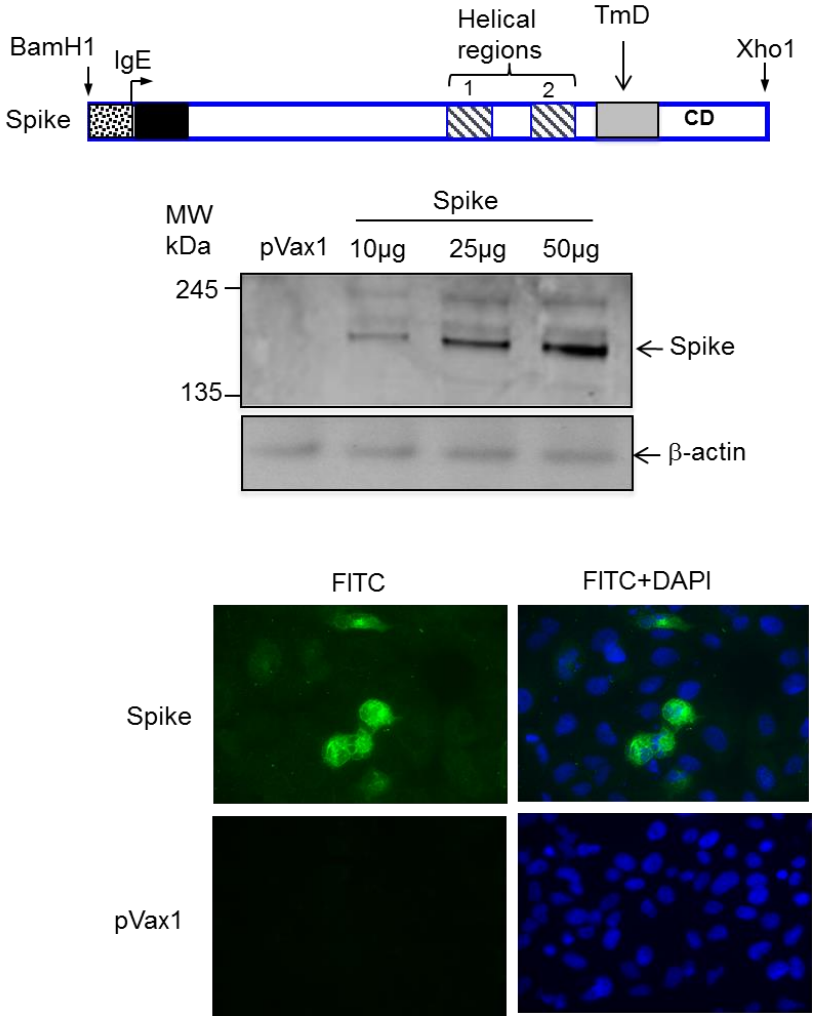
GeneOne/Inovio MERS DNA vaccine

Most advanced candidate in development

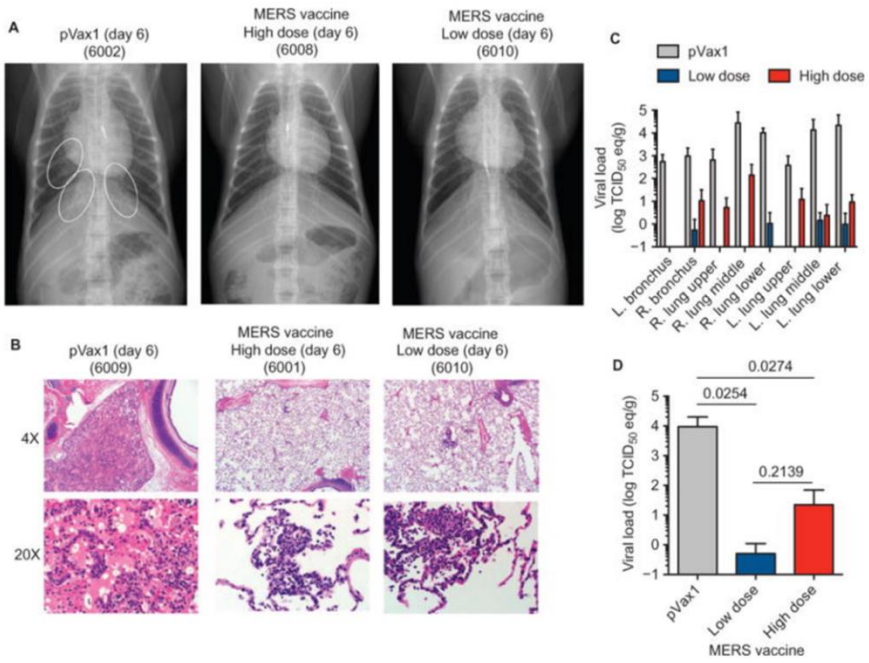
pVax1 plasmid DNA coding full-length S glycoprotein using consensus sequence

Given with electroporation





Rhesus: Summary of 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.

US Phase I first-in-human MERS vaccine trial

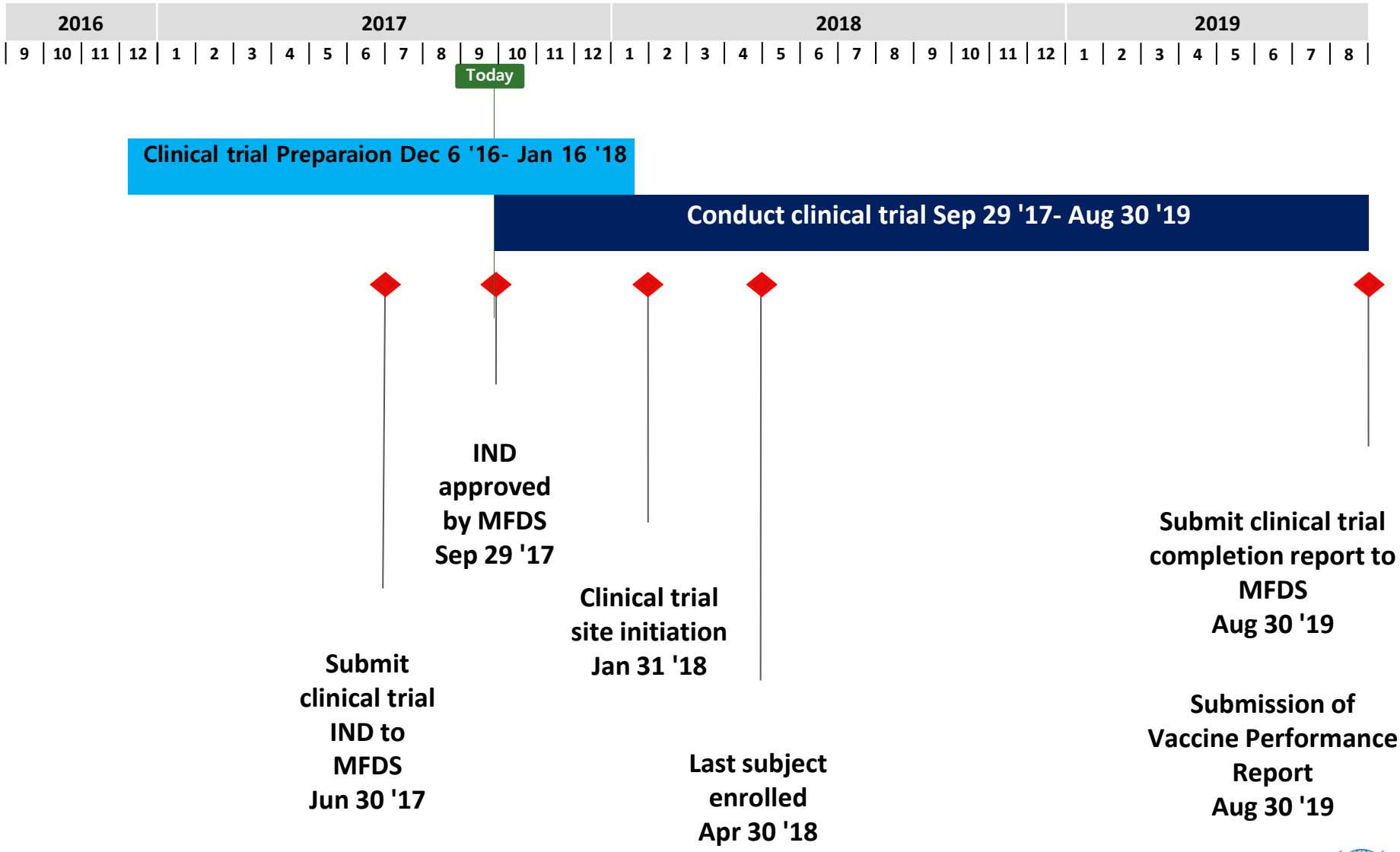
- Randomized, open-label trial of GeneOne MERS DNA vaccine (GLS-5300)
  - 75 healthy adults in 3 dose groups (0.67 mg, 2 mg, 6 mg)
  - Vaccinations at 0, 4 and 12 weeks administered by electroporation
- Primary objective
  - Safety up to 60 wks
- Secondary objectives
  - Immunogenicity
    - 1, 2, 3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

Human Clinical Data
- Binding Ab by EIA: 92% (57/62 vol)
- Bab or cellular response: 98% (61/62 vol)

US Phase I first-in-human MERS vaccine trial

- Progress
  - Subject enrollment initiated in Feb 2016
  - Enrollment completed in Aug 2016
  - Last dose administered in Nov 2016
- No safety issues
- Immunogenicity results up to 2 wks after 3rd dose (i.e., at 14 wks) expected to be available by Apr 2017
  - Binding ELISA for S glycoprotein
  - Neutralizing antibody assay (TCID50)
  - Pseudotyped virus assay (cross-neutralization)
  - IFN-gamma ELISpot
  - ICS

IVI-GeneOne clinical trial milestones



SUMMARY

- MERS CoV vaccine development will complicated by the unique features of viral transmission and outbreak epidemiology.
- There is a large pipeline of potential candidates, and the Coalition for Epidemic Preparedness Innovations has prioritized MERS CoV vaccine development.
- The IVI MERS vaccine program is moving forward with its initial candidate and is anticipating work on a second potential candidate.

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