LKS Faculty of Medicine
The University of Hong Kong
香港大學李嘉誠醫學院

MERS-questions of public health importance: The “known unknowns”

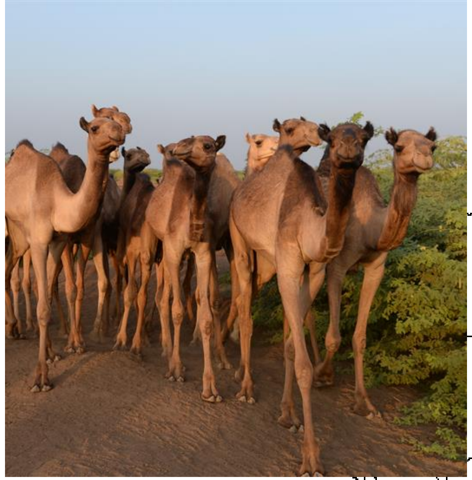
Malik Peiris

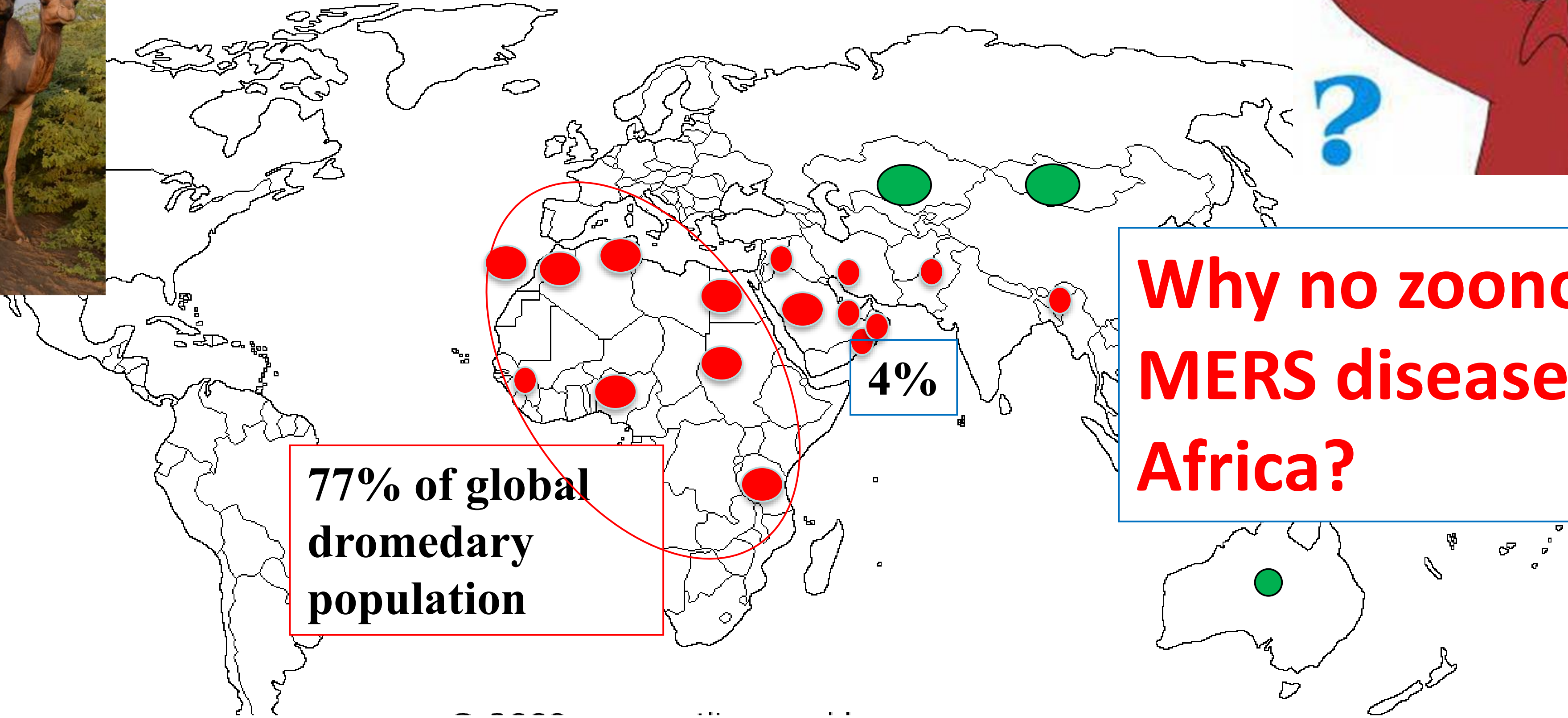
School of Public Health

The University of Hong Kong

malik@hku.hk

MERS CoV: Geographic virus distribution i





Reusken et al EID 2014; Perera et al EID 2013; Hemida et al 2014; Chan et al 2015; Miguel et al EID 2015; Miguel et al Eurosurveillance 2017; Chu et al Eurosurveillance 2015

Why "no" zoonotic MERS disease in Africa? Hypotheses

Exposure

↓

? Infection

↓

Disease

↓

Medical attention

↓

Diagnosis

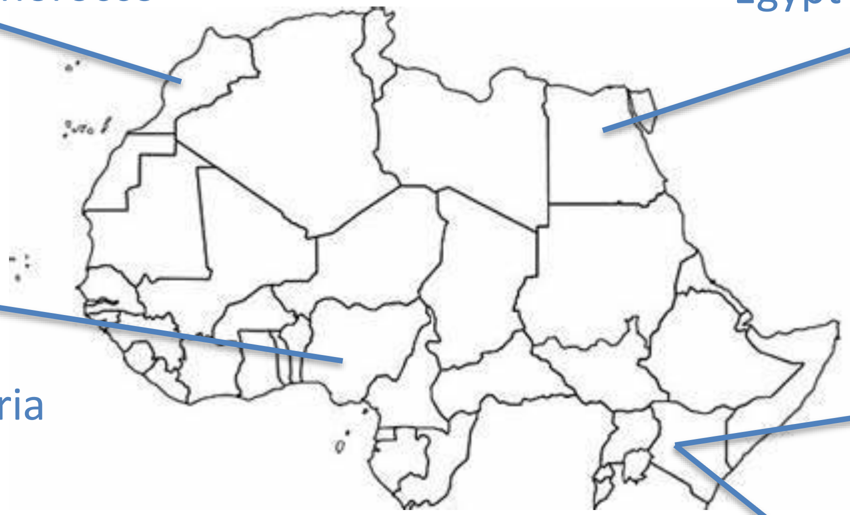
Exposure → Infection:
- *Infected animals*
- *Behavioural factors*

Infection → Disease:
- *Viral genetics*
- *Host genetics*

Medical attention → Diagnosis:
- *Recognition*
- *Diagnostics*

So et al Eurosurveillance 2018
Abbad et al Eurosurveill 2019

Is human infection taking place in Africa?



Seroprevalence:
0.8% of 379 camel exposed humans *(Nourlil et al. 2019)*

Seroprevalence:
0% of 260 camel abattoir workers *(So et al. 2018)*

Seroprevalence:
0% of 179 camel abattoir workers *(Hemida et al. 2014)*

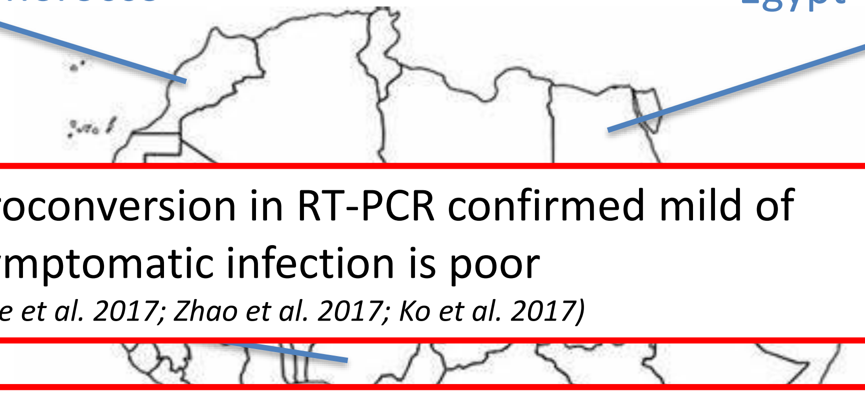
Seroprevalence:
- 0% of 760 camel exposed people *(Munyua et al. 2017)*
- General population: 0.18% of 1222 *(Liljander et al. 2016)*
- Camel handlers: 4 (4.3%) of 93 *(Kiyong et al. 2020)*

RNA:
3 (1.2%) of camel exposed humans, concurrent with virus infection in camels *(Ngere et al. 2022)*

Is human infection taking place in Africa?

Seroprevalence:
0.8% of 379 camel exposed humans *(Nourlil et al. 2019)*

Seroprevalence:
0% of 260 camel abattoir workers *(So et al. 2018)*



Seroprevalence:
0% of 179 camel abattoir workers *(Hemida et al. 2014)*

Seroconversion in RT-PCR confirmed mild of asymptomatic infection is poor
(Choe et al. 2017; Zhao et al. 2017; Ko et al. 2017)

MERS-CoV specific T cell responses may be detectable in infected sero-negative individuals in Saudi Arabia *(Perlman et al. 2017)*

Seroprevalence:

- 0% of 760 camel exposed people *(Munyua et al. 2017)*
- General population: 0.18% of 1222 *(Liljander et al. 2016)*
- Camel handlers: 4 (4.3%) of 93 *(Kiyong et al. 2020)*

RNA:
3 (1.2%) of camel exposed humans, concurrent with virus infection in camels *(Ngere et al. 2022)*

18 (30%) of 61 camel abattoir workers in Nigeria had MERS-CoV specific CD4+ or CD8+ T cell responses, even though they were MERS-CoV antibody negative. In comparison, none of control population had MERS-CoV specific T cell responses (Mok CKP.. Oladipo J, Kuranga S .. et al 2021)

Needs confirmatory studies

Why “no” zoonotic MERS in Africa? Hypotheses

Exposure

Infection

- *Infected animals*
- *Behavioural factors*

So et al Eurosurveillance 2018
Abbad et al Eurosurveill 2019

Disease

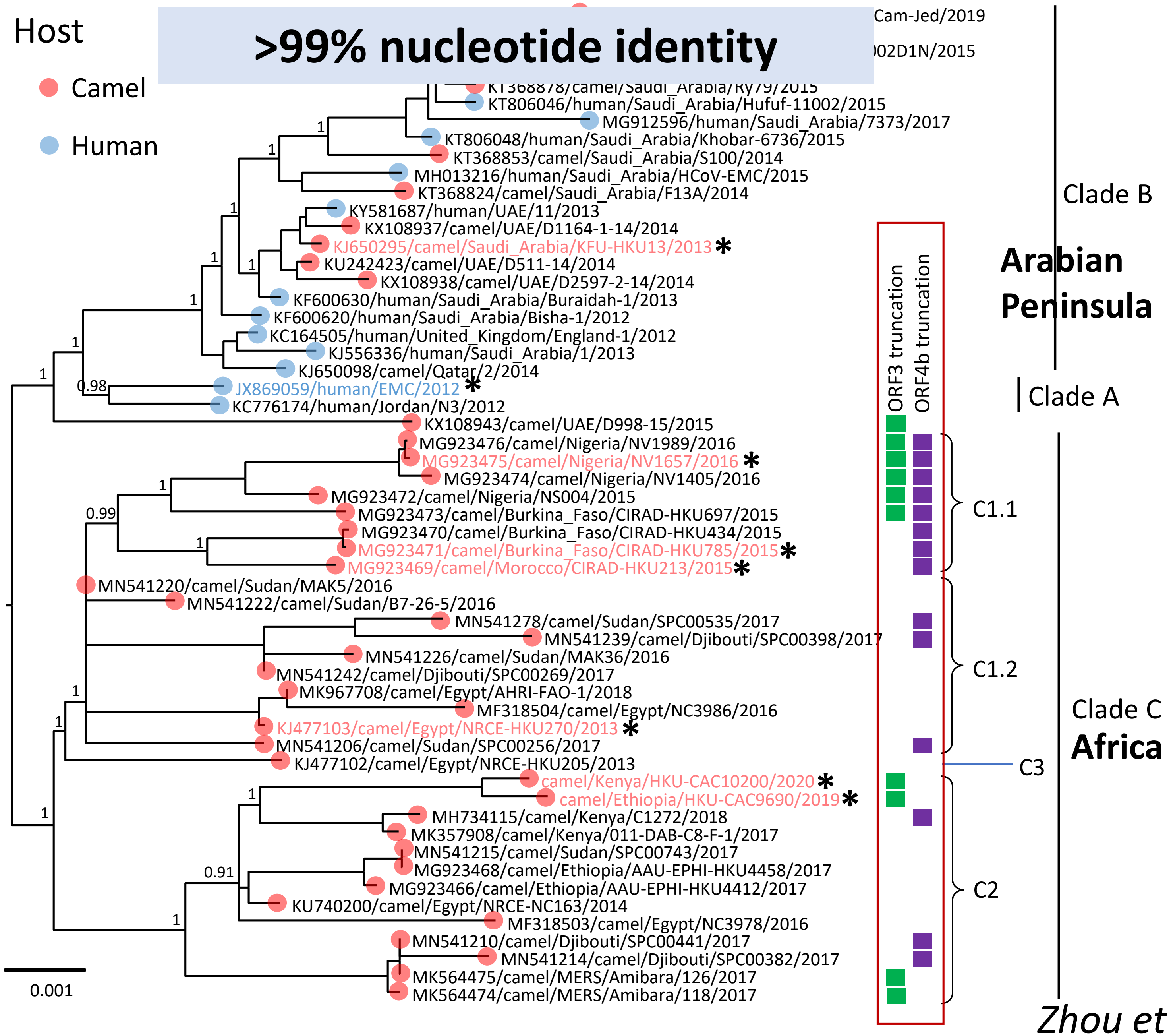
- *Viral genetics*

Medical attention

Diagnosis

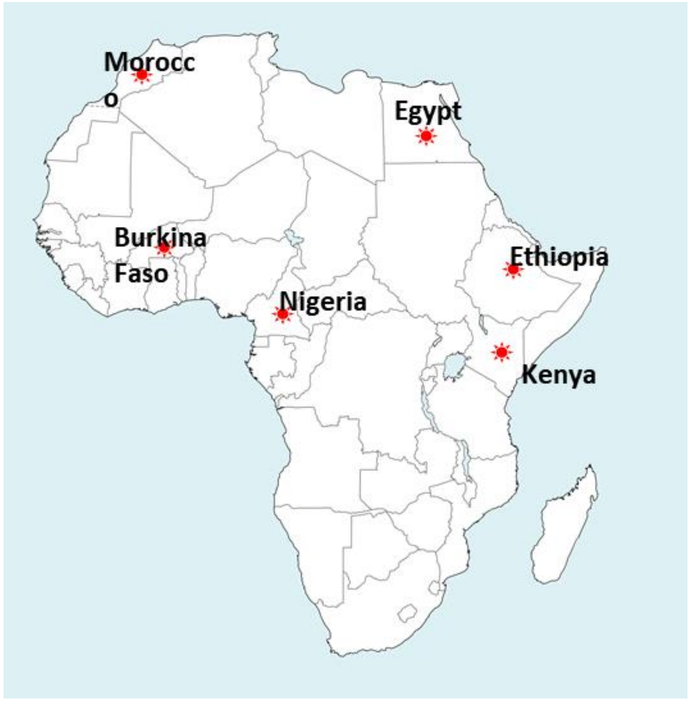
- *Recognition*
- *Diagnostics*

Phylogenetics of MERS coronaviruses



*** Virus strains phenotyped in this study**

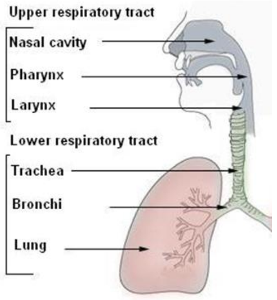
Clade	Strain	Species	Country	Sampling date
A	EMC/2012	Human	Saudi Arabia	13/6/2012
B	AH13	dromedary	Saudi Arabia	30/12/2013
C1.2	C270	dromedary	Egypt	2013
C1.1	BF785	dromedary	Burkina Faso	18/3/2015
C1.1	Nig1657	dromedary	Nigeria	3/2/2016
C1.1	MOR213	dromedary	Morocco	3/3/2015
C2	CAC9690	dromedary	Ethiopia	24/11/2019
C2	CAC10200	dromedary	Kenya	19/3/2020

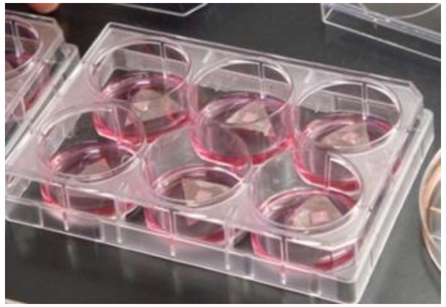


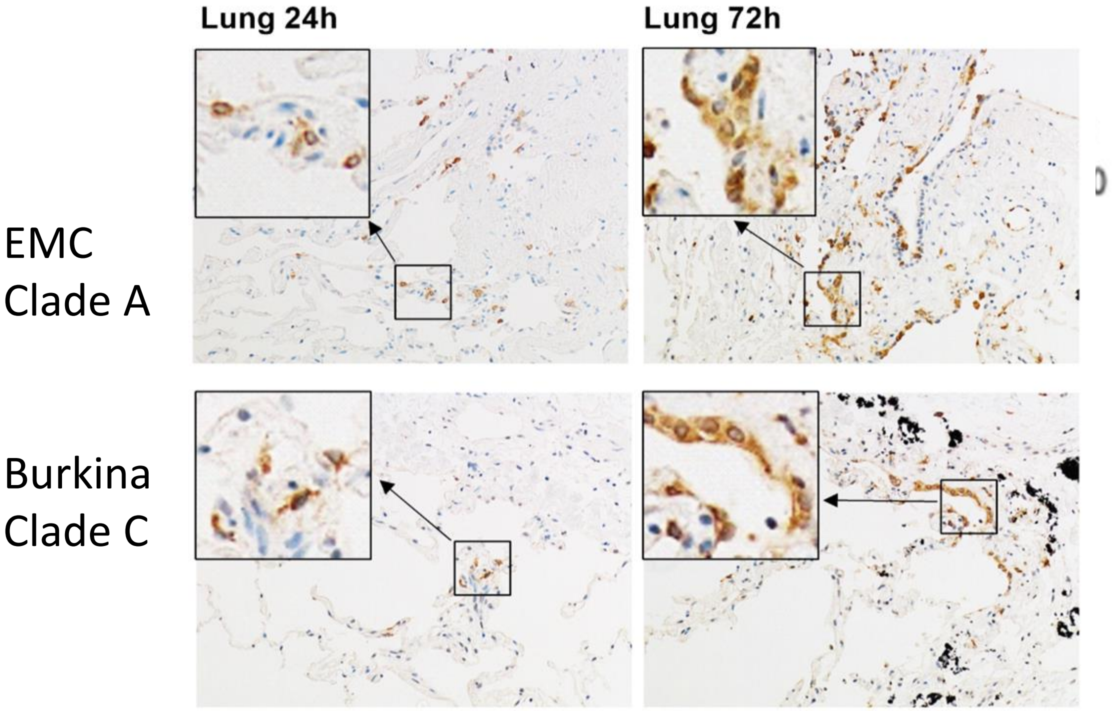
Zhou et al PNAS 2021; 118(25):e2103984118.

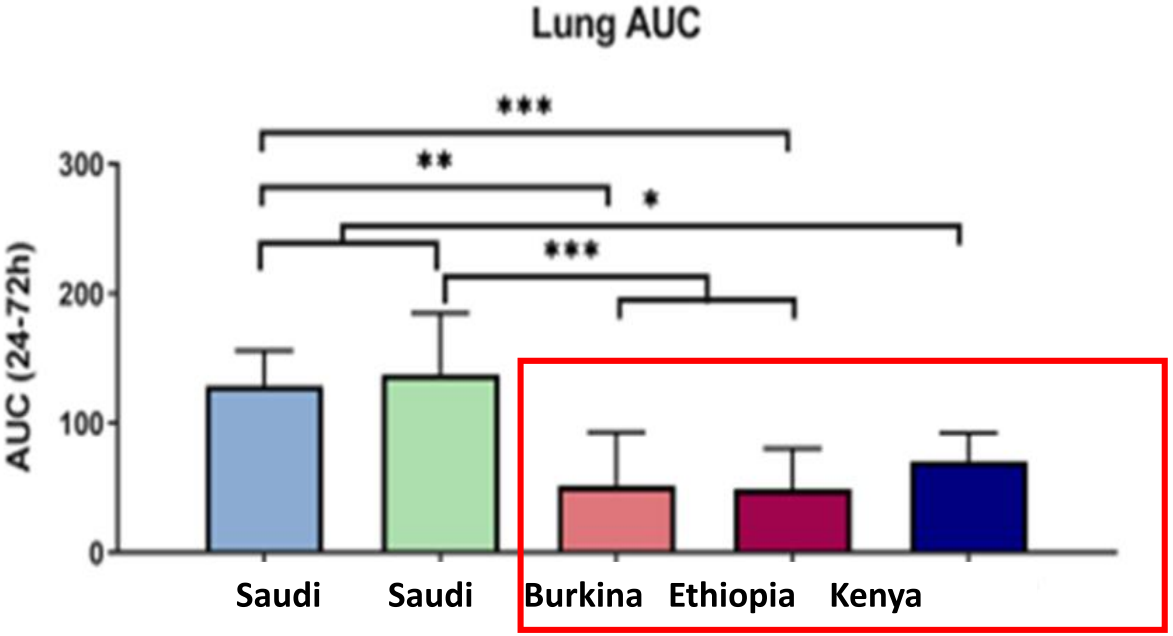
Compared with clade A & B MERS-CoV from Saudi Arabia, viruses from Africa (clade C) (Burkina, Ethiopia, Kenya, *Nigeria, Morocco*) have lower replication competence ex-vivo cultures of human lung (and Calu-3 cells).

Candy Zhou





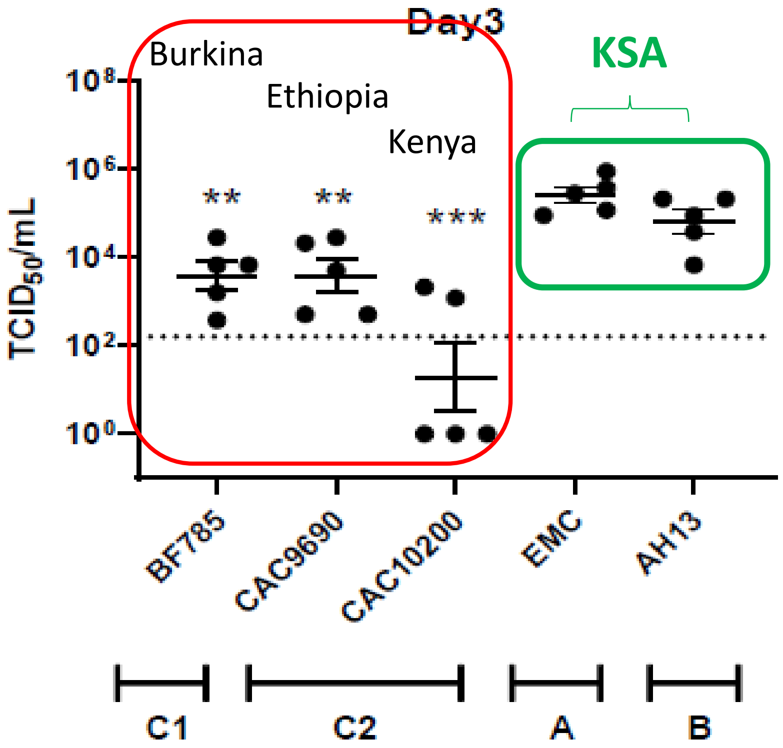




Also for Nigerian, Moroccan and Egyptian isolates

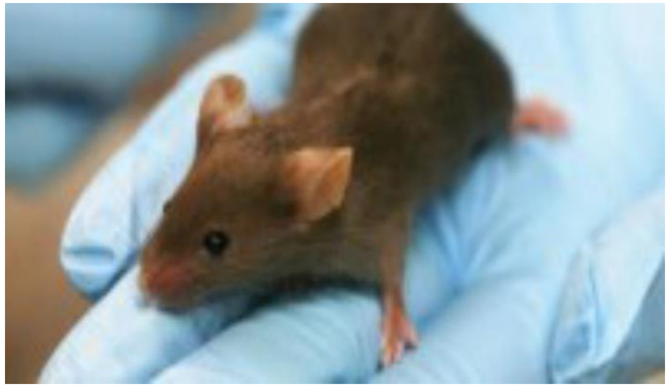
Zhou et al PNAS 2021; 118(25):e2103984118.

Lower viral replication competence of MERS coronaviruses from Africa (Burkina, Ethiopia, Nigeria, Morocco, Egypt) in mouse model



Chris Mok

Candy Zhou



Humanising exons 10-12 of mouse DPP4 provided by Stanley Perlman
Li K et al PNAS 2017

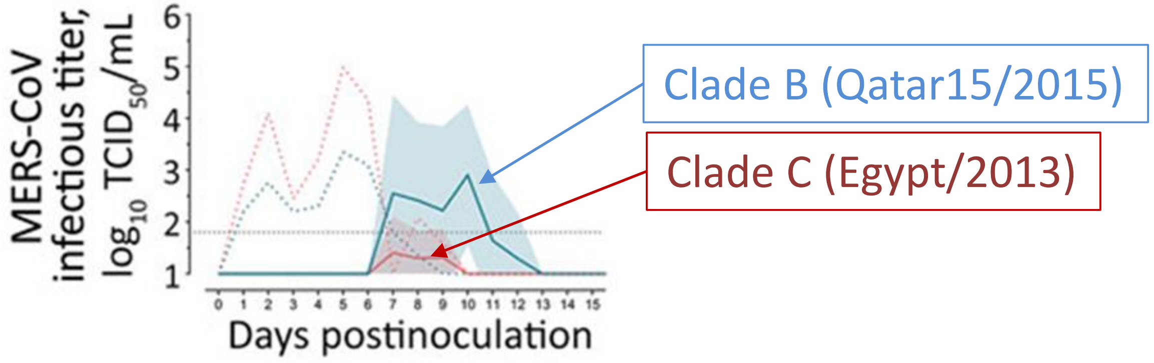
Also for Nigerian, Moroccan and Egyptian isolates

Zhou et al PNAS 2021

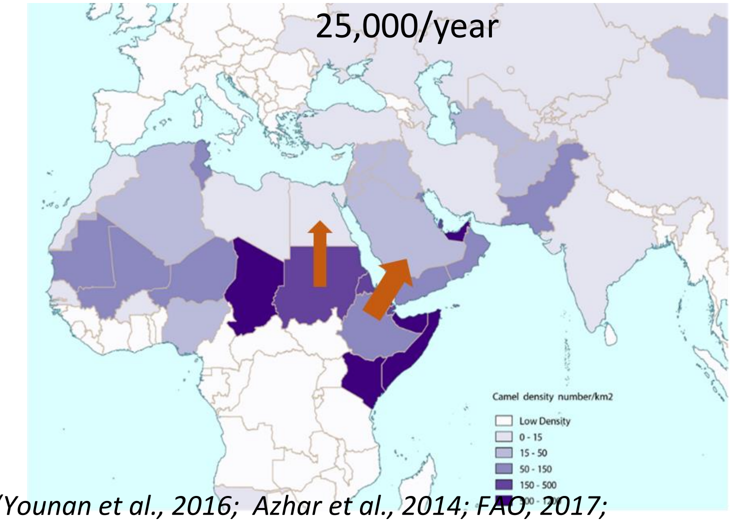
What are implications for viral genetic diversity for infection in dromedary camels?

- Clade C: viral replication levels in naturally transmitted animals was lower. Transmission efficiency also lower *(Rodon .. Segales et al EID 2023)*
- Suggests that fitness in camels of clade B > clade C
- Explains why clade C virus does not get established in Arabian Peninsula in spite of repeated importations of dromedaries (and virus) from Africa.
- Danger: If Clade B virus gets introduced into Africa, it will potentially become dominant in Africa? → Implications for zoonotic potential?

Experimental infection and transmission clade B vs clade C virus in Llamas (a surrogate for camels)



Camel density and trade routes



(Younan et al., 2016; Azhar et al., 2014; FAO, 2017; Anthony et al., 2017; Moreno et al., 2017)

Why "no" zoonotic MERS in Africa? Hypotheses

Exposure → Infection
- *Infected animals*
- *Behavioural factors*

So et al Eurosurveillance 2018
Abbad et al Eurosurveill 2019

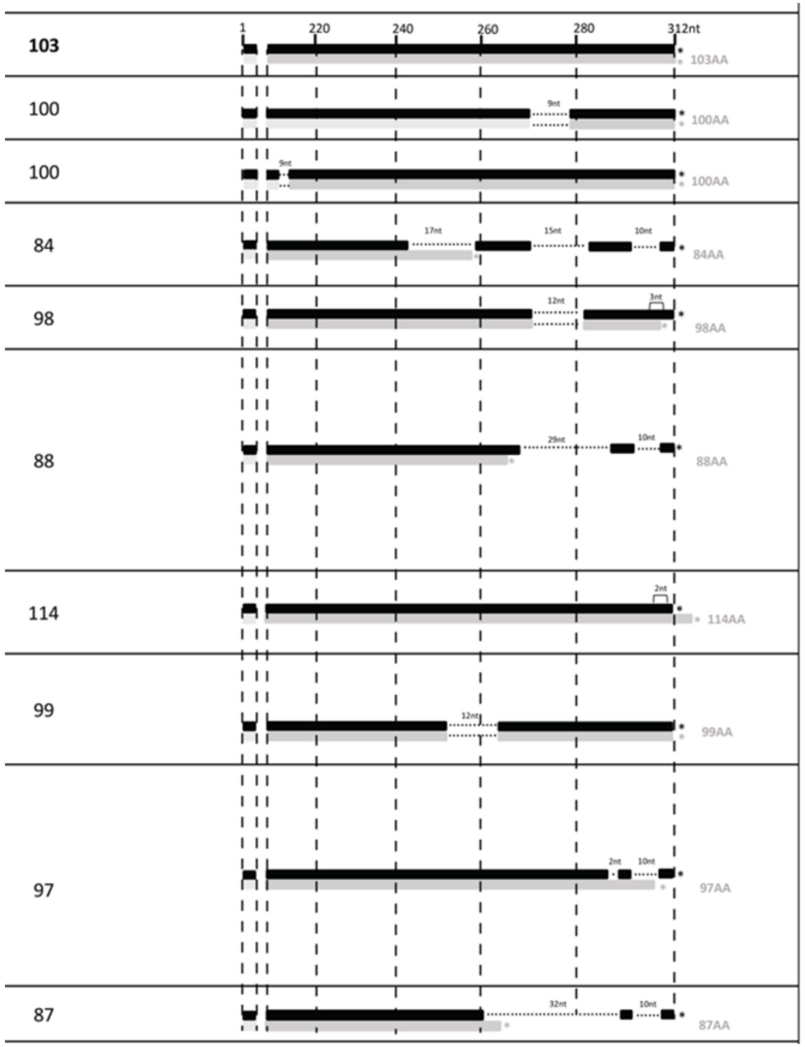
Infection → Disease
- *Viral genetics*

Viruses from Africa (clade C)
- Genetically distinct (Zhou et al 2021)
- Lower replication competence in human lung, possibly suggesting lower pathogenicity in humans (Zhou et al 2021).
- May partially explain why severe human disease is not prominent?
- But repeated exposure and unsuspected infection in large numbers of people may lead to virus adaptation to humans → pandemic emergence.

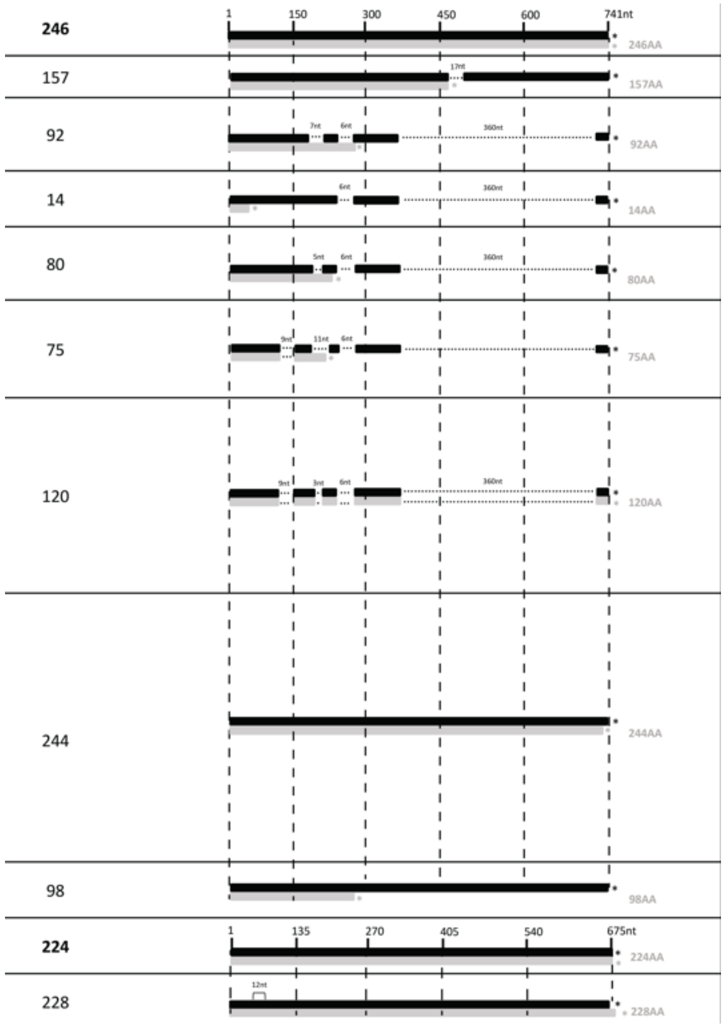
Disease → Medical attention → Diagnosis
- *Recognition*
- *Diagnostics*

Diverse genome deletions and insertions in MERS-CoV genomes in dromedary camels in Africa

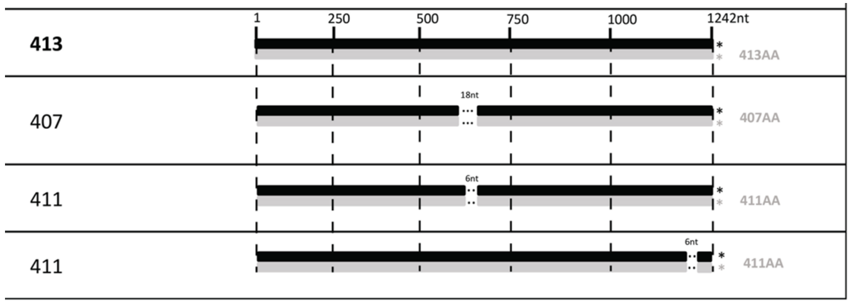
AA ORF3 deletions



AA ORF4b deletions



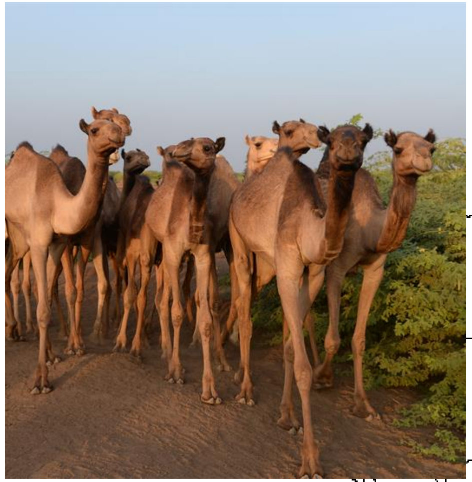
AA N protein deletions

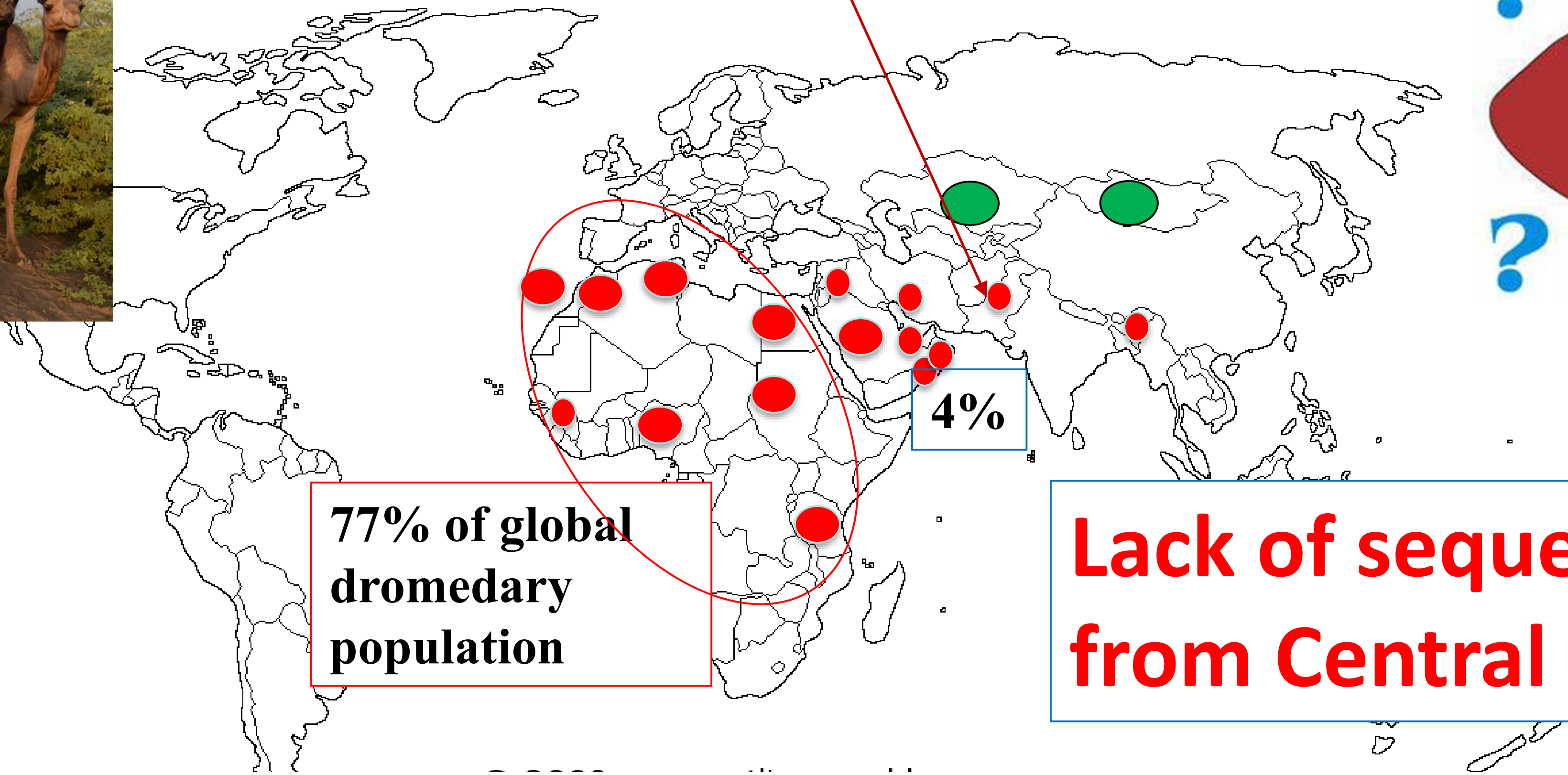


- MERS-CoV in African camels genetically unstable (Zhou et al Emerging Microbes & Infections 2023)

- **ORF8 deletion of SARS-CoV-1 was associated with the emergence of the SARS epidemic in 2003 (Guan et al 2003)**

MERS CoV: Geographic virus distribution in camels





What is viral lineage in Central Asia?

77% of global dromedary population

4%

Lack of sequence data from Central Asia?

Reusken et al EID 2014; Perera et al EID 2013; Hemida et al 2014; Chan et al 2015; Miguel et al EID 2015; Miguel et al Eurosurveillance 2017; Chu et al Eurosurveillance 2015

Why "no" zoonotic MERS in Africa? Hypotheses

Exposure

Infection

Disease

- *Infected animals*
- *Behavioural factors*
- *Viral genetics*

So et al Eurosurveillance 2018
Abbad et al Eurosurveill 2019

Medical attention

Diagnosis

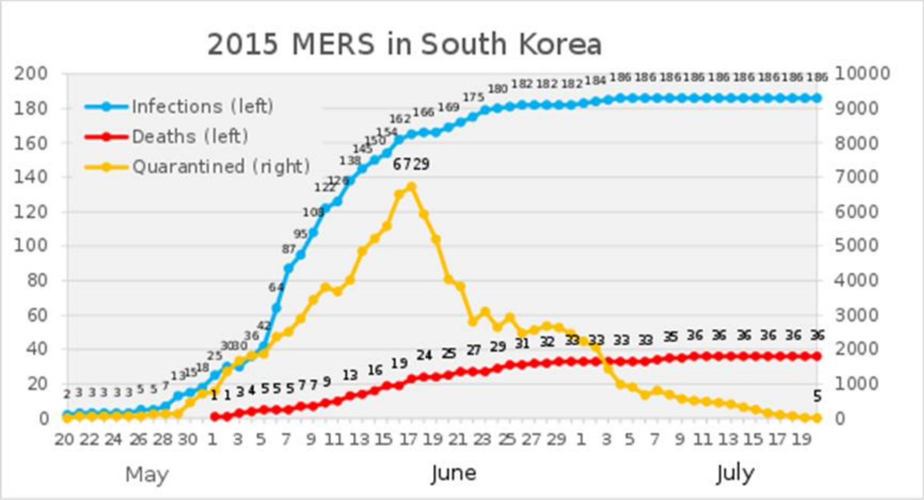
- *Recognition*
- *Diagnostics*

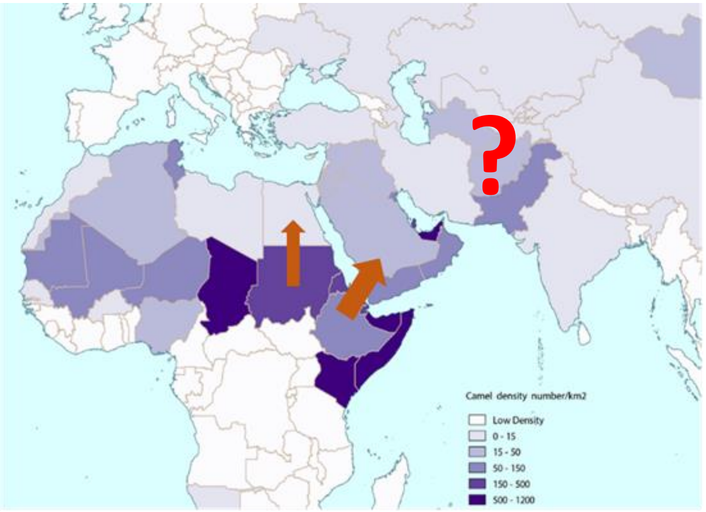
Human respiratory surveillance & Health care workers in Africa:

- **How aware** that MERS-CoV may be causing mild or severe respiratory disease in camel herding regions of East, West and North Africa?
- How many ILI/SARI **surveillance sites are situated in proximity to camel exposed populations**?
- How many ILI and SARI surveillance specimens in camel herding / exposed areas are being **tested for MERS-CoV?**

Summary of knowledge gaps

- Transmission within health care facilities can be efficient (more so that for avian flu H5N1, H7N9 etc.), but less efficient in the community? Can that change?
- Majority of MERS-CoV infected dromedaries are in Africa but no reported zoonotic disease there?
- Need more surveillance at the camel-human interface in <u>camel-herding</u> regions of Africa?
- Gaps in surveillance and sequence data from Central Asia
- Few recent MERS-CoV sequences in public data-bases
- **MERS remains a pandemic threat and development of counter-measures are a priority**





Thank you for your attention
… and to many research collaborators in Africa

Phenotypic and genetic characterization of MERS coronaviruses from Africa to understand their zoonotic potential

Ziqi Zhou[a,1], Kenrie P. Y. Hui[a,1], Ray T. Y. So[b], Huibin Lv[b], Ranawaka A. P. M. Perera[a], Daniel K. W. Chu[a], Esayas Gelaye[c], Harry Oyas[d], Obadiah Njagi[d], Takele Abayneh[c], Wilson Kuria[d], Elias Walelign[e], Rinah Wanglia[f], Ihab El Masry[g], Sophie Von Dobschuetz[g], Wantanee Kalpravidh[g], Véronique Chevalier[h,i], Eve Miguel[j,k], Ouafaa Fassi-Fihri[l], Amadou Trarore[m], Weiwen Liang[b], Yanqun Wang[n], John M. Nicholls[o], Jincun Zhao[n], Michael C. W. Chan[a], Leo L. M. Poon[a,b], Chris Ka Pun Mok[b,p,2], and Malik Peiris[a,b,2]

[a]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong (HKU), Pokfulam, Hong Kong Special Administrative Region, People's Republic of China; [b]HKU-Pasteur Research Pole, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China; [c]National Veterinary Institute, Debre Zeit, Ethiopia; [d]Directorate of Veterinary Services, Nairobi, Kenya; [e]Food and Agriculture Organization, Emergency Centre for Transboundary Animal Diseases, Addis Ababa, Ethiopia; [f]Food and Agriculture Organization, Emergency Centre for Transboundary Animal Diseases, Nairobi, Kenya; [g]Food and Agriculture Organization of the United Nations, Rome 00153, Italy; [h]Centre de Coopération Internationale en Recherche Agronomique pour le Développement, UMR Animal, Health, Territories, Risk, Ecosystems (ASTRE) Animal, Santé, Territoires, Risques et Ecosystèmes, Institut National de la Recherche Agronomique, Université de Montpellier, F-34398 Montpellier, France; [i]Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia; [j]Animal, Santé, Territoires, Risques et Ecosystèmes, Centre de Coopération Internationale en Recherche Agronomique pour le Développement, Institut National de la Recherche Agronomique, Université de Montpellier, F-34398 Montpellier, France; [k]Maladies Infectieuses et Vecteurs: Ecologie Genetique, Evolution et Controle, L'Institut de Recherche pour le Developpment, CNRS, 34090 Montpellier, France; [l]Laboratoire de Biologie et Santé Animals, L'Institut de l'Environnement et de Recherches Agricoles du Burkina Faso/Centre National de la Recherche Scientifique et Technologique, 04 BP 8645 Ouagadougou 04, Burkina Faso; [m]Institut Agronomique et Vétérinaire, Hassan II Université, B.P. 6202 Rabat-Instituts, Rabat, Morocco; [n]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, People's Republic of China; [o]Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China; and [p]The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, People's Republic of China

Proceedings of National Academy of Science, 2021

Genetic diversity and molecular epidemiology of Middle East Respiratory Syndrome Coronavirus in dromedaries in Ethiopia, 2017–2020

Ziqi Zhou, Abraham Ali, Elias Walelign, Getnet F. Demissie, Ihab El Masry, Takele Abayneh, Belayneh Getachew, Pavithra Krishnan, Daisy Y.M. Ng, Emma Gardner, Yilma Makonnen, Eve Miguel, Véronique Chevalier, Daniel K. Chu, Ray T. Y. So, Sophie Von Dobschuetz, Gezahegne Mamo, Leo L. M. Poon & Malik Peiris

Emerging Microbes and Infections 2023