

are too big to study in most biosafety facilities. These limitations restrict vaccination tests in camels.

It is increasingly recognised that a One Health approach is needed for effective investigation, prevention, and control of emerging zoonotic diseases. In the context of emerging zoonoses, human and veterinary medicines must work together. The eradication of MERS coronavirus in dromedary camels is the primary condition for the control of this disease in the Arabian Peninsula. If the virus continues to circulate in camels, it might attain new mutations that enable human-to-human transmission, resulting in the generation of super-spreader strains. A comprehensive MERS prevention and control effort should focus not only on a human vaccine but also on camel vaccination.

We declare no competing interests.

This work was supported by grants from the National Natural Science Foundation of China (number 31822056) and Guangdong Natural Science Funds for Distinguished Young Scholar (number 2014A030306046).

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- 1 Modjarrad K, Roberts CC, Mills KT, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019; **19**: 1013–22.
- 2 WHO. WHO MERS global summary and assessment of risk. 2018. https://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf?ua=1 (accessed Sept 3, 2019).
- 3 Sabir JSM, Lam TTY, Ahmed MMM, et al. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science* 2016; **351**: 81–84.
- 4 Reusken CB, Haagmans BL, Muller MA, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. *Lancet Infect Dis* 2013; **13**: 859–66.

- 5 Haagmans BL, van den Brand JMA, Raj VS, et al. An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. *Science* 2016; **351**: 77–81.
- 6 Muthumani K, Falzarano D, Reuschel EL, et al. A synthetic consensus anti-spike protein DNA vaccine induces protective immunity against Middle East respiratory syndrome coronavirus in nonhuman primates. *Sci Transl Med* 2015; **7**: 301ra132.

The phase 1, open-label, single-arm, first-in-human evaluation of the Middle East respiratory syndrome (MERS) coronavirus DNA vaccine by Kayvon Modjarrad and colleagues¹ is an important step forward for achieving one of the WHO R&D Blueprint for MERS aims, which calls for development of two types of human MERS vaccines² for long-term protection of people at high exposure risk and for reactive use in outbreak settings. Modjarrad and colleagues' results should be viewed with cautious optimism. Apart from overcoming the operational challenges stated in the accompanying Comment by In-Kyu Yoon and Jerome Kim,³ advancement of this DNA vaccine to a second phase 1 or 2a trial will need to overcome other operational and logistical challenges and must target those most at risk of succumbing to the disease.

The high mortality and severe disease seen in MERS are positively correlated with age and presence of comorbidities, including chronic liver, kidney, and heart disease, diabetes, and immunosuppressive conditions.⁴ Furthermore, host immune responses to MERS coronavirus could contribute to disease severity and outcomes. Thus, vaccine-induced immune responses in populations with these high-risk characteristics could potentially have harmful effects. These barriers were encountered in severe acute respiratory syndrome coronavirus vaccine development over 15 years ago, and might also hold true for MERS coronavirus.⁵ Therefore, any MERS coronavirus vaccine must specifically target the most vulnerable populations and assess safety and generation

of robust, long-lasting protective immune responses.⁶ At week 60, the MERS DNA vaccine induced humoral and cellular responses in only 51 (77%) of 66 participants and 42 (64%) of 66 participants, respectively, and only two (3%) of 66 participants maintained neutralising antibodies until the end of the study. Thus, generation of humoral and cellular immune responses might not equate with long-term protection.

The phase 1 DNA vaccine developed for the US military aptly illustrates that advances in technology, vaccine platforms, clinical trial designs, and bioinformatics, together with serious investment by stakeholders, provide opportunities for rapid vaccine development and evaluation. Countries where MERS is endemic must invest more seriously in both human and camel vaccine development. With the continuing outbreaks of MERS coronavirus 7 years after it was first discovered, effective human vaccines could be the ideal way to prevent spread and evolution of the virus. Logistical issues of the small and sporadic number of new MERS cases at different geographical locations need to be overcome by a more coordinated approach for research, something that needs to be advanced more rapidly than the current pace of research and development.⁷ Being a DNA vaccine candidate, the GLS-5300 MERS coronavirus vaccine allowed for rapid design and production and was advanced into the clinic within 9 months of preclinical candidate vaccine selection. The encouraging results of the phase 1 MERS DNA vaccine study¹ should be advanced quickly to include studies with adequate numbers of elderly and comorbid populations, with careful consideration of safety and of the longevity of the protective response, thereby mitigating future outbreaks and alleviating disease burden from the most susceptible populations—elderly people, immunosuppressed people, and health-care workers.

All authors have an academic interest in Middle East respiratory syndrome coronavirus. SP reports grants from National Institutes of Health USA related to the content of this letter. All other authors declare no competing interests.

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- 1 Modjarrad K, Roberts CC, Mills KT, et al. Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial. *Lancet Infect Dis* 2019; **19**: 1013–22.
- 2 WHO. WHO target product profiles for MERS-CoV vaccines. May, 2017. https://www.who.int/blueprint/what/research-development/MERS_CoV_TPP_15052017.pdf (accessed Aug 3, 2019).
- 3 Yoon I-K, Kim JH. First clinical trial of a MERS coronavirus DNA vaccine. *Lancet Infect Dis* 2019; **19**: 924–25.
- 4 Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* 2018; **18**: e217–27.
- 5 Maslow JN. Vaccines for emerging infectious diseases: lessons from MERS coronavirus and Zika virus. *Hum Vaccin Immunother* 2017; **13**: 2918–30.
- 6 Schindewolf C, Menachery VD. Middle East respiratory syndrome vaccine candidates: cautious optimism. *Viruses* 2019; **11**: e74.
- 7 Perlman S, Azhar EI, Memish ZA, Hui DS, Zumla A. Confronting the persisting threat of the Middle East respiratory syndrome to global health security. *Lancet Infect Dis* 2019; published online July 3. [https://doi.org/10.1016/S1473-3099\(19\)30347-0](https://doi.org/10.1016/S1473-3099(19)30347-0).

Early N-acetylcysteine for hospitalised patients with yellow fever

We read with interest the Article by Esper Kallas and colleagues¹ on the

predictors of mortality in patients with severe forms of yellow fever. Among the 76 hospitalised patients in São Paulo, Brazil, who were included in the study, 27 (36%) died. High viral load was found to be a key determinant of fatal outcome, suggesting that an antiviral drug that is effective against the virus would help patient recovery.

In multivariate analysis, other factors associated with death included older age, neutrophil count, and higher baseline values of serum aspartate aminotransferase. The prognostic value of indirect bilirubin was found to be just above the two-tailed α level of 0.05 in the multivariate analysis—possibly because of the small sample size—but was highly significant in univariate analysis, as was the international normalised ratio, a key prognostic factor in acute liver diseases, which was not included in the multivariate analysis. Moreover, some patients developed hepatic encephalopathy. Taken together, these results strongly suggest that most (if not all) patients with yellow fever who died actually developed acute liver injury or liver failure, although the authors did not specify this diagnosis.²

Since symptomatic yellow fever is commonly heralded by persistent fever, it is reasonable to hypothesise that paracetamol is frequently ingested in the interval between onset of symptoms and hospital admission (and even during hospitalisation). Doses of paracetamol greater, and sometimes smaller, than 4 g daily have been associated with unintentional overdose with acute liver failure, especially in people who consume alcohol or during starvation.² Moderately increased bilirubin and high baseline concentrations of serum creatinine, two features of hospitalised patients with yellow fever,¹ are also common in paracetamol-associated acute

liver failure,² thus suggesting that, apart from high viral load, severe paracetamol-induced liver injury could be an important cofactor of liver failure in patients with yellow fever and their 36% fatality rate.¹ Paracetamol was reported as a cofactor of acute liver failure due to hepatotropic viruses A, B, and E.

Accordingly, the following therapeutic recommendations could be proposed for improving the survival of symptomatic patients suspected to have yellow fever: cessation of paracetamol administration and early intravenous administration of N-acetylcysteine, the antidote to paracetamol hepatotoxicity, in patients with an international normalised ratio greater than 1.5, and also in patients in whom recent paracetamol ingestion is denied or absent.² Early administration of N-acetylcysteine was associated with a high survival rate in two independent, uncontrolled, short case series of patients with dengue fever—another arboviral infection—and early acute liver failure.^{3,4}

We declare no competing interests.

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- 1 Kallas EG, D'Elia Zanelli LGFAB, Moreira CHV, et al. Predictors of mortality in patients with yellow fever: an observational cohort study. *Lancet Infect Dis* 2019; **19**: 750–58.
- 2 Lee WM. Acetaminophen (APAP) hepatotoxicity—isn't it time for APAP to go away? *J Hepatol* 2017; **67**: 1324–31.
- 3 Kumarasena RS, Senanayake SM, Sivaraman K, et al. Intravenous N-acetylcysteine in dengue-associated acute liver failure. *Hepatol Int* 2010; **4**: 533–34.
- 4 Tan S-S, Bujang MA. The clinical features and outcomes of ALF associated with dengue infection in adults: a case series. *Braz J Infect Dis* 2013; **17**: 164–69.