MEDICAL COUNTERMEASURES
Status of Supplies and Distribution/Allocation Systems

Prepared by Divya Hosangadi

CAPS Antiviral

- In addition to vaccines, monovalent antibody therapies and antivirals have been investigated for treating coronavirus infections (Table 1).
- In this scenario, **extranavir** is a FICTIONAL antiviral drug.
    - Extranavir is currently used to treat HIV but has been shown to be an effective treatment for CAPS.
    - Extranavir may be an effective prophylactic if given throughout a period of possible exposure to the virus.
    - When used as a therapeutic, extranavir may reduce the severity of disease and length of viral shedding in infected individuals.
    - Extranavir is a generic drug that is manufactured in 5 countries, including the US and China.
    - About 1 million people per day take extranavir to treat HIV.
    - If all extranavir users were switched to a different HIV treatment, current supplies of the antiviral could treat up to 26 million CAPS patients.
    - It may be possible to double production of extranavir by expanding existing manufacturing capacity and by licensing the drug to additional manufacturers. This expansion could allow for 52 million treatment courses per year but would likely require a year to reach that capacity.
    - If extranavir were used broadly as a prophylactic rather than a treatment, a much greater supply of the drug would be needed.

Current Vaccines in Development

- There are no vaccines currently licensed and available for use against any coronavirus. Coronavirus vaccines for SARS and MERS have been technically challenging to develop and have not made it out of clinical trials.[1-3]

- While scientists are researching a vaccine against the FICTIONAL CAPS virus, there is currently no product in development.
- Development of a vaccine against the CAPS virus will likely take years to achieve. The vaccine development process can take more than a decade.[4] In pandemic situations, the timeline for vaccine development could possibly be shortened, but developing and manufacturing a vaccine against CAPS in time to control this pandemic is unlikely.
- Vaccines against SARS or MERS coronaviruses would likely not be protective against CAPS, because coronaviruses are prone to genetic reassortment; therefore, a vaccine against one coronavirus is not cross protective against another coronavirus.[1,5]
- Some experiments have raised the possibility that immunity incurred from certain coronavirus vaccines can be short lived[6,7] and that enhanced disease may result from certain coronavirus vaccines.[6-8] This has prompted some concern that vaccines targeting coronaviruses (eg, MERS, SARS) could lead to adverse events.

Table 1: SARS and MERS Coronavirus Vaccine and Therapy Trials Listed on ClinicalTrials.gov

	Clinical Trial Status	SARS	MERS
Vaccines	Recruiting	0	1[9]
	Active	0	0
	Completed	2[10,11]	0
	Withdrawn or unknown status	2[12,13]	0
Therapies or Treatments	Recruiting	0	1[14]
	Active	0	0
	Completed	0	3[15-17]
	Withdrawn or unknown status	1[18]	1[19]

Current Medical Countermeasure Distribution and Allocation Systems

- Current supply chain mechanisms exist to distribute vaccines and other medical countermeasures (MCMs) on a routine basis. However, a centralized and scalable MCM distribution system for use during pandemics does not exist.
- Multiple systems and stakeholders can facilitate MCM distribution in smaller scale public health emergencies and could be either scaled up or provide lessons for a pandemic context. These include:
    - The International Coordinating Group on Vaccine Provision (ICG),[20] a coordinating group of key global health stakeholders, including the World Health Organization (WHO), UNICEF, Médecins Sans Frontières (MSF), and the International Federation of the Red Cross. The goal of this group is to handle the allocation of particular vaccine stockpiles for specific diseases (cholera, meningococcal meningitis, yellow fever).
    - WHO also has stockpiles for other diseases, including smallpox and pandemic influenza.[21]
    - WHO Contingency Fund for Emergencies[22]
        - Can release initial funds up to $500K in 24 hours
        - Serves as the potential source of funds for initial emergency response if properly funded
    - The US President's Emergency Plan for AIDS Relief (PEPFAR) is a US-funded program to control the HIV/AIDS epidemic and is the largest effort by any one nation to control a disease.[23] PEPFAR funds programs aimed at expanding access to HIV treatments and prevention services in low-income settings.[23,24]
    - Gavi, the Vaccine Alliance, procures vaccines for low-income countries for selected routine and emergency immunization. For example, the organization procured $300 million for Ebola vaccines during the 2014-2016 Ebola outbreak.[25]
- Challenges with ensuring equitable access to and distribution of MCMs have been encountered in the past. Countries have withheld sharing samples in an effort to secure access to MCMs.[26,27]

Medical Countermeasure Development and Manufacturing Is Challenging

- In general, several technical barriers make the rapid scale-up of vaccine manufacturing challenging, including a lack of R&D and manufacturing capacity due to competing interests, the cost of establishing or repurposing manufacturing facilities, regulatory barriers, and the lack of a consistent market.[4,28,29]

References

1. Zhang N, Tang J, Lu L, Jiang S, Du L. Receptor-binding domain-based subunit vaccines against MERS-CoV. *Virus Res* 2015;202:151-159.
2. Song Z, Xu Y, Bao L, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses* 2019;11(1):E59.
3. US Food and Drug Administration. Vaccines Licensed for Use in the United States. Updated May 9, 2019. http://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states. Accessed October 9, 2019.
4. Gouglas D, Thanh Le T, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *Lancet Glob Health* 2018;6(12):e1386-e1396.
5. Menachery VD, Graham RL, Baric RS. Jumping species—a mechanism for coronavirus persistence and survival. *Curr Opin Virol* 2017;23:1-7.
6. Cho H, Excler JL, Kim JH, Yoon IK. Development of Middle East Respiratory Syndrome Coronavirus vaccines—advances and challenges. *Hum Vaccin Immunother* 2018;14(2):304-313.
7. Honda-Okubo Y, Barnard D, Ong CH, Peng B-H, Tseng C-TK, Petrovsky N. Severe acute respiratory syndrome-associated coronavirus vaccines formulated with delta inulin adjuvants provide enhanced protection while ameliorating lung eosinophilic immunopathology. *J Virol* 2015;89(6):2995-3007.
8. Gillim-Ross L, Subbarao K. Emerging respiratory viruses: challenges and vaccine strategies. *Clin Microbiol Rev* 2006;19(4):614-636.
9. National Institutes of Health. Safety and Immunogenicity of a Candidate MERS-CoV Vaccine (MERS001). ClinicalTrials.gov. Updated May 10, 2019. https://clinicaltrials.gov/ct2/show/NCT03399578. Accessed October 8, 2019.

10. National Institutes of Health. Phase I Study of a Vaccine for Severe Acute Respiratory Syndrome (SARS). ClinicalTrials.gov. Updated July 2, 2017. https://clinicaltrials.gov/ct2/show/NCT00099463. Accessed October 8, 2019.
11. National Institutes of Health. Study of Alferon® LDO (Low Dose Oral) in Normal Volunteers. ClinicalTrials.gov. Updated April 17, 2013. https://clinicaltrials.gov/ct2/show/NCT00215826. Accessed October 8, 2019.
12. National Institutes of Health. SARS Coronavirus Vaccine (SARS-CoV). ClinicalTrials.gov. Updated December 3, 2012. https://clinicaltrials.gov/ct2/show/NCT00533741. Accessed October 8, 2019.
13. National Institutes of Health. Phase I Dose Escalation SARS-CoV Recombinant S Protein, With and Without Adjuvant, Vaccine Study. ClinicalTrials.gov. Updated February 15, 2013. https://clinicaltrials.gov/ct2/show/NCT01376765. Accessed October 8, 2019.
14. National Institutes of Health. MERS-CoV Infection Treated with a Combination of Lopinavir /Ritonavir and Interferon Beta-1b. ClinicalTrials.gov. Updated March 7, 2019. https://clinicaltrials.gov/ct2/show/NCT02845843. Accessed October 8, 2019.
15. National Institutes of Health. Safety, Tolerability, and Pharmacokinetics of SAB-301 in Healthy Adults. ClinicalTrials.gov. Updated June 12, 2018. https://clinicaltrials.gov/ct2/show/NCT02788188. Accessed October 8, 2019.
16. National Institutes of Health. Safety, Tolerability and Immunogenicity of Vaccine Candidate MVA-MERS-S. ClinicalTrials.gov. Updated October 2, 2019. https://clinicaltrials.gov/ct2/show/NCT03615911. Accessed October 8, 2019.
17. National Institutes of Health. A Safety, Tolerability, Pharmacokinetics and Immunogenicity Trial of Co-administered MERS-CoV Antibodies REGN3048 and REGN3051. ClinicalTrials.gov. Updated February 1, 2019. https://clinicaltrials.gov/ct2/show/NCT03301090. Accessed October 8, 2019.
18. National Institutes of Health. A Multi-centre, Double-blinded, Randomized, Placebo-controlled Trial on the Efficacy and Safety of Lopinavir/Ritonavir Plus Ribavirin in the Treatment of Severe Acute Respiratory Syndrome. ClinicalTrials.gov. Updated August 22, 2013. https://clinicaltrials.gov/ct2/show/NCT00578825. Accessed October 8, 2019.
19. National Institutes of Health. Anti-MERS-CoV Convalescent Plasma Therapy. ClinicalTrials.gov. Updated November 21, 2018. https://clinicaltrials.gov/ct2/show/NCT02190799. Accessed October 8, 2019.
20. World Health Organization. International Coordinating Group (ICG) on Vaccine Provision. April 3, 2019. http://www.who.int/csr/disease/icg/en/. Accessed October 8, 2019.

21. Yen C, Hyde TB, Costa AJ, et al. The development of global vaccine stockpiles. *Lancet Infect Dis* 2015;15(3):340-347.
22. World Health Organization. *Enabling Quick Action to Save Lives: Contingency Fund for Emergencies*. 2018. http://origin.who.int/emergencies/funding/contributions/cfe-impact-report-web2018.pdf. Accessed October 14, 2019.
23. US Department of State. About Us – PEPFAR. https://www.state.gov/about-us-pepfar/. Accessed October 9, 2019.
24. US Department of State. *PEPFAR 2018 Progress Report: PEPFAR Strategy for Accelerating HIV/AIDS Epidemic Control (2017-2020)*. https://www.state.gov/wp-content/uploads/2019/08/2018-PEPFAR-Strategy-Progress-Report.pdf. Accessed October 14, 2019.
25. Gavi. Gavi commits to purchasing Ebola vaccine for affected countries. December 11, 2014. https://www.gavi.org/library/news/press-releases/2014/gavi-commits-to-purchasing-ebola-vaccine-for-affected-countries/. Accessed October 8, 2019.
26. Baumgaertner E. China has withheld samples of a dangerous flu virus. *New York Times* August 27, 2018. https://www.nytimes.com/2018/08/27/health/china-flu-virus-samples.html. Accessed October 8, 2019.
27. CIDRAP. Roos R. Indonesia details reasons for withholding H5N1 viruses. CIDRAP July 15, 2008. http://www.cidrap.umn.edu/news-perspective/2008/07/indonesia-details-reasons-withholding-h5n1-viruses. Accessed October 8, 2019.
28. Pronker ES, Weenen TC, Commandeur HR, Osterhaus AD, Claassen HJ. The gold industry standard for risk and cost of drug and vaccine development revisited. *Vaccine* 2011;29(35):5846-5849. d
29. Adalja AA, Watson M, Cicero A, Inglesby T. *Vaccine Platforms: State of the Field and Looming Challenges*. Johns Hopkins Center for Health Security. 2019. http://www.centerforhealthsecurity.org/our-work/publications/vaccine-platforms-state-of-the-field-and-looming-challenges. Accessed October 14, 2019.