World Health Organization

WHO consultation on Marburg Vaccines and Therapeutics

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Powering research to prevent epidemics

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Conclusions

Review history, including recent outbreaks, Ghana, Guinea, Uganda. Rousette & other bat vector. 2 recent cases in Ghana appear to be unrelated. 63 contacts identified. One symptomatic HCW tested negative. Guinea 2021 1 case (173 contacts followed). Challenges: accessibility, cultural beliefs/attitudes, contact tracing, human resources, porous borders. Understanding factors that lead to human infections. Transmission rates among humans are variable but R0 can be <1.

Lab investigation in Ghana: 10 June received 2 clinical specimens- human blood sera 3-4 ml each. Panel of VHS (Ebola, Marburg, Lassa, Dengue, Zika); Marburg was positive on both so repeat test was done (also conventional PCR) and test was positive on repeat. 2 suspected cases have been negative Contacts tested so far have been negative.

Developers:

Auro vaccines: rVSV/ Marburg gp. Process Development completed. Engineering run underway. GMP run Late 2022/Early 2023. Phase I Q2, 2023.

JnJ: No active Marburg program, but willing to support evaluation or outbreak control. Clin material from multivalent Ad26 (3500 vials) & MVA-BN-Filo (4800 vials) is available. Some preclinical & Ph I data are available.

Conclusions

PH Vaccines: rVSV-MARV Marburg Angola, protection in GP & cynos. Tox & Biodistribution on Engineering Lot completed. GMP run complete & testing ongoing. Clin assays verified. IND 4Q 2022.

Sabin Institute: ChAd platform single dose. Marburg & Sudan under development. 5K safety database with platform. NHP shows rapid efficacy (within 1 wk) & durability to about 1 yr. IgG anti gp responses correlate (better than neuts) with survival (supporting immunobridging strategy) plus IFN-γ producing T cells. Vaccine safe & produces IgG in human Ph I study @ levels similar to protective level in NHPs, Ph II pending in Africa. Product made & released. ~700 doses available pending shelf life extension. (>10K doses drug material available, but not yet vialed)

BARDA: Investing in several of these candidates & tracking pipeline. Funding non-clin & natural history studies. Goal of intermediate level preparedness with some clinical data & some vaccine on hand.

IAVI: VSVΔG-MARV-GP Musoke. Prelinical complete. Biodistribution, tox, NHP studies complete. GMP for Ph1 Fall 2022, IND & Ph I mid 2023.

Conclusions

Summary of developers: 2 vaccines with phase I data & potential dose availability, others will have phase I data within next year or so. Recommend filling more Sabin vials.

Trial design: multi-center, multi-vaccine, shared placebo. Individual randomization within population @ risk & transmission clusters where feasible, otherwise cluster randomized; allows these designs to be blended. Protocol is available, article in press. Primary endpoint: Rate of virologically confirmed disease, regardless of severity. Sample size 150 cases over two arms (20K per arm in more general population). Contemplated study across outbreaks. Need to avoid multiple small trials.

Practical importance of getting going quickly. What can be done between outbreaks to plan? Workshop to discuss vaccines & protocols? Set of criteria for introducing vaccines into trials, plus transparent process (e.g., prioritization group). What do we need- Target Product Profile that is generally agreed upon. Engage regulators in Africa & elsewhere to inclusively discuss trial sites, capacity etc. Governance framework needed for studies.

There needs to be coordinated vaccine selection in order to have a hope of getting useful results in a clinical trial.

Conclusions

Human to human transmission is rare (< half of cases except in Angola), so ring vaccination by itself may not be sufficient. Need to include cave exposure, minimize arms based on number of cases.

Immediate needs: TPP, prioritization committee (also consider safety/immunogenicity database before entry into study, manufacturing needs & availability), protocol updates, SAP. Consider rolling process. Critical that the consortium stays together on this and collaborates.

THERAPEUTICS

mAb Mappbio:mBP091 binds GP near receptor binding site & neutralizes, high efficacy (100%) in GP & NHP when given @ D4 or D5 post challenge (n=6 each group). CHO cell produced. In phase I. Planning for animal rule.

PEP using vaccines or therapeutics: Angola more aggressive, but NHP studies show protection in PEP with various vaccines or therapeutics. Combination of mAb + remdesivir better than either alone @ d6.

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Remdesivir approval being sought via animal rule. NHP ~80% efficacy. Natural history study completed. Is available for potential off label use.

Human studies are viewed as important. Timing of diagnosis may limit studies of early treatment. Combinations may be more effective than individual agents, though numbers may be too small to do factorial design studies & Ph I data may be needed.

Coordination of studies using a common protocol provides the best hope of collecting useful data, much as has been discussed for vaccines (including similar prioritization scheme). Drugs could be studied under MEURI, randomized study to collect standardized data. A small group will develop plans. Volunteers to help are sought.