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WHO Prioritizes Next-Generation Filovirus Vaccines for Bundibugyo and Sudan Ebola Outbreak Trials

Ebola Virus * Filoviridae * Vaccinology

The Antigenic Blind Spot of First-Generation Zaire Ebola Vaccines

Over the past decade, emergency deployment of the licensed recombinant vesicular stomatitis virus vaccine Ervebo (rVSV-ZEBOV-GP) and the heterologous two-dose regimen Zabdeno/Mvabea (Ad26.ZEBOV + MVA-BN-Filo) transformed the containment of classical Ebola virus disease caused by Orthoebolavirus zairense (EBOV), achieving 97.5% ring- vaccination efficacy during epidemics in West Africa and the Democratic Republic of the Congo (DRC). However, the genus Orthoebolavirus (family Filoviridae) encompasses multiple antigenically distinct species that periodically spill over from chiropteran reservoir hosts into human populations: most notably Orthoebolavirus bundibugyoense (Bundibugyo virus, BDBV) -- first identified in western Uganda in 2007 with case fatality rates of 25% to 51% -- and Orthoebolavirus sudanense (Sudan virus, SUDV) , which carries a historical case fatality rate of 41% to 65%.

The trimeric surface glycoprotein (GP 1,2) is the sole viral envelope protein mediating attachment and endosomal membrane fusion via the host late-endosomal cholesterol transporter Niemann-Pick C1 (NPC1) . Across Orthoebolavirus species, GP 1,2 diverges by 35% to 45% at the amino acid level , with variation concentrated in the heavily glycosylated outer glycan cap and mucin-like domain (MLD) that shield the conserved receptor-binding site prior to endosomal cathepsin B/L proteolysis. Consequently, neutralizing Immunoglobulin G (IgG) antibodies elicited by monovalent Zaire ebolavirus Ervebo fail to cross-neutralize either Bundibugyo virus or Sudan virus in vivo.

The Tumaini and TOKEMEZA Intra-Outbreak Clinical Trial Frameworks

To close this antigenic gap during active filovirus spillovers, the World Health Organization (WHO) independent Technical Advisory Group on Candidate Vaccine Prioritization has backed the integration of two species-specific Bundibugyo vaccine candidates into the ongoing Tumaini clinical trial in the DRC -- spearheaded by the Institut National de Recherche Biom dicale (INRB) in collaboration with Africa CDC, CEPI, and M decins Sans Fronti res (MSF):

* ChAdOx1 BDBV and ChAdOx1-BiEBOV (University of Oxford / Serum Institute of India): Replication-deficient simian adenovirus vector platforms encoding full-length filovirus GP 1,2 antigens, engineered to induce both rapid humoral neutralizing titers and CD8 + cytotoxic T-cell responses without pre-existing human anti-adenovirus-5 immunity.

* mRNA -1469 (Moderna): A nucleoside-modified lipid -nanoparticle (LNP) messenger RNA vaccine encoding native-like trimeric Bundibugyo GP 1,2 , designed to drive high-titer germinal-center B-cell affinity maturation and Fc-mediated

opsonophagocytic clearance.

This expansion directly parallels the TOKEMEZA SVD intra-outbreak ring-vaccination protocol launched in Uganda at the Makerere University Lung Institute within just four days of Sudan virus disease notification, which deployed the International AIDS Vaccine Initiative (IAVI) live-attenuated rVSV-SUDV vector alongside the Sabin Vaccine Institute's chimpanzee adenovirus candidate ChAd3-EBO-S .

Comparative Telemetry of Priority Non-Zaire Orthoebolavirus Vaccine Candidates

| Vaccine Candidate & Developer | | Viral Vector / Delivery Platform | | Target Species & Antigen | | Clinical Trial Framework | | Key Immunogenicity & Deployment Telemetry |

| ChAdOx1 BDBV / ChAdOx1-BiEBOV (Oxford / Serum Institute) | | Non-replicating simian adenovirus (ChAdOx1) | | O. bundibugyoense GP 1,2 (or bivalent EBOV + SUDV GP 1,2) | | Tumaini Trial (INRB / WHO, DRC) & UK/Tanzania Phase 1 | | 100% seroconversion after single intramuscular dose (2.5 x 10 10 viral particles); thermostable cold-chain logistics (2-8 deg C) |

| mRNA-1469 (Moderna / CEPI) | | Ionizable lipid nanoparticle (LNP) modified mRNA | | O. bundibugyoense full-length membrane GP 1,2 | | Tumaini Trial (INRB / WHO, DRC) | | Rapid translation of prefusion-stabilized GP trimers on host antigen-presenting cell surfaces; avoids anti-vector immunity |

| rVSV-SUDV (IAVI / Merck / BARDA) | | Replication-competent vesicular stomatitis virus (rVSVDeltaG) | | O. sudanense (SUDV) surface glycoprotein | | TOKEMEZA SVD Ring Trial (Uganda / WHO) | | Chimeric VSV backbone matching Ervebo; single-dose rapid mucosal and systemic IgM/IgG induction within 7-14 days |

| ChAd3-EBO-S (cAd3-EBO S) (Sabin Vaccine Institute / NIAID VRC) | | Replication-defective chimpanzee adenovirus type 3 | | O. sudanense (SUDV) wild-type glycoprotein | | Uganda Phase 1b & TOKEMEZA SVD preparedness | | Single 1 x 10 10 or 1 x 10 11 particle unit dose elicited binding IgG in 95-100% of Ugandan adults by day 28 with durable memory T cells |

Ring Vaccination Kinetics and Basic Reproduction Number Suppression

Because non-Zaire filovirus outbreaks are sporadic and geographically focal (typically 20 to 200 cases per spillover event), traditional randomized placebo-controlled Phase 3 trials involving tens of thousands of unexposed volunteers cannot accumulate sufficient case endpoints. Instead, WHO's pre-positioned Core Protocol utilizes a cluster-randomized ring vaccination design modeled on the 2015 Guinea Ebola a Suffit! trial. Immediately upon laboratory confirmation of an index case by reverse-transcription quantitative polymerase chain reaction (RT-qPCR), field epidemiologists trace all primary contacts and secondary contacts-of-contacts (forming an epidemiological ring of ~50-100 individuals) and randomize rings to immediate versus delayed (21-day) vaccination. By immunizing rings within a 4-to-7-day operational window -- shorter than the 8-to-12-day mean incubation period of filoviral hemorrhagic fever -- species-matched vaccines drive the effective reproduction number R e below the epidemic threshold of 1.0 while

simultaneously generating licensure-grade vaccine efficacy data during a single outbreak.

References & Primary Sources

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