GVIRF 2018 Workshop 9: Antibody-Mediated Prevention	
Rapporteurs: Paula Bryant (NIAID) and Angela Hwang (Consultant)	
Session Outline	**Chair:** Nina Russell (Deputy Director, HIV, Bill & Melinda Gates Foundation) **Presentations:** *Pipeline of HIV monoclonal antibodies for prevention of HIV,* Barney Graham (Deputy Director, Vaccine Research Center, NIAID) *Monoclonal antibodies for rabies post-exposure prophylaxis,* Erin Sparrow (Technical Officer, WHO) *Monoclonal Antibodies for Influenza Prevention, Therapy, or Vaccine Antigen Design,* Bruce Innes (Global Head, Respiratory Infections and Maternal Immunization, PATH) *Antibody Engineering: Optimization of Antibodies for Commercialization:* Steve Hadley (Senior Program Officer, Bill & Melinda Gates Foundation) **Panelist:** Filip Dubovsky (Vice President, MedImmune)
Objectives of the session	*To discuss:* • The pipeline of monoclonal antibodies (mAbs) to combat HIV, influenza and rabies • The latest developments for therapeutic antibody engineering and optimization
Main outcome	Monoclonal antibodies are an attractive prophylactic and/or therapeutic approach to developing effective countermeasures against infectious diseases. However, for application in low-income countries, costs must be reduced, supply must be increased, and robust regulatory and development guidelines are needed. The establishment of a clear WHO prequalification pathway for prophylactic and therapeutic Abs for infectious diseases is essential.
Summary	**HIV.** Passive antibody prevention of HIV/SHIV infections was shown in non-human primates more than 25 years ago, and broadly neutralizing HIV-1 mAbs for use in humans are currently in development. The Antibody Mediated Prevention (AMP) studies are testing the VRC01 antibody administered intravenously every 8 weeks. These Phase 2 studies in 4600 high risk adults in Africa and the Americas should provide proof-of-concept for antibody-mediated prevention and data on correlates of preventive efficacy in the 2020 timeframe. Additional Phase 1 studies with other monoclonal and bi-specific antibodies are planned and underway. In parallel, antibodies are being optimized to increase half-life, improve potency, and broaden coverage. To avoid escape, combinations of at least 2 mAbs will likely be needed. Combination products are being explored and efficacy data could be available in 2022. Planning for success should include developing new business plans

	for large scale manufacturing and product deployment and will require the establishment of clear approval pathways. **Rabies** causes an estimated 60k deaths per year, mostly in poor rural populations in Africa and Asia. Approximately 15M people are administered post-exposure prophylaxis, consisting of rabies vaccine accompanied in instances of severe exposure by rabies immunoglobulin (RIG) administered to the wound. Because human and equine blood-derived RIG are expensive and in short supply globally, prophylactic mAbs are seen as an attractive potential alternative to supplement supply, reduce production costs, and improve safety. The first rabies mAb, Rabishield, has been approved in India based on neutralizing titers compared to RIG. Two other products are in Phase 3 clinical trials. To facilitate the licensure and use of rabies mAbs, the US FDA has held a workshop to clarify regulatory considerations and SAGE is issuing recommendations for use of rabies mAbs. Inclusion in the WHO Essential Medicines list, treatment guidelines, WHO prequalification, and procurement and supply are still needed to enable widespread use. **Influenza**. Broadly protective mAbs for influenza have applications in the treatment of severe influenza; prevention of infection, especially when vaccination is infeasible such as during an advancing pandemic; and for vaccine antigen discovery. The influenza mAb pipeline includes candidates targeting the hemagglutinin stalk and matrix protein 2 ectodomain. All of these mAbs have been evaluated in human challenge models with a confirmed effect on virus shedding when administered post-challenge. The clinical relevance of reduced virus shedding remains uncertain and an improved human challenge system that accurately models human disease would invigorate the field. Additional areas to explore include anti-neuraminidase mAbs, which also have the potential to be broadly protective, and aerosol delivery via inhalation using nebulizers, which can deliver antibodies more efficiently to the respiratory tract. **Antibody engineering** is being used to improve potency, pharmacokinetics and productivity of mAbs in order to meet challenging target product profiles. Improved variants of candidate HIV mAbs identified by computational analysis show improved thermal stability and other characteristics which support developability. These variants could potentially be produced using an optimized CHO platform for as little as $10/kg. Innovative manufacturing approaches to reduce production costs include alternative hosts and novel expression systems such as nucleic acid delivery or synthetic biology.