GPP Case Study: Passive Immunization Efficacy Trials

Background

Passive immunization refers to the transfer of pre-made antibodies to a person to protect against a particular pathogen. By contrast, traditional, preventive vaccines prompt the recipient's immune system to create antibodies on its own and remember the response. Passive immunity occurs in nature, e.g., maternal antibodies are transferred to infants during breast-feeding.

Research

Passive immunization has been used for other diseases, e.g., individuals receive pre-existing antibodies against hepatitis A and rabies as part of vaccination or treatment. For HIV, transfer of antibodies has been studied as a possible treatment approach after infection. Studies in the early years of the epidemic that investigated the efficacy of passive immunization in mother-to-child-transmission (MTCT) did not demonstrate evidence of protection. However, in subsequent years, scientists have identified a new generation of more potent broadly neutralizing antibodies (bNAbs). Certain bNAbs are now being studied for passive immunization.

Scientists are researching other new technologies for producing antibodies against HIV in the laboratory setting, which led them to be considered for study in humans. As of 2014, research included laboratory and animal studies as well as some early clinical studies in pregnant women and in other HIV-positive and HIV-negative individuals. To determine if the approach is effective for prevention, large efficacy trials would need to be conducted in populations of higher HIV risk whose likely time of exposure could be identified. One ideal population would be pregnant women and their newborn infants, especially pairs where the mother was not on GPP Case Study: Passive Immunization Efficacy Trials ART during pregnancy, for prevention of vertical transmission.

The Scenario

Despite the increase in HIV prevention strategies using anti-retroviral therapy (ART) across the developing world, finding effective ways to improve prevention among pregnant women, new mothers, and their infants still remains a public health priority. The majority of MTCT occurs after birth through breast-feeding, but women's access to and uptake of ART is sometimes complicated by social, economic, and cultural barriers, especially in resource limited countries. Implementation challenges associated with the scale up of HIV treatment in these countries, such as cost, logistics, and inadequate health systems, may also prohibit access to ART. Women who are infected with HIV late in pregnancy or during lactation have high rates of breast milk transmission, are often missed by treatment strategies, and may benefit from additional prevention options such as passive immunization. Designing and conducting feasible and acceptable clinical trials to

demonstrate the efficacy of this approach, however, is a complex and expensive undertaking that requires preparedness of the surrounding communities and potential participants as well as broad stakeholder support.

GPP-Relevant Issues

Scientific validity and integrity. Given global HIV treatment scale-up both in terms of targets and coverage, one may question the necessity and validity of passive immunization research. Trials are logistically and ethically complex and can raise expectations or cause controversy among stakeholders. Some may argue that ongoing investment in scale-up of existing ART programs should be the public health priority.

Participant protection. Passive immunization trials require a large number of pregnant women who are at higher risk of HIV transmission and start ART only in the last stage of pregnancy. Typically, these women present late to antenatal care, e.g., during third trimester, and are often times more vulnerable due to structural factors. Reproductive health advocates have historically expressed concern about pronounced vulnerability of pregnant women and unborn children in the research context; a woman's ability to give voluntary informed consent for herself and her fetus during a late stage of pregnancy – when possibly grappling with a recent HIV diagnosis – may be debatable. In order to ensure that trial procedures adequately protect participants' rights and welfare, researchers can work with stakeholders to design thoughtful approaches to educating and assessing comprehension of participants, engagement of male partners, and mitigation of trial-related harms, like disclosure of participant HIV status.

Research literacy and innovative trial design. Stakeholders external to research typically have more limited experience or understanding of passive immunization and its rationale. Individuals may also may have difficulty distinguishing between passive immunity and long-term immunity induced by traditional vaccines. Research teams will need to collaborate with local NGOs, potential participants, media, and other community representatives to discuss recruitment and retention strategies, appropriate standards of care for mothers and their infants, communications and messaging, and ways of managing community perceptions and expectations of the trial.

GPP-Relevant Actions

Early stakeholder engagement and follow-up. A particular research group works to identify bNAbs that may be effective in passive immunization. Working with a number of collaborators, the group organized a consultation to begin to look at design of a large-scale efficacy trial in sub-Saharan Africa. This consultation brought together invested research groups, reproductive health sector representatives, policymakers, and AIDS civil society representatives. Participants discussed the scientific rationale and key considerations for the design and conduct of a large-scale passive immunization trial, including the trial population, sample size, and possibilities of obtaining informed consent from pregnant women during the late stages of pregnancy.

While the research group's plans for efficacy trials were still in early planning stages, this consultation helped clarify some of the complexities of trial design through stakeholder input,

including from those who may question or oppose the trial if they had not helped shape these pieces of it.

The case also highlights the complexities of limited relationships between research groups and stakeholders, especially well in advance of a trial. If stakeholders, especially those who may not be regularly engaged with research, are consulted early in the planning process, they will likely need regular follow up. A meeting report was circulated following the described consultation; however, even over a year post-consultation, stakeholders had not received updates from research groups on plans and processes for a potential trial.

Lessons Learned

Conducting complex clinical trials with vulnerable groups raises a number of ethical and logistical challenges. This case study provides an example of innovative good participatory practices for protocol development and informed consent and illustrates that early engagement of stakeholders:

- Helps clarify complex issues around trial design, and issues that will impact long-term, advance planning for efficacy trials;
- Can be effective when well planned and executed with needs and interests of stakeholders in mind;
- Requires, at minimum, semi-regular follow-up with stakeholders to maintain their support and to ensure their input is incorporated as plans progress;
- Must be done carefully, especially when timelines and concrete plans are still unclear, so as not to raise community stakeholder expectations.