A UNIVERSAL INFLUENZA VIRUS VACCINE CANDIDATE CONFERS PROTECTION AGAINST PANDEMIC H1N1 INFECTION IN FERRETS

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Influenza viruses can cause severe disease and mortality in humans. Due to constant change in their immuno-dominant antigenic sites they can evade adaptive immune responses. Current seasonal influenza virus vaccines therefore require annual re-formulation and re-administration to confer protection from circulating viruses. Additionally, these vaccines cannot protect against novel pandemic influenza virus strains. Novel vaccination approaches attempt to refocus antibody responses towards more conserved domains like the hemagglutinin stalk. Antibodies against the stalk domain are broadly-reactive and can neutralize multiple influenza virus subtypes. However, the stalk domain is immuno-subdominant and not preferentially targeted by the immune system. In this study, we tested if a vaccination strategy based on influenza viruses expressing chimeric hemagglutinins (cH) that contain exotic, divergent head domains, but a conserved H1 stalk domain could induce cross-protective antibody responses in ferrets. We compared a heterologous live-attenuated virus (cH8/1N1) prime followed by an inactivated split virus (cH5/1N1) boost combination approach to two doses of split-virus vaccines (cH8/1N1/cH5/1N1) and the impact of adjuvant on the immune response. Additionally, a ‘standard of care’ control group received 2 rounds of a human trivalent influenza virus vaccine. We found that all universal influenza virus vaccination approaches were successful at inducing stalk-reactive antibody responses in serum. Virus replication was limited to the nasopharynx in the live attenuated/split vaccine groups and nasal wash titers were lower than in the 'standard of care' control group. No virus replication was detected in the lungs of attenuated/split vaccinated ferrets, while the 'standard of care' group had similarly high titers as an unvaccinated control group. Our findings demonstrate that - using a chimeric hemagglutinin based heterologous attenuated/split combination strategy - our candidate universal influenza virus vaccine can successfully protect ferrets from pandemic H1N1 infection. The data support further development of this vaccination approach and advancement into clinical trials.