World Health Organization

Statistical and Mathematical Modeling for H5N1 Pandemic

Meeting summary

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Outline of current threat and potential mitigation

Increased frequency of mammalian outbreaks, including in companion animals, so far with limited transmission, indicates that current H5N1 HPAI virus is most dangerous yet. In cows, respiratory infection is transient. Some potential spread from cattle to poultry. Differences between receptors, pH phenotype for cattle vs human infection. Cattle vaccination may be considered. Recommendation: active surveillance (w. whole genomic sequencing), sensitization of stakeholders, emergency preparedness & contingency planning for HPAI. Suggested areas for modeling: human animal interface, animal transmission

Constant animal outbreaks. 360 outbreaks worldwide since 1 October 2024. So far, human cases are associated with animal outbreaks. US 2.3.4.4b: 7% of participating US dairy workers seropositive, all mild or no symptoms. SE Asia: recent active reassortment between earlier 2.3.2.1c and 2.3.4.4b. Current vaccine candidates reasonably cover 2.3.4.4b viruses but not 2.3.2.1.c viruses. New candidates being developed. Current risk for global public health considered low, but risk for occupational exposure low-moderate.

Outline of current threat and potential mitigation

Summarize key epi parameters for 2.3.4.4b H5N1 in humans. Human cases have been relatively mild. R0 0.04-0.05 (upper bound 0.08-0.09). 2007 Indonesia outbreak estimated R0 >1.0 with human to human transmission. Seroprevalence overall meta analysis 0.3%; Higher in exposed workers in US & Egypt. Serial interval ~8-9 days and incubation period 3.5-5 d are longer than in other flu. Infectious period uncertain, possibly longer than other flu. Viral load detectable many days after infection. Fatality risk high but variable. US no deaths/46 cases.

US plans include CSL sequirus vaccine, Sanofi/GSK (combined Sanofi egg-based plus AS03, not approved as adjuvanted vaccine) and GSK (antigen+ AS03). Response to US outbreak: 3 Clin trials, additional antigen procurement. GSK Ph I/II formulations of A/Astrakhan/3212/2020 H5N8 as 2 dose series; CSL/Sequirus: n=480 Ph 2 Heterologous prime/boost with H5N8 (Astrakhan) or H5N6 MF59 adjuvanted; BARDA n=23*60 Sanofi vaccine adjuvanted with AS03 or MF59

Outline of current threat and potential mitigation

Antivirals: neuraminidase inhibitors (oseltamivir, peramivir, IV zanamivir) and cap-dependent endonuclease inhibitor baloxivir (single dose, more rapid impact on viral load, reduced transmission, though no difference in clinical outcomes). Drugs work for treatment, post-exposure prophylaxis. Oseltamivir significantly reduces hospitalizations, and survival improves with early initiation of treatment. Zanamivir less likely than oseltamivir or paramavir to induce resistance. In H5N1, oseltamivir treatment improved clinical outcome but resistant virus developed.. Pre-pandemic oseltamivir resistance H1N1 was ubiquitous, but resistance is currently low.

Non pharmaceutical Interventions: Reducing person to person contacts, making person to person contacts safer. Personal protective environmental, targeted, travel, community. Facemasks have limited effects in households, but lifting mask mandate in Hong Kong appeared to trigger influenza return. Some school based measures may have prevented COVID transmission. Decentralized digital contact tracing reduced COVID transmsisison iN UK. Lockdowns were most effective at preventing COVID transmission.

Characterizing a new virus in terms of critical epidemiological parameters

Early studies can estimate key epi parameters related to transmissibility and case severity. FFX= first few X (e.g., hundred) cases study to evaluate case severity and secondary infection risk, prospectively follow index cases and contacts 28 days & test for infection. Unity protocols also include other templates for key early studies.

Modeling tools can provide credible epidemiological parameters including citations. Other tools can analyze tranmission chains & estimate R0 and k from cluster sizes to predict outbreak sizes, epi delays, forecast/nowcaset infections, long term dynamics.

Gaps: Additional animal studies include domestic pig. Transmission and disease parameters once we see human-human transmission, identification of high risk groups. Combining datasets to accu

mulate aggregate numbers needed to accurately estimate parameters. Important to keep re-estimating parameters. Need surveillance systems to provide real-time data. Stakeholder engagement will increase quality of data and trust in models/modeling community. Many unknowns, need to collect and share more data.

Modelling effectiveness of containment measures during disease emergence

Early needs: targeted antivirals (treat cases and exposed), non-phamacolgoic interventions, pre- or rapidly deployed vaccines. Efficacy depends on early R0. Modeling of pandemic flu in Thailand considered different interventions, geographic targeted antivirals could contain epidemic if given early enough, but large number of modeling runs needed. Prevaccination even with low efficacy vaccine or mobile antiviral stockpile could be useful (5 million courses if feasible) if R0 is <1.4 and intervention occurs early enough..

Contact tracing should be methodical: case investigation, contact listing, contact follow-up, management of symptomatic contacts, contact discharge. Need accurate case definitions (confirmed, probable, suspected), community engagement and ownership with sensitive communication. Modeling needs to account for uncertainties in quality of execution of contact tracing.

Key needs: geographic modeling of spread (data are controlled by private entities which may impair accurate modeling, proxies may be useful). Modeling interaction of severity and disease detection. Addtional modeling with updated parameters. Model slowing down (as opposed to complete containment). Zoonotic modeling requires additional data inputs. ~~Deidentified data. Contact tracing, transmission chain reconstruction,~~

Modeling mitigation strategies in a global pandemic

Early modeling showed potential for improved public health outcomes, but may have included optimistic assumptions about case ascertainment and stockpiling. Some parameters may need to be updated (especially early in pandemic). Didn't model viral evolution, adaptive policies, border restrictions, contact tracing, healthcare demand, economic impacts. For 2009 H1N1 limitations included early estimates of CFR/IFR, changing estimates over time, data gaps. Many challenges persist, greater appreciation for political context and tension between different goals of different strategies, importance of considering range of scenarios. Need innovation in transmission models, improved global capacity and collaboration.

Geographical modeling has many limitations, but quite a bit can done. We can use models to look at the effectiveness of isolation, travel restrictions, border screening. Models can show that travel restrictions can possibly delay transmission by a day or two. The future utility of these models is substantial.