What research is important to prepare and respond to H5N1 influenza outbreaks?

Summary of key knowledge gaps and research priorities

Simon Funnell

What research is important to prepare and respond to H5N1 influenza outbreaks? Meeting overview of key knowledge gaps and research priorities

Current state of H5N1 mutations

Key knowledge gaps. H5N1 human cases seen in last year but more in 2015. Sustained human transmission not yet seen. 2.3.4.4b genotypes are dynamic and reassorting. Ferrets in Europe, sea mammals in South America and cows, mink, mice, alpaca, cats and birds (but not pigs) all affected in Texas. Position 199 appears to be the site responsible. **Possible spillover from D1.1 avian virus? How did it get into cows? How can we prevent further bovine infections?** Better surveillance of antiviral resistance. Conversion of IC50 to clinical efficacy. Sub-consensus level sequence analyses (raw reads uploaded). **Is human reassortment occurring in spillover cases? Could new immune modulators be present in emerging variants?**

Research priority. Surveillance. Which mutations should we be looking for? Should we target animals or humans? Proactive reporting in humans and animals to monitor genetic diversity for risk assessment. *e.g.* Milk silo testing. **Sensitive rapid diagnostics for real time monitoring.** Assurance that current countermeasures remain effective against new reassortments. **New infection models needed focus on human data**.

13:20 – 13:30 Overview of H5N1 Epidemiology Maria Van Kerkhove (WHO)
13:30 – 13:50 What have we learned about virus distributions from monitoring mutations? Michael Worobey (Uni Arizona)
13:50 – 14:00 Rate of virus mutation Sebastian Maurer-Stroh (GISAID)
14:00 – 14:10 Relationship between mutations and pathogenicity Barney Graham

Panel Discussion: Surveillance research

Key knowledge gap. Need to look at full genomes as well as HA. **Phenotypic impact of genetic changes**. New tools (**human infection models**) to assess impact of genotype changes on human infection. Genomic surveillance in animals (wild, livestock pets) and humans. Alternatives could be environmental sampling. Is **wastewater** testing feasible? Can we use **Bioinformatics and metagenomic sequencing** to accelerate agile risk assessment.

Research priority. Co-ordinated surveillance. Rapid full genome uploads (Nanopore). Diagnosis could be compromised unless specific PCR are designed from new mutations? Common mutation database with metadata. Strong veterinary and human laboratories. Need to share and match datasets and metadata. LFD equivalent (H5N1 or subtypes) for low cost and bedside or field testing. Tools to assess impact of reassortments. Assessment of high-risk occupations and environments. **One health connections**

What kind of surveillance is required?
How can we build proactive surveillance with sequencing looking at mutations in HA that would make increase sialic acid binding (especially aa positions 226 and 190)? Mutations beyond this?
How can research help expand continuous monitoring to understand and mitigate the potential public health risk associated with these developments? What research studies will lead to better understanding of serology in humans? What are the key research gaps?
Moderator Kanta Subbarao (Université Laval, Canada) - Bruno Lina (ANSES, France) - Anne Marie Rameix-Wleti (Pasteur, France) – Michael Worobey (University of Arizona) - Filip Claes (FAO, Italy) - Angeliki Melidou (ECDC, Sweden) - Hendra Wibawa (Disease Investigation Centre, Indonesia) - Faizah Hanim Mohd Saeid (Veterinary Research Institute, Malaysia) - Isabella Eckerle (Univ. Geneva)

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Overview of H5N1 vaccines

Key knowledge gap. More than 100 in development. 21 approved, 1 live attenuated. Most are 2 dose and inactivated. 10 indicated for children and elderly. Most target H1N1 and H5N1. SAE are rare but we should be prepared for late or low level sequalae. Most vet vaccines are inactivated. Vector vaccines, rH5N1 and mRNA. **Are we ready for next generation vaccines?** Regulatory hurdles are high.

14:50 – 15:00 Licensed and stockpiled vaccines Wenqing Zhang (WHO)
15:00 – 15:10 Influenza vaccines: Safety considerations Hanna Nohynek (Finnish Ins. Health & Welfare)

What animal vaccines exist or are under development, and what could be their potential role? (Ian Brown)

Key knowledge gap. Uncertainty of the market for vaccines. Surveillance. Should we include wildlife?
Research priority. Vaccinate or ring vaccinate? Marine wildlife and holiday period risk (animal/human interface). **Live attenuated preference** fulfill Ian's 8 criteria. **Passive vaccination (probiotics)**. Reverse genetic vaccines licensed. Multispecies vaccines (condors). Is a global license for chickens and turkeys rapidly achievable? Is a replication defective vaccine effective across species? Could a veterinary vaccine also be usable for humans?

Panel Moderated by Ian Brown (Pirbright, UK) - Alan Young (Medgene Labs) - Rafael Medina (Emory University, USA) - Daniel Perez (University of Georgia, US) - Leticia Frizzo da Silva (Zoetis) - Gert Zimmer (Ins. Virology and Immunology, Switzerland) Nicolas Eterradossi (ANSES, France), Yasuo Yoshioka (Osaka Univ, Japan)

Key knowledge gap. Why do some squalene adjuvants work less effectively for some antigens? Can we reduce reliance on such adjuvants? Has narcolepsy interfered with vaccine hesitancy? If risk is high for disease, hesitancy diminishes. **Was AS03 or H3N1 antigen the cause?** Are there human genetic propensities? **Answer = use more than one vaccine to compare outcomes. Duration of protection currently unchartered. Is self administration possible (mitigates pandemic risk)**
Research priority. Standard oil in water adjuvant available for use by developers without licensing agreement. 100 million/annum doses possible, can increase 10-fold (does not require squalene). Other product (saponin based, 2 billion/annum capacity possible) available and used for COVID-19. **Can these adjuvants result in cross-protective immunity. Is single-dose administration possible? Can these provide Th1 and Th2 responses? T-cell immunity (N and matrix, PA, NSPs *etc*). Correlates of protection**

Can rapid assays without the need for SRID (1978) be developed?

Key knowledge gap. Reagent production has been improved. Alternatives are possible. Ab dep and An ind assays exist. Needs to be established now, not during an outbreak. Library of antigen reagents need to be developed now before a pandemic.
Mixtures of McAb and/or sheep sera are being developed from broadly cross-reactive reagents.

15:30 – 15:40 Role and importance of adjuvants & thermostability considerations Martin Friede (WHO) Need reduced from ~90ug to ~7ug15:40 – 16:10 Panel Discussion Can regulatory agencies prepare, calibrate, and distribute SRID reagent standards necessary for testing influenza vaccines? Are there other methods for a replacement of a strain-specific (homologous) antiserum in the SRID potency assay that can be explored? Can we conduct and sponsor **basic and clinical research on adjuvants for influenza vaccines to enhances their safety and efficacy against H5N1**?
What is the availability now? Are there stockpiles? **Is squalene the adjuvant bottleneck that needs to be addressed?** What are the key research gaps?
Moderator Martin Friede (WHO) - Huw Davies (UCI) - Hanna Nohynek (Finnish Ins. Health & Welfare) - Othmar Engelhardt (NIBSC) - Ruxandra Draghia (Novavax) - Feng-Cai Zhu (JPCDC, China) - Bali Pulendran (Stanford Univ., USA) - Nicolas Collin (Vaccine Formulation Inst) - Beverly Taylor (Seqiris) - Kathleen Kaas-Leach (Sanofi) - John K Billington (GSK)

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Pathway for novel vaccines (and strain changes) evaluation

Key knowledge gap. Can AI assist mathematical modelling for risk assessment? **Alternative *in vitro* human models (MPS). Neurotropism in cows and birds? Why are pigs safe?** Why is respiratory transmission not occurring? **Field data needed.** Can H5 mRNA-LNP protect cows? Male calves responded well after prime-boost. **Female cow challenge study underway**.

Research priority. Continued surveillance to inform novel vaccines. Zoonotic risk assessment. **Harmonisation.** Capacity to test different genotypes. What is significance of Neuraminidase N1 activity despite no HI to H5N1? **Correlates of protection**. Explore new COP. FcR biding? T-cell immunity? **Mucosal immunity gap. Standards.** Swine and avian H5N1 challenge studies.

16:10 – 16:20 Estimated impact of mitigation measures: Overview of mathematical modelling consultation Ira Longini (Univ. Florida, USA) Pathway for novel vaccines (and strain changes) evaluation
16:20 – 16:30 Coverage of emerging strains by available vaccines Lead of WHO Collaborating Center (Magdi Samaan)
16:30 – 16:40 Critical research needs on Assays & Animal Models Martin Beer (FLI, Germany) Malik Peiris (Hong Kong Univ.)
16:40 – 16:50 Evaluation of the immune response after vaccination Scott Hensley (Penn Medicine, USA)
16:50 – 17:00 Regulatory considerations for the evaluation of a new H5N1 candidate vaccine including mRNA Charlene Young (Health Canada)

17:00 – 17:30 Panel Discussion - Can mRNA flu vaccines be licensed on the basis of immune response data?

Key knowledge gap. **HAI titers sufficient for now so could be used for H5 mRNA vaccines in emergency.**
New (Non-HA) antigens will require new approach.

Research priority. Can we rely on HAI alone to extrapolate mRNA vs protein vaccine protection?
Is M2 protein capable of inducing cross-protection?
Can human challenge studies provide rapid assurance?
Collaborative effort with developers and regulators to provide new ways to provide assurance that new vaccines are protective
Can essential data required for a EUA be pre-generated?

Do advances in genomics and proteomics aid in identifying new surrogate markers and in improving existing ones?
Can techniques like CRISPR/Cas9 for genetic modification and next-generation sequencing for viral genome analysis provide promising tools for developing mRNA vaccines and how regulators would approach their evaluation?
How do we bring scientists and regulators together to discuss surrogate markers for HPAI viruses, particularly H5N1 which exhibits significant antigenic variability?
Marco Cavaleri (EMA) Plenary Regulatory Reps17:30 – 17:40 Overview of investigational products including broad protection Daniele Focosi (Universitaria Pisana, Italy)

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Other pharmaceuticals as preventative tools

Key knowledge gap. Is human polyclonal therapy possible in an emergency? Could we reproduce the phenomenal cross-reactivity seen in rabies? Will McAb therapy interfere with vaccine immunogenicity? There is **confidence that antiviral drugs will protect humans against H5N1**
Research priority. How does a non-neutralizing McAb protect? How does IN McAb application protect in the absence of Fc dependency?

18:10 – 18:20 Monoclonals
18:20 – 18:30 Long-acting antivirals Bin Cao (Tsinghua University-Peking University, China)

18:30–19:00 Panel Discussion. Can we develop MAbs that are broadly neutralizing and remain effective for emerging mutations?

Key knowledge gap. Is human polyclonal therapy possible in an EUA? McAb could be useful in immunocompromised patients. **How do we bridge the preclinical to human efficacy gap? Correlates of protection.**

Research priority. How frequently should IN McAb be administered for long term protection? Can we use immunomodulatory drugs in a pandemic?

What research can help to better optimize cross-reactivity of MAbs being developed? What research is needed to evaluate the effectiveness of approved antiviral against emerging H5N1 strains? What novel approaches to develop antivirals are being explored such DAAs and HDAs? What research is needed to understand how H5N1 develops resistance to antivirals? How can research help to scale-up manufacturing to ensure therapeutics can be produced in sufficient quantities during an outbreak? What are the key research gaps? Moderator Anna Beukenhorst (Leyden Labs) - Ahmed Moustafa Mohamed Elsayed (Texas Biomed) - Frederick Hayden (Virginia) - Hassan Zaraket (Roche) - Jennifer Towne (VIR) - Les Tari (Cidara) - Jintanat Ananworanich (Leyden Labs) - Simon Portsmouth (Shionogi)

A WHO roadmap will now be developed using these valuable discussions

19:00 – 19:10 Next Steps WHO – Summary Simon Funnell