

15 March 2009

1st Meeting of the Influenza Scientific Advisory Group

Wellcome Trust, London, 5 January 2009

Executive Summary

1.0 Summary

The first meeting of the Wellcome Trust's Influenza Scientific Advisory Group (SAG) was convened by Prof. Frederick Hayden at the Wellcome Trust in London on 5 January 2009. The SAG was formed in an expert advisory capacity to assist in the development of an influenza research agenda that addresses gaps in need of support from funding organizations. Meeting participants were experts in their fields of investigation and many were also representatives of international research institutions. The need for a coordinated research agenda to avoid unwanted duplication, unfulfilled needs, missed opportunities for collaboration was identified during discussions in meetings of major international research organizations over the past several years and during discussions between the Wellcome Trust and WHO starting in January 2007.

The Trust and its partners have prioritised three areas of influenza-related research for review:

- **Vaccines and Prevention**
- **Therapeutics and Disease Pathogenesis**
- **Population Sciences**

The overarching goal of the influenza research agenda initiative is to develop a framework for action leading to new information that will help reduce the risks and threats of seasonal, pandemic and animal influenza over the next ten years. The agenda will be developed at the Wellcome Trust with guidance from an influenza research steering committee and through working relationships with stakeholders including WHO as a global public health good. There have been other influenza research road mapping projects in the past, many of which have focussed on either institutions or specific research topics. We envisage a global approach for the Wellcome Trust agenda that encompasses public and privately funded research.

1.1 Meeting objectives

To identify and describe recent, current and planned influenza research activities within three priority research areas. To identify gaps in knowledge and understanding and to suggest priority research activities to address these gaps.

Participants were asked to present overviews of their field of research with special emphasis on:

(a) key scientific questions- to identify unmet needs or gaps in knowledge, answers to which will enhance our understanding of influenza biology and disease, thus enabling improved risk reduction interventions and management

(b) research priorities- to describe feasible experiments that would answer these scientific questions

1.2 Summary of research priorities

Overviews were given of influenza research activities at the WHO and the EU. The Global Influenza Programme (GIP) at WHO is embarking on an initiative to develop an influenza research agenda that will focus on public health needs.

Vaccines and Prevention

Vaccines offer a key means of influenza prevention and in the event of an emerging pandemic virus vaccination could be used to help contain the spread as well as protecting populations at risk. Optimal development of seasonal and pandemic vaccines is to make advances in increasing efficacy, immunogenicity, safety and feasible technology and infrastructure for developing countries. The WHO is central to coordinating global pandemic preparedness and has initiated efforts to create an H5N1 vaccine stockpile. Whether this should be used to vaccinate in this inter-pandemic period is an immediate priority question and this and other related questions are currently under consideration by a sub-group of the WHO SAGE Committee.

Summary of key research priorities:

- Promote development of novel vaccine technologies
 - *Recombinant, universal antigen, vectors*
- Increase immunogenicity and efficacy in risk populations (especially elderly)
- Improve efficiency and speed of manufacturing
- Explore optimization of dose and routes of administration (e.g., intradermal, oral) and adjuvants
- Define immunologic correlates of protection
- Define evaluation criteria for vaccine efficiency
 - *Validation of assays*
 - *Human challenge and animal models*
- Assess relative importance of transmission routes (contact vs droplet vs small particle aerosols (SPA) vs fomites)
- Determine effectiveness of non-pharmaceutical interventions (e.g., masks, hand hygiene, social distancing)
- Develop reliable means of real-time evaluation of vaccine effectiveness through surveillance

Therapeutics and disease pathogenesis

Recent H5N1 infections in humans have markedly increased individual morbidity and case mortality as compared to seasonal influenza. This is linked to both high levels of viral replication and exuberant, perhaps dysregulated inflammatory responses. Emergence of resistance, limited effectiveness, and restrictions on routes of administration are limitations to the current repertoire of anti-viral drugs. Recently, non-anti-viral therapies, specifically various immunomodulators, have been proposed to modify disease pathogenesis in severe influenza, although to date little published information about their effectiveness in influenza is available. The ability to conduct such research is dependent upon research facility infrastructure, which in turn is heavily dependent upon national policies and financial support. This infrastructure is insufficient in much of the developing world, and both infrastructure development and adequately trained human resources are essential to carry out necessary biological research.

Summary of key research priorities:

- Improve understanding of influenza pathogenesis in humans
 - *Innate & cellular responses*
 - *Genetic factors in susceptibility and disease*
 - *Animal model validation & reagents*
- Strengthen infrastructure for clinical research
 - *Developing countries*
 - *Capacity to conduct human challenge studies*
- Test anti-viral treatment in high risk groups (immunocompromised, elderly, infants)
- Develop parenteral and combination antiviral therapies
- Promote new antiviral drug development
- Explore immunomodulatory therapies in animal models and in clinical studies
- Define anti-viral resistance mechanisms and consequences of resistance emergence

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Population sciences

Population sciences broadly covers aspects of influenza within natural avian host reservoirs, susceptible domestic animals and humans. Influenza at the animal-human interface is where potential pandemic viruses will emerge, and prevention or mitigation of this occurrence relies on evidence-driven interventions. Modelling offers a powerful tool in predicting influenza spread and the effects of interventions, but good data are needed to feed into these models. Burden of disease data is currently lacking for seasonal influenza, especially in developing countries, and is needed to inform vaccine policies. Better low cost, reliable point-of-care diagnostic kits are needed. In terms of policy and pandemic preparedness, it will also be important to understand human behavioural responses and economic effects in the event of a pandemic. Although these points are highlighted in the summary, the topic was not discussed in detail at this meeting.

Summary of key research priorities:

- Promote burden of disease studies
 - *Developing countries*
 - *Hospitalized cardiopulmonary illness patients*
- Develop improved, inexpensive point-of-care diagnostics
- Sharing of information and reagents
 - *Virus sequences*
 - *Human & Animal model reagents*
- Develop infrastructure for surveillance & research especially in countries likely to be affected early on in a pandemic and in underdeveloped countries
- Improve understanding of viral epidemiology and evolution in avian species
- Study transmission factors at the animal-human interface
 - Viral and host genetic factors
 - Virus receptor interactions
- Use modelling to understand spatio-temporal transmission dynamics & seasonality of influenza
- Develop operational real-time analysis tools to monitor a pandemic and help predict its course
- Investigate likely social responses in the event of a pandemic

Next steps

It is anticipated that teleconferences will be held with individual members of the SAG on an as-needed basis and that the full SAG will reconvene in approximately six months to review new data from recent meetings, progress development of the research agenda, and identify specific research study designs of merit.

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