CONSISE: Consortium for the Standardization of Influenza Seroepidemiology

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Brief Background

- It is widely recognized that timely seroepidemiological data are needed to estimate severity and attack rates and to inform policy decisions.
- Following 2009 influenza pandemic, it was widely recognized that better comparability and interpretation of influenza serologic studies was needed.
1st International Influenza Seroprevalence Meeting*

— Hosted by Public Health Agency of Canada and held in Ottawa, Canada, February 9-10 2011

— Several conclusions and actions agreed

  • Formed the basis for discussions for next meeting to be held in Stockholm in Dec 2011

— Meeting report published in IORV:

  • Laurie et al. 2012 Influenza serological studies to inform public health action: best practices to optimise timing, quality and reporting, Influenza Other Respi Viruses. 2012 Apr 30. doi: 10.1111/j.1750-2659.2012.0370a.x

2nd International Influenza Seroepidemiology Meeting*

- Hosted by ECDC and held in Stockholm, Sweden 1-2 December 2011

- Continue work on themes identified in Canada and outlined in Laurie et al summary
  - Epidemiologic Standardization
  - Laboratory Standardization and Quality Control
  - Sustainability and Links to Seroepidemiology for other Vaccine Preventable Diseases

CONSISE

- A number of influenza scientists came together and formed the Consortium for the standardization of influenza seroepidemiology (CONSISE)

- Objective: A global partnership to develop influenza investigation protocols and standardize seroepidemiology to inform public health policy
CONSISE Partners and Organization

• Partnership includes a number of institutions
  – Aim: to generate best practices for flu seroepidemiologic investigations to better inform public health policy
  – Consortium is growing and we welcome input from interested groups

• CONSISE has a steering committee and is organized into two interactive working groups
  – Epidemiology group: Chair Maria Van Kerkhove, Imperial College London
  – Laboratory group: Co-Chairs John Wood & Othmar Engelhardt, NIBSC, HPA
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Laboratory working group: work plan and progress
Background

Agreement in previous meetings*

- To optimise timing, quality & reporting of serological studies
- To co-ordinate and standardise the international laboratory response
  - develop an international network of laboratories for conducting serological studies and ensuring a common approach to generating comparable sero-epidemiological data
  - establish commitment for production of international antibody standard and control panels
  - establish collaboration/coordination between laboratory, clinical and epidemiological partners to access serum and virological samples rapidly in outbreak

*Laurie et al 2012 ISIRV
Previous serology collaborative studies

• Results of international serology collaborative studies comparing haemagglutination inhibition assay and microneutralization assay:
  ▪ Within-laboratory reproducibility is generally good
  ▪ Between-laboratory reproducibility is generally poor
  ▪ Interpretation of assay results very difficult
  ▪ Sources of assay variability: Differences in assay protocols and materials
  ▪ Serum standards can reduce variability between the laboratories by 50%
    ▪ International standards for H5N1 (clade 1) and H1N1pdm09 exist
  ▪ Good correlation between HI and MN within a laboratory but not between laboratories

Wagner et al. 2012 Vaccine [link]
Wood et al. 2012 Vaccine [link]
Outcomes of laboratory working group meeting in December 2011

Three main work areas identified:

1. Standardization
2. Quality assurance and assessment
3. Cooperation
Standardization

1. **Haemagglutination inhibition (HI) assay**
   - Group strongly in favor of keeping HI as the primary serology assay
   - To assess how the assay can be better standardized.
   - To use international standards for A(H1N1)pdm09 and A(H5N1) as antibody standards for this assay.

2. **Microneutralization (MN) assay**
   - Agreement was reached on definition of starting dilution (before addition of virus)
   - 7-day cytopathic effect (CPE) endpoint protocol not being used and will not be pursued
   - Two main protocols will be evaluated side-by-side: a standard protocol for MN assay protocols (2-day ELISA endpoint assay (WHO GISN protocol) and 3-day HA endpoint assay)
     - Several laboratories agreed to compare protocols and to undertake laboratory exercise
     - Objective: To inform the consortium and other international networks of standardization and training needs

3. **Neuraminidase inhibition (NI) assay**
   - Establish standard neuraminidase inhibition assay in some of the consortium laboratories
   - Comparison of methods and evaluation of the results for further needs for standardization or training
   - Maryna Eichelberger (NIH) agreed to provide protocols
Quality assessment

- Exploration of possibilities for external quality assessment for laboratories performing serological assays for influenza
  
  - **Primary objective**: To explore possibilities for an external quality assessment scheme for serological assays.

  - **Secondary objective**: To undertake external quality assessment with the participant laboratories and to compare results and to develop further standardization based on the information.

- European Directorate for the Quality of Medicines and Health Care (EDQM) will be asked if they could coordinate serology proficiency studies

- NIBSC has been asked for commitment to provide serology standards
Cooperation

- **Laboratory network**
  - To form a laboratory network to actively participate in the standardization work
  - To standardize the methods across the different laboratories

- **Cooperation with those undertaking influenza serology work for regulatory purposes and for evaluation of the response to vaccines**
  - To collaborate with and inform the international actors involved in the regulatory and development work of influenza vaccines about the recommendations of this laboratory working group
  - To evaluate whether the needs of regulatory laboratories and vaccine manufacturers can be assimilated within CONSISE
Progress since December 2011

- **MN assay comparison**
  - Karen Laurie (AUS) coordinating comparison of 2d ELISA WHO and 3d HA consensus protocols
  - Very good consensus across protocols between the laboratories
  - Laboratory comparison exercise starting soon, results in January 2013
    - Comparison of two methods within laboratories not between laboratories

- **NI assay**
  - Maryna Eichelberger (NIH) has supplied NI protocols to some laboratories

- **Quality assessment**
  - Small group to plan intended serology proficiency studies study and then to contact EDQM
    - Which laboratories would be included in study?
  - NIBSC asked for commitment to provide serology standards
    - Needs a commitment from the laboratory network to evaluate the standard quickly
Epidemiology Working Group: Work Plan and Progress
Best practises to optimise timing, quality & reporting of serological studies*

• Adopt a common framework for serological studies, standardise methodology & reporting

• Use either a cohort or serial cross-sectional design and link serological data with epidemiological and clinical data

• Plan for outbreak studies to identify asymptomatic and symptomatic infection, enabling severity and transmissibility calculations

• Use national serum banks to ensure baseline serum availability and enable rolling convenience serum collection during outbreak

• Conduct prior research ethics review and promote public transparency on the secondary use of residual blood samples

*Laurie et al 2012 ISIRV
Aim of Dec 2011 ECDC Meeting

• Focus on epidemiological standardisation including:
  – Study design
  – Aims and objectives
  – Timing of sera collection
  – Minimum dataset to be collected with sera

• Decisions taken prior to meeting
  – Global Focus

• Intention of the epi working group
  – Agree on study designs to be developed for pandemic/epidemic influenza and seasonal influenza
  – Agree on a minimum list of epidemiological data that should be collected with specimens

• Preparation and intended outputs
  – Protocols with recommended data items for consideration
Decisions from ECDC Dec 2011 Meeting

Next Steps

• Gather existing seroepidemiologic protocols used
  • During the 2009 pandemic
  • For routine serologic collection
  • For zoonotic outbreak investigations (e.g., H5N1, H7N7)

• Based on the research question of interest, develop detailed generic study protocols of the 3 agreed-upon study designs
  • Longitudinal seroepidemiologic studies
  • Serial cross-sectional studies
  • Transmission studies

• Develop generic data collection forms for each study design including minimum set of variables identified by the working group
  • Age, gender, location, symptoms, underlying conditions, risk factors for infection (and severe disease (other than underlying conditions), vaccination (seasonal and pandemic) use, and antiviral use

• Arrange small epidemiology working group meeting in Spring 2012 to start drafting protocols
Small Epidemiology Working Group Meeting:
London 25-27 April 2012 Imperial College London

• **10 participants**  
  – Imperial College London, ECDC, U of Hong Kong, UK HPA, Norway, Netherlands  
  – Invited but unable to attend: US CDC, Vietnam

• **Scope meeting**  
  – Review existing protocols provided to CONSISE: pandemic, zoonotic, seasonal  
  – Global focus  
  – Need to reach agreement on:  
    • which protocols to draft  
    • research objective(s)/question(s) for each study design  
    • minimum dataset to be collected with each study design  
  – “Assign” protocols to working group members  
    • Start drafting, reconvene at the end of each day to discuss progress

• **By end of meeting, regroup and discuss next steps**  
  – Share results with laboratory working group (Othmar Engelhardt)
Outputs from London meeting

• Agreement on protocol study designs develop and draft
  – Pandemic/Epidemic Protocols
    • Longitudinal studies: Paired sera collection
    • Serial cross sectional seroprevalence studies of pre and pandemic wave sera
    • Outbreak investigations
      • Transmission studies in enclosed settings
      • Transmission studies in households
  – Seasonal Influenza
    • Routine Nationally Based Serologic Collection
  – Zoonotic Influenza
    • Outbreak investigations (starting w household/rural settings) for endemic/recurrent countries

• Build on previous experience by reviewing existing protocols
Protocols under development

Pandemic/Epidemic Influenza Investigations

1. Longitudinal cohort study of influenza infection during epidemic periods
   – Primary objective:
     – To determine the age specific cumulative incidence during an influenza epidemic

2. Cross sectional seroprevalence study of cross-reactive antibodies before and after a novel influenza virus epidemic
   – Primary objectives:
     – Determine age specific cumulative incidence of infection with a novel influenza virus in the population
     – Measure prevalence of cross-reactive antibodies to the novel virus
Protocols under development (continued)

Pandemic Outbreak Investigations

3. Household transmission studies for pandemic influenza
   - Primary objectives
     • To estimate the household secondary infection risk, and factors associated with variation in the secondary infection risk
     • To characterize secondary cases including their clinical presentation and the asymptomatic fraction
     • To investigate serologic response following confirmed influenza infection

4. Closed setting outbreak investigation protocol for pandemic influenza
   - Primary objectives
     • Describe clinical spectrum of infection including proportion asymptomatic
     • Estimate overall clinical attack rates (by subgroup and clinical risk group)
     • Describe correlation between infection, disease and serology
Protocols under development (continued)

Seasonal Influenza
5. Seroepidemiology of human influenza infection using residual sera/convenience samples for establishing baselines and/or monitoring trends over time
   - Primary objectives
     - Estimate Population immune status/susceptibility to relevant influenza viruses
     - Estimate previous-season impact/attack rates for the different relevant influenza viruses

Zoonotic Influenza
6. Outbreak investigation of zoonotic infection in humans exposed to a confirmed source
   - Primary objectives
     - Measure age-specific infection in relation to zoonotic exposure
     - Identify (modifiable) risk factors for human infection
     - Determine proportion of asymptomatic infection
Next Steps

• Work continues in both working groups*
  – Seeking shared ownership of protocols

• TCs with Steering Group Committee Members
  – Regional meeting in Hong Kong in late Dec ‘12/early Jan ’13
  – Global Meeting at Options 2013

• Sharing project with member states and research groups

• Iterating and finalizing draft protocols

• Widely sharing protocols with interested parties

• Launch of accepted protocols on freely accessible website

• Validation of protocols in selected sites

*Van Kerkhove, Broberg, Engelhardt, Wood and Nicoll Consortium for the Standardization of Influenza Seroepidemiology (CONSISE): A Global Partnership to Standardize Influenza Seroepidemiology and Develop Influenza Investigation Protocols to Inform Public Health Policy“ In press IORV
Many Thanks to the Steering Committee,
especially Angus Nicoll, John Wood, Othmar Engelhardt
and Eeva Broberg,
members of both working groups
& to countries who shared protocols with CONSISE