**MEETING** REPORT

# Surveillance and studies in a pandemic: Fourth meeting of the SSiaP working group

Stockholm, July 2009

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# Abbreviations

| | |
|---|---|
| ARI | acute respiratory illness |
| DSN | dedicated surveillance network |
| ECDC | European Centre for Disease Prevention and Control, Stockholm |
| ILI | influenza-like illness |
| SARI | severe acute respiratory infections |
| SiaP | surveillance in a pandemic |
| SSiaP | surveillance and studies in a pandemic |

# 1 Background

The European Centre for Disease Prevention and Control (ECDC) is an EU agency with a mandate to operate the EU surveillance networks (including former dedicated surveillance networks, DSNs) and identify, assess, and communicate current and emerging threats to human health from communicable diseases (CDs). As such, it also has a mandate to coordinate and conduct scientific work in relation to this.

Recognising the importance of surveillance in a pandemic (SiaP), ECDC, together with the EU/EEA Member States, has been developing European thinking on SiaP. This has been accomplished through a series of meetings and papers, originally started in 2006. ECDC's efforts in this area also covered mathematical modelling, i.e. the attempt to mathematically model the progress of an infectious disease in order to discover the likely outcome of an epidemic or pandemic. This approach has been developed in parallel with similar WHO endeavours and recommendations. In addition to merely studying the reporting components, there are a number of unknowns (or gaps) that need to be estimated in order to inform, improve and evaluate the responses at both country and EU levels. Consequently, ECDC has expanded the scope of its efforts from the initial 'surveillance in a pandemic' to 'surveillance and studies in a pandemic', or SSiaP for short.

Due to the continued threat of influenza A(H5N1) and the current H1N1 pandemic, several countries have already implemented a number of the theoretical reporting systems and concepts described earlier by ECDC [1] and WHO [2].

The previous SiaP meeting had concluded that some of the tasks at hand should be performed by all countries, whereas some of the work could be carried out by only a small subset of countries, as long as protocols are comparable and data and analyses are rapidly shared. In order to assure comparability and to allow for more powerful studies combining data, the methods used in these countries need to be standardised.

This meeting, organised at short notice, was attended by participants from 19 EU/EEA countries. In addition, the meeting saw representatives from the European Commission, two candidate countries and two potential candidate countries. Invited speakers came from WHO headquarters (Geneva) and the US Centers for Disease Control and Prevention (Atlanta). Also attending were representatives from the Australian Department of Health and Ageing (Canberra) and the Public Health Agency of Canada (Ottawa).

# 2 Objectives

The objectives of the meeting were:

- to share the countries' experiences with the H1N1 pandemic to date and discuss the various strategic parameters related to action;
- to learn from experiences abroad, particularly from North America;
- to identify groups and investigators who are conducting relevant work in Europe and other regions of the world in order to enable ECDC to access their knowledge, experiences and lessons learned, so as to share them with other countries;
- to specifically address the issue of monitoring in a pandemic (WHO component 3) and reach an agreement on the minimum that EU Member States can reasonably deliver in a pandemic; and
- to plan joint work through the rest of 2009 and the first half of 2010.

# 3 Presentations and discussions

## 3.1 Overview of SSiaP

Andrea Ammon, ECDC, put the meeting in the context of the current H1N1 pandemic, previous working group meetings and WHO guidelines and then proceeded to present the meeting's purpose and intended outcomes.

During the last SiaP meeting in November 2008, a number of strategic parameters for the early comprehensive assessment of a pandemic had been identified. These parameters are commonly addressed by ILI/ARI surveillance, virological surveillance, individual case reporting, SARI surveillance, mortality monitoring, outbreak studies, and serological studies. Based on the results of this meeting, ECDC developed a concept paper [1]. In April 2009, WHO published its interim guidance paper [2].

By the end of August 2009, a functioning system for pandemic influenza surveillance should be in place in each Member State and at the European level.

### Intended outcomes of the fourth SSiaP meeting

- Agreement on:
  - which surveillance activities should be carried out in all countries;
  - which surveillance and research activities should be only carried out in some countries; and
  - using common protocols to enhance data comparability and pooling.
- Commitment to share protocols and possibly also results.

## 3.2 Influenza surveillance in the current pandemic

Tony Mounts, WHO headquarters, Geneva, gave a presentation on global pandemic influenza surveillance.

WHO uses the following data sources:

- regional and country reports including IHR reports;
- FluNet (virological data);
- information from national web updates;
- media scanning; and
- clinical, epidemiological, virological and personal networks.

WHO publishes revised surveillance guidance [3].

- Surveillance should focus on:
  - changes in the epidemiological, virological or clinical presentation;
  - any unusual or unexpected public health events, including clusters of severe unexplained acute respiratory illness or unexplained deaths.
- Laboratory testing priorities:
  - Confirmation of infections in new areas
  - Testing severe cases.
  - Monitoring the co-circulation of the influenza A(H1N1)v virus and seasonal viruses.
- Continuous monitoring of:
  - global geographic spread;
  - disease trends;
  - prevalence;
  - impact of the pandemic on healthcare services;
  - changes in viral antigenicity and antiviral sensitivity; and
  - deaths from acute respiratory disease.
- Outputs expected:
  - A composite picture of severity and transmission characteristics, primarily based on local interpretation of data and investigations.
  - The information needed for making an initial assessment.
  - An emerging picture of clinical presentation, course, complications, and risk factors.
  - The information needed for monitoring the progress and impact of the pandemic.

# 3.3 The pandemic (H1N1) 2009 experience in the United States

Lynnette Brammer, Centers for Disease Control and Prevention (US CDC), presented the epidemiology of the pandemic influenza in the United States.

## Main results

- Secondary ILI attack rate in household contacts: 12 %.
- Overall proportion of hospitalisations: 8 %.
- Overall case fatality: 0.2 %.
- Most cases (58 %) and highest incidence in 5–24 years age group, but second highest incidence in children under five years of age.
- Most hospitalisations (34 %) in 5–24 years age group, but highest age-specific hospitalisation rate per 100 000 population in children under five years of age.
- Highest age-specific proportion of hospitalisations in cases of influenza A(H1N1)v infection is 65 years of age and older.
- Most deaths in 5–24 years age group, but highest case-fatality ratio in persons 65 years of age and older.
- Evidence of higher prevalence of the following underlying conditions among hospitalised or deceased A(H1N1)v influenza patients, compared with the general US population:
  - Diabetes.
  - Chronic cardio-vascular disease (excluding hypertension).
  - Neuromuscular disorder.
  - Pregnancy.
  - Seizure disorder and other neurodegenerative disease.

  Also evidence of higher prevalence of the following underlying conditions among deceased influenza A(H1N1)v patients, compared with the general US population:
  - Chronic renal disease stages III and IV.
  - Cancer.
  - Obesity.
- Persons who died from influenza A(H1N1)v virus infection and suffered from underlying neurocognitive, neuromuscular or seizure disorders tended to be 18 years of age or younger.

## Conclusions

- The pandemic has proven many expectations wrong.
- Change in scenario required flexible surveillance: focus on outpatient ILI, rather than hospitalisation and death.
- Pandemic planning and exercises proved valuable.
- Some of the biggest surveillance challenges were related to IT/data management.
- Pandemic activity is currently declining in the US, but transmission is persisting, and an increase in infections is expected in the autumn.
- Vaccine priority groups will be finalised in an ACIP meeting.
- The focus of surveillance will shift toward:
  - monitoring of changes in risk groups;
  - the severe end of the disease spectrum;
  - vaccine effectiveness and adverse events;
  - more focused virological surveillance; and
  - putting an end to the production of numbers (exception: estimates from modelling).
- The level of surveillance carried out in the spring of 2009 will not be sustainable during peak activity.
  - Need to change expectations now.
  - Build a level of understanding for the data that will be available.

## Plenary discussion

Question: Has the US seen a clear cut-off in pandemic influenza-related morbidity and mortality between age cohorts born before and after 1957?
Answer: The assumption of a partial or relative immunity in the elderly rests on serological findings. The US epidemiology of the current pandemic suggests that the elderly may be less susceptible to infection than younger persons but more prone to severe disease and death if they do get infected.

Question: Have there been many severe cases without underlying illness?
Answer: This has not been specifically addressed yet, but there is no evidence of higher mortality in previously healthy children.

Question: What has the impact of the pandemic influenza been on society, especially the healthcare system?
Answer: There has been a huge increase in hospital emergency department visits, and both surveillance and laboratory systems have been severely stressed. Participants from Canada and Australia added that some patients required massive sedation, ventilation and even extracorporeal membrane oxygenation, which had an impact on both ICU staff and equipment.

# 3.4 Case-based reporting of influenza A(H1N1)v

Isabelle Devaux, ECDC, introduced the topic by presenting the currently reported variables and listing some options for focusing case-based reporting on selected populations (most severe cases, children, elderly, persons with underlying conditions).

Silvia Jiménez Jorge, Centro Nacional de Epidemiología, Spain, presented the Spanish strategy for surveillance of the pandemic.

## Spanish surveillance systems

- Case-based reporting of suspected, probable and confirmed cases to the Spanish Ministry of Health and Social Affairs.
- A(H1N1)v influenza cluster detection and investigation;
- Surveillance of confirmed severe cases in at least one sentinel hospital in each Spanish region, i.e. reporting of:
  - ILI cases requiring hospitalisation; and
  - sporadic cases of pneumonia with unknown cause resulting in admission to ICU.
- Enhanced influenza sentinel surveillance.

## Spanish perspective

- Because of the increasing circulation of the A(H1N1)v virus, sentinel surveillance has become more important for describing the epidemiological situation.
- Both cluster investigation and surveillance of all severe cases remain crucial.

## Plenary discussion

Question: Are Australia and Canada still using case-based reporting for the surveillance of the pandemic?
Answer: Australia is moving away from online case-based reporting towards routine national notification of laboratory-confirmed cases of influenza and ILI surveillance. Canada relies on aggregate reporting of severe cases, hospitalisations and deaths through enhanced sentinel surveillance.

The working group agreed that the A(H1N1)v influenza-related case-fatality ratio is generally overestimated due to underdiagnosis of cases and that there should be a focus on the severe end of the pandemic.

# 3.5 Surveillance of ILI/ARI during the pandemic

Flaviu Plata, ECDC, introduced the topic and pointed out the existing system's limitations if the networks are overwhelmed or if patients are redirected away from their GPs.

John Watson, Health Protection Agency, United Kingdom (UK), presented the British experience with ILI surveillance and some of the responses in the UK. The surveillance outputs are now consolidated and published weekly (for the duration of the pandemic) at: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1247816558780?p=1231252394302. The UK has moved from a containment strategy to a treatment strategy. This implied moving from case-based reporting to aggregate ILI reporting through sentinel GP networks. The GP consultation rates have shown good

congruence with the individual case numbers. However, it was considered necessary for surveillance to also cover symptomatic patients that are not seeking medical care. In England and Wales this is achieved by monitoring NHS Direct, a telephone helpline for people self-diagnosed with influenza-like symptoms. A subset of callers also participate in a self-sampling scheme for virological confirmation.

## Plenary discussion

Question: What is the future of ILI surveillance if the pandemic affects Europe even more severely in autumn?
Answer: In the UK, telephone services are supposed to take some pressure off the GPs. In previous pandemics, UK sentinel surveillance systems never stopped functioning. It can thus be assumed that they will also remain operational this time, although there may be some distortion because of the alternative services.

Question: Why is the UK so much more affected by the H1N1 pandemic than any other country in Europe?
Answer: This remains unknown, but possible reasons include a high amount of seeding in schools during the initial phase of the outbreak and a certain element of chance.

# 3.6 Monitoring the pandemic

Andrew Amato, ECDC, introduced the topic by presenting the quantitative and qualitative components of monitoring.

Lynnette Brammer, CDC, gave a presentation on the monitoring of the pandemic in the United States. Thereafter, Tony Mounts, WHO, presented the WHO perspective on global pandemic monitoring.

## Current US surveillance

Current US surveillance components are consolidated into a weekly 'FluView' report (http://www.cdc.gov/flu/weekly/). They are subject to change as the pandemic evolves. Table 1 summarises what the US is moving towards in the initiation period.

**Table 1: US surveillance components**

| System | Frequency |
|---|---|
| WHO & NREVSS[1] collaborating laboratories | daily |
| Novel Influenza Case Report | not required |
| Line List System of all cases | weekly – transitioning out |
| Aggregate case reporting by state | weekly – transitioning in |
| Emerging Infections Program (EIP)/NVSN[2]: hospitalisations | weekly |
| 122 Cities Mortality Reporting System | daily |
| Influenza-associated paediatric mortality | daily |
| ILINet | daily |
| State and Territorial Epi Report | daily – weekly |
| BioSense | daily |

[1] The National Respiratory and Enteric Virus Surveillance System
[2] New Vaccine Surveillance Network

## US surveillance planning for autumn (likely scenario)

- Laboratory surveillance
  - WHO laboratories: daily reporting (subset may take on wider role and perform additional tests).
  - NREVSS laboratories: weekly reporting.
- Outpatient ILI surveillance
  - Maintain ILINet with subset of daily reporters.
  - Incorporate additional data sources with daily electronic data.
  - Influenza incidence pilot project.
- State and territorial activity level assessments (weekly, with option to make modifications within the week if activity changes).
- Hospitalisation
  - EIP data collected weekly.
  - Data from non-EIP states?

- Mortality
  - Maintain 122 Cities Mortality Reporting System with subset of daily reporters (use data to estimate national number of deaths every week).
  - Maintain paediatric mortality reporting.
  - Method to obtain more detailed information on a subset of deaths among adults?
- Community illness: Behavioural Risk Factor Surveillance System (BRFSS) or BRFSS-like survey — weekly?
- Improved data analysis/display
  - Demand for more local level data.
  - Desire for summary values that incorporate data from multiple surveillance components — influenza 'weather map'.

## WHO monitoring plans

- Qualitative indicators
  - Geographic spread: the distribution of sites reporting influenza activity.
  - Trend: changes in the level of respiratory disease activity compared with the previous week.
  - Prevalence: an estimate of the overall level of acute respiratory disease activity in the population (compared with previous influenza seasons or acute respiratory disease activity in the previous week).
  - Impact: the degree of disruption of healthcare services as a result of influenza.
  - Mortality data: Number of deaths related to acute respiratory disease by age group and population covered.
- Quantitative data
  - Data that can be derived from existing surveillance systems for respiratory disease, influenza or mortality.
  - ILI sentinel surveillance data if available.
  - SARI surveillance data if available: (a) number of new SARI cases admitted in the past one-week period by age group and sex (if available); (b) number of total admissions (from same facilities as number of SARI cases reported), or population covered; (c) number of SARI-related deaths by age (if available); (d) number of SARI sentinel sites reporting.
- Virological monitoring (through the current GISN system).

## Plenary discussion

Question: How are Australia and Canada monitoring the pandemic?
Answer: The Australian government is still receiving daily numbers of laboratory-confirmed cases, hospitalisations and deaths. In addition, absenteeism is being monitored through the Australian postal service system. Like in the United States, there is some pressure to generate an Australian pandemic influenza 'weather map' that combines all data in one picture. In contrast, Canada is focusing on surveillance of severe cases in addition to its routine surveillance.

Question: Why is the United States planning extensive monitoring for the autumn?
Answer: The monitoring should enable health authorities to detect changes.

Question: Are the European national surveillance systems flexible enough to adopt the legally binding EU case definition?
Answer: In theory, the EU case definition is broad enough to cover national case definitions, but in practice it is unlikely to replace them, given the amount of international variation.

Question: How should national surveillance data providers cope with the necessary but very time-consuming dual reporting of two different case-based datasets to ECDC and WHO?
Answer: High-level negotiations between WHO, the European Commission and ECDC are underway to find a solution.

# 3.7 Hospital surveillance, including severe acute respiratory infections (SARI)

Phillip Zucs, ECDC, introduced the topic by presenting the WHO SARI case definition, the objectives and the potential problems of SARI surveillance.

Florin Popovici, National Institute of Public Health, Romania, presented plans for establishing SARI surveillance in his country.

## Clinical component of Romanian SARI surveillance

- Five sentinel districts with two sentinel hospitals each (infectious diseases and paediatric, respectively).
- WHO SARI case definition.

## Laboratory component of Romanian SARI surveillance

- Setup of four regional laboratories for detection of influenza A(H1N1)v viruses by RT-PCR;
- Testing capacity per laboratory: 400 specimens per year, daily results.
- Virological sampling in a random selection of hospitalised SARI patients admitted in the last 24 hours.

## Plenary discussion

The working group agreed that focusing on SARI might lead to overlooking influenza-related deaths, given the fact that around 80 % of influenza-related excess deaths are known not to be attributed to influenza. On the other hand, actual influenza-related mortality is difficult to study on an individual basis and can only be monitored through time-series studies. Canada uses deaths of confirmed cases to quantify the mortality related to influenza A(H1N1) v virus infection.

Question: Have countries with many cases seen any sizeable proportion of bacterial superinfection?
Answer: Bacterial superinfection in cases of influenza A(H1N1)v virus infection was infrequent both in Australia and the United States.

Question: How feasible is it to set up sentinel SARI surveillance in a country?
Answer: This depends on a country's infrastructure and also on the careful selection of sentinel sites. There are mainly logistical issues that need to be solved, like specimen collection, labelling, transport, etc. Mexico accomplished this task very quickly.

# 3.8 Outbreak investigations

Viviane Bremer, ECDC, introduced the topic by listing some of the clinical and epidemiological parameters that can be estimated by outbreak investigations. Her introduction was followed by two presentations on approaches in two countries: a specific study in Germany and a more national picture from Denmark.

Udo Buchholz, Robert Koch Institute, Germany, presented the methodology and initial results of a shedding study in household index cases and symptomatic or asymptomatic household members.

## Preliminary results from German shedding study

- Crude household attack rate: 13 % (not yet stratified by neuraminidase inhibitor therapy).
- Viral shedding after symptom onset: 7–8 days (maximum: 15 days).
- Viral shedding after symptom onset in patients under neuraminidase inhibitor therapy: up to seven days (study limitation: most cases caught late in illness history, i.e. day 4 or 5).

Steffen Glisman, Statens Serum Institut, Denmark, presented the Danish experience with the ongoing influenza pandemic.

## Lessons learned in Denmark

- The pandemic preparedness plan worked well but should be adjustable to disease severity.
- Containment was more labour-intensive than expected.
- The discrepancy between high alert level and low disease severity may cause 'pandemic fatigue'.
- The change from containment to mitigation was relatively easy to explain.

## Danish planning for autumn

- Continue surveillance through sentinel system, emergency services and mortality monitoring.
- Establish surveillance of hospitalisations and investigate cases with severe disease.
- Prepare serological studies.
- Develop a plan for pandemic vaccination.

## Plenary discussion

Question: Who is supposed to fill in the questionnaires on hospitalised patients in Denmark?
Answer: This requires an agreement between epidemiologists and clinicians, but Statens Serum Institut is willing to assist hospitals.

ECDC invited the working group members to share their study protocols through ECDC's dedicated website (password-protected).

## 3.9 Mortality monitoring

Piotr Kramarz introduced the topic by presenting various methods of mortality monitoring in a pandemic.

Anne Mazick, Serum Statens Institut, Denmark, presented the EuroMOMO project which aims at European monitoring of excess mortality related to influenza and other public health threats. The project is funded by the European Commission until January 2011. It covers 21 European countries and is coordinated by the Serum Statens Institut in Denmark.

### EuroMOMO methods

- Simple cyclical Poisson regression model fitted to weekly all-cause mortality in spring and autumn.
- Reference period: last 3–5 years (until May 2009).
- Correction for reporting delay.
- Model available in STATA.
- Weekly bulletin and map of Z scores (based on standard deviation around baseline).

### EuroMOMO timeline

- Summer 2009: pilot implementation and testing.
- 7–9 September 2009: pilot evaluation workshop in Copenhagen.
- October 09: start weekly monitoring with revised pilot.
- March/April 2010: EuroMOMO plenary meeting for second pilot evaluation.
- September 2010: EuroMOMO workshop for data providers and end users.
- October 2010: third pilot evaluation.
- January 2011: final recommendation.

### Next steps

- Introduce age-specific mortality monitoring.
- Define indicators.
- Translate at least into R (the freeware language and environment for statistical computing and graphics).
- Expand to more countries.

## 3.10 Laboratory-based studies

Maria Zambon, Health Protection Agency, UK, presented the surveillance of influenza A(H1N1)v virus infections in the UK, with special emphasis on laboratory aspects. She reminded participants that parts of the UK were experiencing intense pandemic activity, even though they were only in the initiation phase. In addition, she made two HPA papers available to the meeting participants.

### HPA laboratory activities during the treatment phase

- Discontinued or reduced: laboratory reporting of all confirmed cases.
- Maintained or augmented: antiviral resistance monitoring and viral sequencing.
- New: virological self-sampling of a random selection of NHS direct callers for enhanced community surveillance.

### HPA laboratory methods

- Virological testing for influenza A(H1N1)v virus:
  - Antigenic characterisation.
  - Haemagglutinin sequencing (of selected isolates).
  - Whole genome sequencing (of selected isolates).
- Antiviral susceptibility testing:
  - Rapid quantitative pyrosequencing (H275Y mutation in neuraminidase, and amantadine sensitivity).
  - Neuraminidase inhibition testing.
  - Haemagglutinin and neuraminidase sequencing (of selected isolates).
  - Detailed characterisation (of selected isolates), e.g. replicative efficiency and transmissibility.
  - Whole genome sequencing (of selected isolates).
- Serological assay development.

## HPA laboratory surveillance priorities

- Representative samples.
- Serious illness and death.
- Antigenic variants.
- Antiviral surveillance:
  - Community isolates.
  - Post treatment.
  - Risk groups (immunocompromised, pregnant women etc.).
- Serology.
- Detection of change.

## Plenary discussion

Question: Is there a big challenge in detecting co-circulation of other influenza (sub-)types?
Answer: This challenge can be met if regional laboratories have the capability to accurately subtype influenza viruses.

Question: Has Australia seen any co-circulation of seasonal and pandemic viruses?
Answer: Australia has seen co-circulation of influenza A(H3N2) virus. In Victoria, the first affected state, it was completely replaced by the pandemic strain; in other states the proportion of influenza A(H1N1)v virus infections now ranges from 30 to 80 %.

Question: Is there any value in using non-paired sera for serological testing?
Answer: Non-paired sera might be useful, but there is a lack of experience.

Question: Is there a need for standardising virological/serological studies across Europe?
Answer: Countries with a solid background in this area should share their experience with those countries still developing their capabilities. ECDC could facilitate the exchange of information by hosting a serology workshop.

# 3.11 Analytical studies

Bruno Ciancio, ECDC, introduced the topic by presenting several methodological approaches and the results of analytical studies on influenza A(H1N1)v. He also mentioned key decisions that could be based on theses approaches/studies (e.g. vaccination strategies, use of antivirals).

Isabelle Bonmarin, Institut de veille sanitaire (InVS), France, presented plans for a national case-control study to identify clinical, epidemiological, immunological and virological determinants associated with severe disease and death due to A(H1N1)v influenza.

## Methods of planned French case-control study

- Duration: 6–12 months (start in September 2009).
- Cases: laboratory-confirmed severe cases of influenza A(H1N1)v virus infection enrolled in hospital centres:
  - Daily clinical follow-up until discharge and final follow-up one month after enrolment.
  - Nasopharyngeal swabs and blood samples at regular intervals.
- Controls: mild laboratory-confirmed cases enrolled with GP practices:
  - Matched 1:1 to cases on week of recruitment and administrative region.
  - Initial clinical examination and final follow-up one month after enrolment.
  - Swab on enrolment.
  - Blood sample one month after enrolment.

## Plenary discussion

Question: Have you considered increasing the number of controls to increase the statistical power of your study?
Answer: The protocol is still under discussion.

Comment (Susan Hahné, RIVM, Netherlands): The study results may become available too late to inform vaccination strategy.

# 3.12 Serological studies

Angus Nicoll, ECDC, introduced the topic by presenting the main objectives of serological studies and noted that his introduction was based on work done by Mika Salminen. There are no simple methods, and the possibility of cross-reaction presents difficulties, which means that quality control is paramount. The two methods that can presently be employed are microneutralisation (requires live virus) and haemagglutination inhibition.

## Objectives of serological studies

Objectives are to:

- estimate the proportion of asymptomatic infections in populations (prospectively);
- estimate the attack rate (concurrently or retrospectively);
- estimate pre-existing immunity (retrospectively); and
- study cross-reactivity between seasonal A(H1N1) and the pandemic A(H1N1)v immune responses and/or protective effect (already done in the United States).

Udo Buchholz, Robert Koch Institute, Germany, presented plans for four serological studies.

## Seroepidemiologic studies planned in Germany

- Contact study
  - 150–200 high-risk contacts (household, etc.) and 50–100 lower-risk contacts (colleagues, etc.) of confirmed cases of influenza A(H1N1)v virus infection.
  - Proportion of infected persons who become symptomatic?
  - Attack rate in high versus low risk contacts?
  - Risk factors?
- Cohort study
  - 4–5 weekly samplings of 500–700 plasma donors.
  - Dynamics of the increasing seroprevalence?
  - Seroprevalence at the end of the second wave?
- Population-based seroprevalence study
  - German adult health survey: serum and epidemiological information from 1200 participants.
  - Prevalence of pre-existing immunity against the A(H1N1)v virus?
- Seroprevalence study among veterinarians attending a conference
  - Serum samples from 450 veterinarians.
  - Seroprevalence of antibody against the A(H1N1)v virus?

Ilkka Julkunen, National Institute for Health and Welfare, Finland, gave a presentation on influenza surveillance and research in Finland.

## Seroepidemiologic studies planned in Finland

- Retrospective study:
  - 3200 serum samples collected prior to introducing influenza vaccination for young children.
  - Specimens were sent to a large clinical microbiology lab for viral diagnostic purposes.
  - Pre-existing immunity against the A(H1N1)v virus?
  - Influenza attack rate in early childhood?
  - Vaccine prioritization?
- Prospective study:
  - Collection of serum materials during and after the pandemic (n=100–200/5–10 year age groups).
  - Homologous and heterologous immune responses against different A(H1N1)v virus isolates?
  - Age-specific attack rate in the absence of vaccination?

## Plenary discussion

Question: Given the evidence of pre-existing immunity against A(H1N1)v virus among the elderly, could vaccination be simplified by only administering one dose to them?
Answer: In view of the expected vaccine shortage, prioritization of target groups will be inevitable, but the decision on whom to vaccinate when and how is up to each country.

Question: Does the evidence of a possible partial immunity in about 30 % of the elderly help in prioritising vaccination target groups?
Answer: No, it does not.

Comments: It is important to learn more about other similar studies in other countries (Angus Nicoll, ECDC).

The new pandemic vaccine strain is growing poorly. Clinical trials are about to start in August 2009 (Kari Johansen, ECDC).

There is no genetic basis for the pandemic virus becoming more pathogenic in autumn (Ilkka Julkunnen).

# 3.13 ECDC pandemic (H1N1) 2009 modelling group

Tommi Asikainen, ECDC, introduced the topic by presenting the objectives of the modelling group and the challenges of undertaking pandemic (H1N1) 2009-specific forecasting due to lacking values on several important parameters of the infection.

Andrea Pugliese, University of Trento, Italy, presented a model for predicting the spread of influenza in Europe.

## Pandemic spread prediction model

- Based on UK and Italian household age distributions, Eurostat data on school/workplace size and location, and rail/air travel intensity.
- Fictitious population.
- Model seeded with cases arriving in the EU by long-distance travel in several countries.
- Simulation of spread within each country takes into account cross-border diffusion.
- Assumption: 50 % of cases remain asymptomatic (subject to change as influenza A(H1N1)v-specific estimates become available).
- During a series of early runs of the model (with the virus being introduced in different places), the model predicted a high early transmission rate for the UK.

Matthias an der Heiden, Robert Koch Institute, Germany, presented a model to predict how public health measures could defer the peak of the H1N1 pandemic.

## Public health impact model

- SEIR (susceptible, exposed, infectious, recovered) model.
- Scenario(s):
  - Limited supply of antivirals.
  - First 100 or 500 cases: Full contact tracing and post-exposure prophylaxis.
  - 100/500–10000 cases: no active search and prophylaxis only for household contacts.
  - Thereafter only treatment of cases.
  - Various basic reproduction numbers ($R_0$).
  - Various proportions of cases diagnosed early enough to prevent secondary cases.
  - Two or five imported cases per day.
- Results:
  - The pandemic can only be stopped if $R_0<1.3$ and the detection rate of symptomatic cases is at least 30 % (assuming the vast majority of cases is symptomatic).
  - The pandemic peak can only be delayed if the number of cases is not too high already.
  - The extent of the delay depends heavily on $R_0$ and on early case detection.

## Plenary discussion

Australian modellers were quickly facing limits in terms of data availability and data quality. The Australian experience also shows that communicating modelling results to decision makers can be a challenge. In Europe, many modelling activities appear to be underway, but mostly in academic circles. Only in the UK is modelling integral to policy making and used as a potential source for official reports (estimated numbers of cases, deaths, etc.).

# 4 Working groups: Conclusions

## 4.1 Case-based reporting and surveillance of severe acute respiratory infection (SARI)

### Case-based reporting

- Each country decides when to switch from general case-based to aggregate reporting of influenza A(H1N1)v.
- It should be possible to upload case data files to TESSy in batches, rather than having to input each case individually online.
- ECDC should focus case-based reporting on severe disease and provide a surveillance protocol.
- In some countries, case-based surveillance in vulnerable populations (e.g. ethnic groups) may be relevant.

### SARI sentinel surveillance

- ECDC should collate and monitor European data on severe disease and death due to A(H1N1)v virus infections.
- Only data on laboratory-confirmed SARI cases should be reported at European level (no consensus on whether or not to include cases due to subtypes other than the pandemic strain).
- SARI reporting should be based on the WHO minimum dataset, but complications (ARDS, intensive care admission) should be added.
- Reporting of treatment data and post-mortem findings could be considered.

## 4.2 Virological surveillance and serological studies

### Virus resistance

- Questions to answer: Prevalence? Clinical impact? Rate of emergence under treatment?
- Methods: Phenotypical monitoring and N gene sequencing (CNRL and national institutes).
- Populations that should be under surveillance:
  - General population (representative sample).
  - Sentinel populations (immunocompromised persons, children, treated patients, treatment failures, prophylaxis failures).

### Virus antigenicity

- Question to answer: virus matching the vaccine?
- Also important for serological test development.
- Method: sequencing (global influenza surveillance network, CNRL and national influenza centres).
- Representative sample of viruses.

### Virus pathogenicity

- Question to answer: Is there any increased pathogenicity in the viruses circulating?
- Methods: sequencing pathogenicity markers, animal studies, cell culture experiments, linking case-control studies into risk factors for severe disease (national institutes, national influenza centres, research groups); SARI surveillance including pathogenicity markers and co-factors (ECDC).
- Population:
  - Previously healthy persons with serious disease or death related to A(H1N1)v influenza.
  - Contact persons of severe cases: also seriously afflicted?
- It may require clinical networks within countries and at European level to link clinical, virological and epidemiological information.

### Seroepidemiology

- Prevalence of pre-existing immunity:
  - Question to answer: age-specific and location-specific pre-existing immunity?
  - Haemagglutination inhibition and virus neutralisation on existing serum collections and according to a common testing protocol with quality control, possibly by CNRL.

- Population attack rate:
  - Questions to answer: age-specific proportion infected after first wave? Proportion of infected persons seeking medical attention?
  - Haemagglutination inhibition and virus neutralisation on sera (neither oral fluid nor dried blood spots currently possible).
  - Cohort of plasma donors (could detect seroconversions because of frequent donation).
  - Outbreak investigations in closed settings (schools, families).
  - Residual clinical serum samples.
  - Population sample after first wave.
- ECDC should facilitate international collaboration.

### Plenary discussion

Question: Will ECDC collect and share information on ongoing studies?
Answer: ECDC will collect information on public health related and seroepidemiologic studies and share it on its website. The ongoing EPI Concept (www.epi-concept.fr) influenza vaccine effectiveness project will be expanded to cover the pandemic influenza vaccine. ECDC will also collaborate with EMEA and the Brighton Collaboration (www.brightoncollaboration.org) in the surveillance of vaccine-related adverse events.

## 4.3 ILI/ARI surveillance and monitoring of the pandemic

### ILI/ARI surveillance

- Sentinel surveillance should be continued.
- The EU case definition is very broad and accommodates most national case definitions used in Europe; efforts to use the existing common case definition should continue.
- Countries should report the indicator (ILI/ARI) they normally report; it is neither feasible nor advisable to change the system now.
- Do not change the age cohorts (age groups).
- ECDC should test the candidate baseline methods on country data and suggest a common method for baseline/excess estimation to be used at the European level.

### To be monitored

- Activity ('Has virus arrived in … [country]?' 'Yes/no/no report available'), based on laboratory reports.
- Geographic spread, based on regional laboratory reports.
- Trend (increasing/unchanged/decreasing/no information), based on country risk assessment using information from sentinel surveillance as well as from other indicator- and event-based surveillance systems.
- Intensity, to be based on ILI/ARI rates.
- Clinical impact, to be based on mortality monitoring.
- Impact on healthcare system; composite indicator to be based on bed occupancy, cancelled elective surgery, etc; traffic-light labelling (green/amber/red).

### Plenary discussion

Earlier in the year, a subgroup of ECDC's Advisory Forum had discussed national monitoring efforts and as a result had expressed concerns over measures that were too complex and therefore too difficult to implement for many countries. Generally, qualitative monitoring was the preferred method. The epidemiology of influenza presented a problem in itself: even in a pandemic, the distribution of cases tends to be heterogeneous, making it difficult to produce a clear and concise description of the epidemiological situation in the larger and more complex countries.

No consensus was reached on whether to include the suggested indicator for monitoring the pandemic's impact on healthcare systems.

Pro arguments:

- Some countries are able to monitor the impact on their healthcare system.
- Information derived from a country's impact indicator could be useful for predicting the future impact in less affected countries.
- Important for health capacity planning.
- Gives countries that lack good surveillance the option to assess the impact of the pandemic and inform about it.

Con arguments:

- Regional differences in big countries are very likely.
- Which traffic light colour to choose if a country performs well in one area and poorly in another?
- Some information might be considered politically too sensitive to be made public, particularly if it implies that national health services are not coping well.
- Indicator too simplistic for monitoring highly complex issues.

# 5 Action plan

ECDC does not expect the Member States to carry out all actions listed below. For some items, the participation of Member States will depend on available infrastructure, capacity and willingness. These items are marked '(optional)' in the second column.

**Table 2: ECDC action plan**

| Actions to be taken | Responsible |
|---|---|
| **Before the end of August 2009** | |
| Share relevant study protocols (e.g. outbreak investigations) with each other and ECDC, e.g. using the dedicated protected website maintained by ECDC. | Member States (optional), CNRL |
| Prepare ECDC's TESSy database for migration of case-based data of pandemic (H1N1) 2009 from EWRS. | ECDC (Surveillance Unit) |
| Implement case-based reporting of influenza-related SARI in TESSy. | ECDC (Surveillance Unit) |
| Provide SARI surveillance protocol to the Member States. | ECDC (Surveillance Unit) |
| Not discussed but required: Implement aggregate reporting of pandemic (H1N1) 2009 in TESSy. | ECDC (Surveillance Unit) |
| Agree on method for calculating national ILI/ARI baselines and implement in TESSy. | ECDC (Surveillance Unit) and Member States |
| Sustain virological surveillance for circulating influenza viruses (pandemic and seasonal) and antiviral resistance. | ECDC (Surveillance Unit), sentinel networks in Member States, involved laboratories, CNRL |
| **Before the beginning of the influenza season 2009/2010** | |
| Implement SARI sentinel surveillance at national level. | Member States (optional) |
| Revise EuroMOMO pilot according to evaluation outcomes (Copenhagen, 7–9 September 2009) and define indicators. | EuroMOMO |
| Start weekly monitoring of age-specific all-cause excess mortality in countries currently participating in EuroMOMO (and possibly beyond), using the revised pilot. | EuroMOMO and Member Sates (optional) |
| Implement qualitative monitoring of geographic spread, intensity, trend and impact as well as quantitative monitoring at European and national levels. | ECDC (Surveillance Unit) and Member States |
| Organise a seroepidemiology workshop. | ECDC, CNRL |
| Share results of relevant studies with each other and ECDC, e.g. using the dedicated protected website maintained by ECDC. | Member States (optional), CNRL |
| **Continuously** | |
| Continue sentinel surveillance of ILI/ARI and virological case detection. | ECDC (Surveillance Unit), sentinel networks in Member States, involved laboratories, CNRL |
| Share protocols and results of relevant studies (e.g. outbreak investigations) with each other and ECDC, e.g. using the dedicated protected website maintained by ECDC. | Member States (optional), CNRL |

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6. ECDC. Working group 'influenza surveillance in a pandemic', August 2007. Available from: http://ecdc.europa.eu/en/Health_topics/Pandemic_Influenza/pdf/070801_Influenza_surveillance.pdf

# Annex 1. Meeting programme

**14 July 2009**

| | |
|---|---|
| 08:30 – 09:00 | Registration at ECDC |
| 09:00 – 09:15 | Welcome and reminder where we are now — Andrea Ammon, ECDC |
| Session One | (Chair: Andrea Ammon, ECDC) |
| 09:15 – 09:30 | Overview of surveillance and studies in a pandemic — Andrea Ammon, ECDC |
| 09:30 – 10:00 | Update on WHO plans for surveillance in a pandemic — Tony Mounts, WHO HQ |
| 10:00 – 10:30 | The North American experience — Lynette Brammer, CDC, USA |
| 10:30 – 10:45 | Coffee break |
| Session Two | (Chair: Andrew Amato, ECDC) |
| 10:45 – 11:15 | Case-based reporting and analysis in a pandemic (introduced by Isabelle Devaux, ECDC)<br>Country experience: Spain — Silvia Jimenez Jorge, Istituto de Salud Carlos III, Spain |
| 11:15 – 11:45 | ILI surveillance (introduced by Flaviu Plata, ECDC)<br>Country experience: UK — John Watson, Health Protection Agency, UK |
| 11:45 – 12:15 | Monitoring in a pandemic (introduced by Andrew Amato-Gauci, ECDC)<br>Country experience: USA — Lynette Brammer, CDC,USA<br>WHO plans — Tony Mounts, WHO HQ |
| 12:15 – 12:30 | Discussion |
| 12:30 – 13:30 | Lunch |
| 13:30 – 15:00 | Surveillance and studies in a pandemic — the gaps |
| 13:30 – 14:00 | Hospital surveillance including SARI (introduced by Phillip Zucs, ECDC)<br>Country experience: Romania — Florin Popovici, National Institute of Public Health, Romania |
| 14:00 – 14:30 | Outbreak investigations (introduced by Viviane Bremer, ECDC)<br>Country experience: Germany — Udo Buchholz, Robert Koch Institute, Germany<br>Country experience: Denmark — Steffen Glismann, Statens Serum Institut, Denmark |
| 14:30 – 15:00 | Mortality monitoring (introduced by Piotr Kramarz, ECDC)<br>EuroMoMo experience — Anne Mazick, Statens Serum Institut, Denmark |
| 15:00 – 15:15 | Coffee break |
| Session Three | (Chair: John Watson, Health Protection Agency, UK) |
| 15:15 – 15:45 | Analytical studies (introduced by Bruno Ciancio, ECDC)<br>Country experience: France — Isabelle Bonmarin, Institut de veille sanitaire (InVS), France |
| 15:45 – 16:15 | Laboratory-based studies<br>Country/CNRL experience: UK — Maria Zambon, Health Protection Agency, UK |
| 16:15 – 16:45 | Serological studies (introduced by Angus Nicholl, ECDC)<br>Country experience: Germany — Udo Buchholz, Robert Koch Institute, Germany<br>Country experience: Finland — Ilkka Julkunen, National Institute for Health and Welfare, Finland |
| 16:45 – 17:00 | Discussion |

**15 July 2009**

| | |
|---|---|
| 09:00 – 09:15 | Summary of the previous days' discussion — Angus Nicoll, ECDC |
| Session Four | (Chair: Angus Nicoll, ECDC) |
| 09:15 –10:45 | Working group 1: Case-based reporting and surveillance of Severe Acute Respiratory Infection (SARI)<br>Working group 2: Serological studies and virological surveillance<br>Working group 3: Influenza-like Illness/Acute Respiratory Infection (ILI/ARI) surveillance and monitoring of the pandemic |
| 10:45 – 11:00 | Coffee break |
| 11:00 – 12:30 | Working groups continued |
| 12:30 – 14:00 | Lunch |
| Session Five | (Chair: Andrew Amato-Gauci, ECDC) |
| 14:00 – 15:00 | Report by the working groups<br>Discussion |
| 15:00 – 15:30 | Coffee break |
| 15:30 – 16:15 | ECDC Influenza A(H1N1) Modelling Group (introduced by Tommi Asikainen, ECDC)<br>Modelling spread of flu and effects of intervention on European level through different models — Andrea Pugliese, University of Trento, Italy<br>Modelling Influenza A(H1N1)v in Germany — Mathias an der Heiden, Robert Koch Institute, Germany<br>Discussion |
| 16:15 – 16:45 | Discussion on the next steps |
| 16:45 – 17:00 | Closing remarks (Andrew Amato-Gauci, ECDC) |

# Annex 2. List of participants

| Name | Country | Affiliation |
|---|---|---|
| Alban Ylli | Albania | National Institute of Public Health |
| Leslee Roberts | Australia | Department of Health and Ageing |
| Mira Kojouharova | Bulgaria | National Center of Infectious and Parasitic Diseases |
| Rachel Rodin | Canada | University of Toronto |
| Sanja Kurecic Filipovic | Croatia | Croatian National Institute of Public Health. |
| Jan Kyncl | Czech Republic | National institute for Public Health |
| Steffen Glismann | Denmark | Statens Serum Institut |
| Anne Mazick | Denmark | Statens Serum Institut |
| Irina Dontšenko | Estonia | Health Protection Inspectorate |
| Ilkka Julkunen | Finland | National Institute for Health and Welfare (THL) |
| Isabelle Bonmarin | France | Institut de veille sanitaire (InVS) |
| Mathias an der Heiden | Germany | Robert Koch Institute |
| Udo Buchholz | Germany | Robert Koch Institute |
| Ágnes Csohán | Hungary | Állami Népegészségügyi és Tisztiorvosi Szolgálat |
| Joan O'Donnell | Ireland | Health Protection Surveillance Centre (HPSC) |
| Andrea Pugliese | Italy | University of Trento |
| Tanya Melillo (participated via teleconference)* | Malta | Department of Health Promotion and Disease Prevention, Ministry for Social Policy |
| Susan Hahne | Netherlands | National Institute for Public Health and the Environment (RIVM) |
| Preben Aavitsland | Norway | Norwegian Institute of Public Health |
| Carlos Manuel Orta Gomes | Portugal | General Directorate of Health |
| Naser Ramadani | Republic of Kosovo | National Institute of Public Health |
| Florin Popovici | Romania | Institute of Public Health |
| Maja Sočan | Slovenia | National Institute of Public Health |
| Silvia Jimenez Jorge | Spain | Instituto de Salud Carlos III |
| Annika Linde | Sweden | Swedish Institute for Infectious Disease Control |
| Anders Tegnell | Sweden | The National Board of Health and Welfare |
| Levent AKIN | Turkey | Hacettepe University |
| Maria Zambon * | United Kingdom | Health Protection Agency |
| John Watson | United Kingdom | Health Protection Agency |
| Emma Quinn | United Kingdom | Coordinator Pandemic Influenza Preparedness Programme, Global Health and Security Initiative representative |
| Lynnette Brammer | USA | Influenza Division, Centers for Disease Control and Prevention |
| Anthony Mounts | | WHO HQ |
| Franz Karcher * | | European Commission |
| Andrea Ammon | | ECDC |
| Andrew Amato | | ECDC |
| Flaviu Plata | | ECDC |
| Angus Nicoll | | ECDC |
| Tommi Asikainen | | ECDC |
| Vicente Lopez | | ECDC |
| Piotr Kramarz | | ECDC |
| Andrea Würz | | ECDC |
| Bruno Ciancio | | ECDC |
| Rene Snacken | | ECDC |
| Isabelle Devaux | | ECDC |
| Phillip Zucs | | ECDC |
| Per Rolfhamre | | ECDC |
| Todd Weber | | CDC, ECDC |