MEETING REPORT

Molecular surveillance strategy for human influenza in Europe

Stockholm,17–18 November 2011

Summary

On 17–18 November 2011, ECDC convened an expert group meeting on the goals, objectives and strategies for the molecular surveillance of human influenza in Europe. The meeting, which took place at ECDC in Stockholm, Sweden, served as a starting point for discussions on the aims and structure of a molecular surveillance strategy for human influenza in Europe.

The main aim of virus characterisation data reporting is to attain a representative and up-to-date overview of the proportion of influenza virus antigenic and genetic variants in Europe. This information is used for the annual selection of the viruses for vaccine recommendations and production. The aim of the molecular surveillance database is to provide a sustainable and centralised source of antigenic and genetic characterisation data linked to the epidemiological data for EISN and ECDC.

The expert meeting reviewed the current reporting schemes and the different models options for future characterisation data reporting. The expert group proposed a model for reporting influenza virus characterisation and antiviral susceptibility data that requires changing the reporting scheme for the EISN laboratory data and thus also for the ECDC-hosted surveillance database, TESSy. The proposed model would involve reporting all genetic data together with metadata to the GISAID EpiFlu database. As the data is currently reported on an aggregated basis by the countries, the proposed model would require disaggregated reporting for the characterisation data which is already available in the laboratories. The challenge is how to transfer data from GISAID EpiFlu to TESSy efficiently, and in a way that all parties can agree on, since the EU/EEA Member States are obliged to report surveillance data to ECDC but reporting to GISAID EpiFlu is voluntary.

Based on the outcome of this molecular surveillance strategy meeting, a proposal will be written for the EISN and further discussed with the national surveillance contact points for influenza.

Stockholm, April 2012

1 Background

1.1 Background to influenza virus molecular surveillance

Influenza remains a significant cause of illness and death, especially in the elderly and other vulnerable groups. It is also a major cause of absenteeism with economic impact throughout the world (1, 2).

Influenza viruses continuously undergo genetic changes. Along with regular epidemics caused by seasonal viruses, novel strains may emerge sporadically as a result of mutations in and reassortment of the viral genome (3). Viruses overcome immunity induced by infection or vaccination through genetic variation associated with antigenic shift (often in connection with pandemics) or antigenic drift (during recurrent epidemics) of their surface glycoproteins (HA and NA). Similarly, antiviral drug susceptibility can be affected by virus genetic variation. Continuous surveillance of the antigenic characteristics and genetic composition of influenza viruses is therefore crucial, especially for epidemic surveillance and pandemic preparedness. This information makes a vital contribution to recommendations for the optimal composition of seasonal influenza vaccines and the preparation of pre-pandemic candidate vaccines (http://www.who.int/influenza/vaccines/virus/recommendations/en/). Vaccination itself remains the single best intervention against influenza virus infection and its consequences (4) (5).

Human influenza virus surveillance at the type, subtype and molecular level is well established in Europe. In 2003, in order to formalise the network of collaborating national influenza reference laboratories participating in the European Influenza Surveillance Scheme (EISS, later EISN), the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) was established (6). The CNRL laboratories have been collecting antigenic (AG), genetic (GEN) and antiviral susceptibility (AVS) characterisation data ever since and have already made significant achievements in terms of improving and standardising laboratory methodology and characterisation techniques (7). ECDC coordinates the activities of the network and supports the strengthening of laboratory capacities in the EU/EEA Member States, candidate and potential candidate countries in collaboration with the Commission, Competent Bodies and the National Microbiology Focal Points. The European influenza surveillance data is automatically shared upon upload by those countries with WHO Regional Office for Europe EuroFlu and later with the Global Influenza Surveillance and Response System (GISRS).

In 2008, ECDC developed a Molecular Surveillance concept paper that has recently been updated and reviewed by the Advisory Forum and the ECDC National Microbiological Focal Points (2011). The aim of molecular surveillance integration in The European Surveillance System (TESSy) is for typing results to be interpreted in the context of all available clinical and epidemiological information and to avoid the duplication of data collection. Building and implementing a strategy for the integration of molecular typing data with epidemiological data is one of the key objectives of the overall ECDC strategy for collaboration with laboratories. Current work in this area includes making a roadmap to identify suitable pathogens for integration, and developing a practical pilot including four pathogens: multidrug-resistant *M. Tuberculosis*, *Salmonella*, *Listeria* and verotoxin-producing *Escherichia coli*. In so doing, TESSy will be upgraded to version 3.0 (TESSy v3), which will contain a technical platform for hosting and analysis of molecular surveillance data at ECDC.

1.2 Short description of GISAID (Global Initiative on Sharing All Influenza Data)

Several specific influenza databases already exist in the influenza field. One of these is GISAID EpiFlu™, which focuses on influenza virus sequences.

GISAID actively promotes the sharing of all influenza type virus sequences, associated with clinical and epidemiological data for human isolates, and associated with geographic and species-specific data for avian and other animal isolates (8). Admission to GISAID's publicly accessible platform is free of charge. It is accessible to anyone who agrees to its basic premise of observing scientific etiquette. Users agree to acknowledge the laboratories providing the specimen and the submitting laboratories generating the sequence data. No restrictions are attached to data made available through GISAID's EpiFlu™ database (e.g. including any fraction of the sequence data obtained from GISAID in a patent application) to ensure that researchers will have unlimited access to the data for future generations to come. GISAID's scientific etiquette actively promotes collaboration among researchers by sharing data openly and respecting the rights and interests of all parties involved.

The EpiFlu™ database offered by GISAID (hereinafter GISAID) goes beyond maintaining a data archive as it provides a set of software tools that will continue to be developed and grow over time.

2 Meeting objectives and questions

2.1 Objectives

The aim of the meeting was to trigger discussion on the goals, objectives and strategies for the molecular surveillance of influenza in Europe. The meeting served as a starting point for discussions on the aims and structure of a molecular surveillance strategy for human influenza in Europe. The expert group is expected to develop the meeting report into a concept paper on European molecular surveillance strategy.

The objectives of the meeting were:

- to discuss the need for molecular surveillance of human influenza in Europe
- to identify the objectives for molecular surveillance of human influenza
- to propose a mechanism for data sharing in the most efficient way
- to explore the feasibility of using both GISAID and TESSy in parallel or in an interconnected manner.
- to find the best possible structure for data flow/analysis.

2.2 Questions for the molecular surveillance strategy meeting participants

Strategic requirements of molecular flu surveillance at the EU/EEA level

- What do we want to achieve with molecular surveillance of influenza? What are the goals for EU/EEA influenza molecular surveillance?
- Which additional molecular surveillance tools are needed in Europe?
- What is the current capability and capacity in the EU/EEA Member States?
- Link between genotypic and phenotypic typing?

Functional requirements of molecular flu surveillance at the EU/EEA level and the structure for linking TESSy v3 and external databases

- How do we reach the goals set in the strategic session?
- What are the functional requirements for achieving the goals?
- What end-user outputs are required?
- What structures are in place for achieving the goals?
- Outline of structures and roadmap for 2012 and beyond.

2.3 Objectives for the integration of influenza virus molecular surveillance in TESSy v3

The main objective is to obtain a representative and up-to-date overview of the prevalence of influenza virus genetic variants in Europe. This is to be done by promoting the sharing of virus characterisation data, cluster and outbreak detection and enhancing surveillance of influenza virus drift/shift and antiviral susceptibility monitoring. To achieve this aim, a sustainable and centralised source of sequence data must be provided that is linked to the epidemiological data for national reference level laboratories. A secondary objective is to improve comparability and validity of data through standardisation and quality assurance (Table 1).

Table 1. Aims and objectives of molecular surveillance of human influenza in Europe

Aim	Objectives
To maintain and further develop the current status	1. To continue the surveillance, data management and analysis activities of the network laboratories as well as the reporting of weekly data to TESSy. 2. To continue and further develop the complex AG and GEN characterisation of influenza viruses together with antiviral susceptibility testing. 3. To continue and improve collection of virus characterisation and drug susceptibility data in TESSy v3.
Data analysis, linkage and cluster investigation	4. To explore linking TESSy v3 to external databases such as GISAID. 5. To explore possible epidemiological links within molecular clusters. 6. To describe the AG and GEN match between circulating viruses and vaccine viruses. 7. To describe the prevalence of antiviral resistance in influenza viruses circulating in Europe. 8. To identify antiviral-resistant clusters of influenza viruses in time and space so that coordinated response action can be taken. 9. To link epidemiological and laboratory data to facilitate detailed analysis of spread and transmission routes of antiviral resistance and severe (hospitalised) influenza.
Improve timeliness, validity and comparability of data through standardisation and quality assurance as well as preparation for future techniques.	10. To collect all EU/EEA influenza surveillance data in one database to improve comparability between different laboratories in and between countries. 11. To ensure quality control of the data through automatic and manual data curation. 12. To ensure that the data is up-to-date through agreements with laboratories to submit their data in a timely manner and by ensuring user-friendly and efficient data analysis and submission procedures. 13. To enable transition from traditional methods and techniques to next-generation laboratory methods for molecular typing of influenza virus, if considered necessary by the network.

3 Current molecular surveillance reporting

Detections and characterisations of influenza viruses are reported weekly to TESSy, hosted by ECDC. GEN and AG characterisation and AVS analysis data are entered in TESSy with the weekly detection data by the Member States. However, the GEN and AG characterisation data are entered mostly in batches of analysis, with different countries applying different analysis schemes. To a varying extent, national influenza reference laboratories collect molecular surveillance data and release the sequence data to publicly available databases. All EU/EEA Member States send representative and any unusual samples for analysis to the WHO Collaborating Centre for Reference and Research on Influenza, based at the MRC National Institute for Medical Research in London (WHO CC London). The WHO CC carries out antigenic analysis of propagated viruses and genetic analysis of a sub-set of viruses. The determined sequences are deposited in the GISAID database, with the permission of the Member State in question. The WHO CCs, five in total and one WHO CC for non-human viruses, are responsible for forming a global evaluation of AG and GEN characteristics of circulating influenza viruses for seasonal influenza vaccine recommendations and assessing the pandemic potential of emerging influenza viruses. Discussions relating to possible improvements in the process of vaccine virus selection are currently underway at WHO (9).

4 Benefits of molecular surveillance of influenza

The main purpose of molecular surveillance of the influenza virus is to enhance the AG analysis to facilitate the annual selection of the viruses for vaccine recommendations and production (Table 2) (10). Part of the public health relevance of molecular surveillance therefore lies in protecting vulnerable populations against influenza through vaccination with an optimal vaccine.

Molecular surveillance is crucial in detecting and monitoring the frequent and constant changes in the genome of circulating influenza viruses and the emergence of new virus variants (11). In particular, this applies to any viral changes associated with more severe infections (12) which may become evident when linking timely molecular typing information to case-based epidemiological data.

The potential for timely analysis of emerging variants through molecular surveillance is further enhanced by complementing the use of virus-specific reagents, such as post-infection ferret antisera. These antisera are needed for AG analysis and can limit the speed at which a full AG characterisation can be attained.

Finally, molecular surveillance makes it possible to monitor for the emergence of antiviral resistance, as was seen in 2007–2008 when resistance to oseltamivir emerged globally (13), following initial detection in Europe (14). With the spatio-temporal investigation of antiviral-resistant influenza outbreaks, it becomes possible to advise family doctors and the general public regarding vaccination, antiviral drugs and other preventive measures.

Table 2. Public health actions linked to molecular surveillance objectives

Surveillance objective	Potential linked public health action	Related actions
Detection of genetic change in circulating influenza viruses	Altering the strain selection for current vaccine (when combined with antigenic data)	Careful analysis to determine the frequency of genetic variants
Detection of novel influenza viruses	Rapid epidemiological investigation	Virological risk assessment and, if necessary, development of diagnostics and seed viruses for vaccines.
Detection of genetic markers in relation to phenotypic data of antiviral resistance	Altering the advice to clinicians	Careful collection of data in connection with cases, contact persons of a case treated with antivirals, etc.

5 Conclusions

The meeting participants reached agreement on several topics and developed proposals for the network as described in detail below.

5.1 Review of the reporting scheme

The participants reviewed the current reporting schemes and identified the following development needs:

- With a view to achieving cost-efficient and timely influenza surveillance in Europe, laboratory guidance on sequencing strategies should be revisited and discussed within the network. There is a need for updated guidance on techniques, sampling schemes, the capabilities of laboratories, which laboratory does what (e.g. MS laboratory vs WHO CC), etc.

  The agreed priorities for the sequencing and linking of data from this meeting are:

  - Sequences of the haemagglutinin (HA) gene should be linked to the AG characterisation whenever possible.
  - Sequences of neuraminidase (NA) should be linked to the phenotypic AVS results whenever possible.

  Pyrosequencing is only recommended for H275Y in N1.

  At present, the Member States are encouraged to report virus-based AVS data.

- The capacity and actual capability in Europe will be reviewed using the results from a questionnaire (CNRL molecular task group, 2010), reported sequences in GISAID and the reports in TESSy (AG and GEN) for season 2010–2011. The results will be presented as maps and added to the molecular surveillance reporting proposal when available. The proposal will be written based on this meeting report.
- Better support is required for the WISO (Weekly Influenza Surveillance Overview) authors and readers. The weekly Excel files containing the country-based virology and syndromic data prepared for the WISO report will be saved on the EISN Extranet. Pie charts showing antigenic and genetic data will be developed for the WISO and/or TESSy reports displayed on the ECDC web portal, as discussed at the October 2011 CNRL Task Group meeting in Prague.

5.2 Suggested new reporting structure

Suggestions for new reporting strategy to be reviewed at the EISN annual meeting, May 2012

In the short term, for the 2012–2013 season, sentinel detection data should be reported by age groups (same groups as for ILI/ARI: 0-4, 5-14, 15-64, 65+) to enable analysis of age-specific virus circulation. The data need to be reported in a timely manner and analysed monthly to be of any value. This proposal should be reviewed by the Member States and a decision should be taken at the annual meeting in 2012, since development in TESSy will need to be done during the summer of 2012.

The long-term goal (for the influenza season 2013–2014 if feasible, subject to decisions and approvals) for EU influenza molecular surveillance is to have more detailed influenza virology data linked to clinical data, especially for ICU/SARI cases. This requires disaggregate, virus-based AG and GEN reporting and should be discussed at the EISN annual meeting in 2012. TESSy will need development time to accommodate the changes requested by the network.

A tool for rapid category assignment of laboratories should be developed with the aim of facilitating rapid and user-friendly GEN data reporting. Similar tools are already implemented in GISAID and those implemented in the future will be investigated to determine if they can fulfill the requirements of the CNRL.

If further improvement of tools is required for data analysis and quality assurance in GISAID it is envisaged that ECDC will share the implementation work with GISAID or develop the required tools in TESSy v3. If specimens are sequenced in a timely manner, data can be shared by submitting all data, including clinical data, AG data, AVS (phenotypic and genotypic) data and other metadata to a publicly available database that can handle influenza-specific data such as GISAID. So far, AG data reporting to GISAID has not been possible as the scope of the database encompasses sequence data only. Unique accession numbers for isolates provided by GISAID can be used to refer to the entries. If all data are submitted to GISAID, there is no need for separate reporting of AVS, GEN and AG data and linkage with epi data for ICU cases in TESSy. Although it is already possible in GISAID to download data in several formats, it would be desirable if those submitting data to GISAID could be assisted in

their reporting to other databases, e.g. by providing a download file in TESSy-readable .csv format. This file would contain the characterisation data by the designated categories and would greatly facilitate reporting to TESSy. Sensitive data that Member States do not want to share in GISAID can be added to the GISAID report before TESSy upload. There will be no sequence data included or stored in TESSy. The entry of the unique (GISAID) accession numbers for the isolates in TESSy will enable recovery and analyses of the sequences in GISAID and thereby obviate storing this information in TESSy. There will be no direct machine-to-machine dialogue or connection between GISAID and TESSy. Reporting responsibilities rest with the Member States, so they will have to upload the GISAID-generated .csv file to TESSy (see Figures 1–3). If only phenotypic AVS data is reported, it will be reported as at present (Model B). If only AG data is reported, virus isolate-based reporting should be encouraged (although this presents a challenge in terms of work load) (Model C). AG, GEN or AVS data that have been reported via GISAID should not be reported in duplicate (i.e. in TESSy in addition to GISAID), although the countries will still be responsible for uploading the .csv file to TESSy.

Data providers will at all times retain the option to submit their data to other influenza-specific or more general sequence archives, e.g. GenBank, after having submitted their data to TESSy.

Several models for the reporting of AG, GEN and AVS data were discussed during the November 2011 expert meeting. The following models were discussed and **Model B was proposed for future reporting workflows** (see legends of Figures 1–3 for descriptions of the models). Table 3 summarises the advantages and disadvantages of the models and Table 4 details the proposed changes, required actions and target season. It should be noted that the proposed changes in reporting schemes would require a substantial amount of work, both from the EU/EEA Member States, who would need to change their reporting systems, and from ECDC's TESSy IT and influenza teams. Significant input would also be required from GISAID EpiFlu working groups, e.g. metadata set changes and report preparations at national and international level.

Figure 1. Model A for reporting molecular surveillance data on human influenza in Europe.

In this model, the entry interface is designed in TESSy v3 and a subset of data would be submitted from TESSy to the GISAID database directly. TESSy would host all the sensitive epidemiological data, but could link virological and epidemiological data through unique identifiers (e.g. GISAID isolate ID).

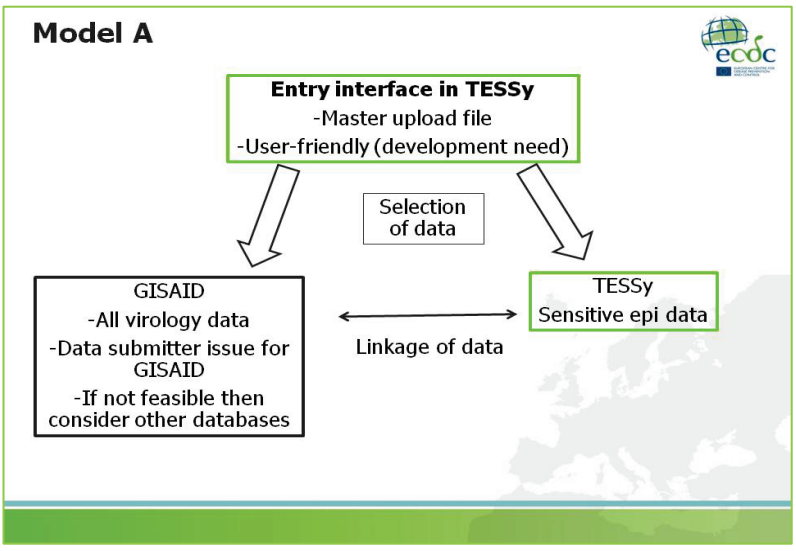

Figure 2a. Model B for reporting molecular surveillance data for human influenza in Europe.

Figure 2a describes the suggested data flow for influenza virus AG characterisation data. In this model, the AG data are reported in their current aggregated format by the Member States to TESSy. Later (target 2013–2014; subject to decisions and approvals) when AG data are available in virus isolate-based format, the TESSy data upload would be adapted accordingly. However, viruses with both AG and GEN data would be reported to GISAID, generating a .csv file that Member States would upload to TESSy.

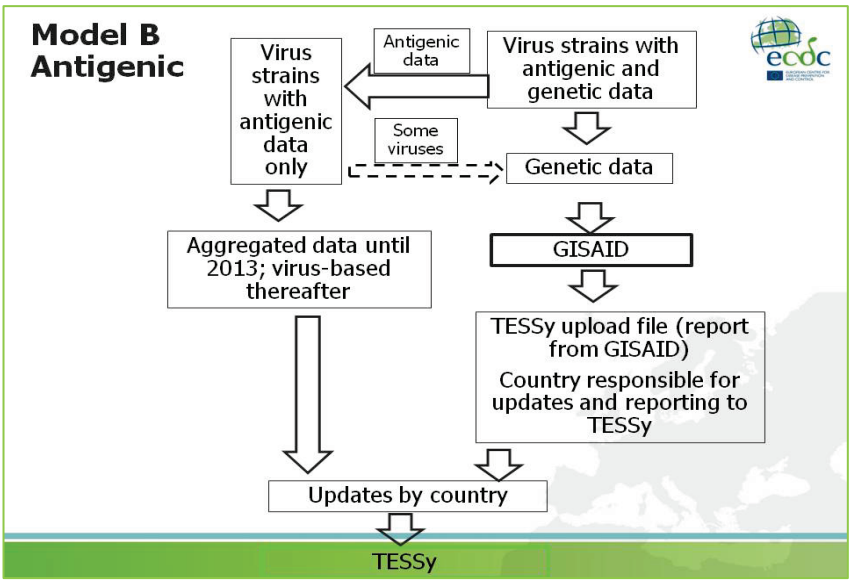

Figure 2b. Model B for reporting molecular surveillance data for human influenza in Europe.

Figure 2b describes the suggested data flow for influenza virus GEN characterisation data. GEN data are available in a virus isolate-based format and the TESSy upload would be adapted accordingly by 2013–2014. In this model, the data are uploaded to GISAID, generating a .csv file that Member States would upload to TESSy.

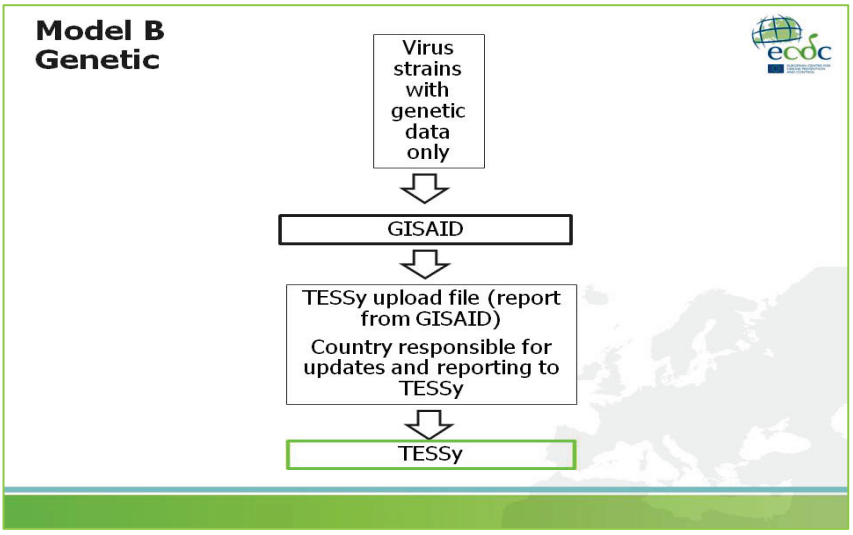

Figure 2c. Model B for reporting molecular surveillance data on human influenza in Europe.

Figure 2c describes the suggested data flow for influenza virus AVS data. In this model, viruses characterised phenotypically (or where only a pyrosequencing result is available), but not genetically, are reported to TESSy in a virus isolate-based format, as is currently the case. For viruses that have been characterised genetically, the data are uploaded to GISAID, generating a .csv file that Member States would upload to TESSy. In TESSy, phenotypically characterised viruses that are later characterised genetically are linked to the data retrieved from GISAID through their GISAID isolate IDs.

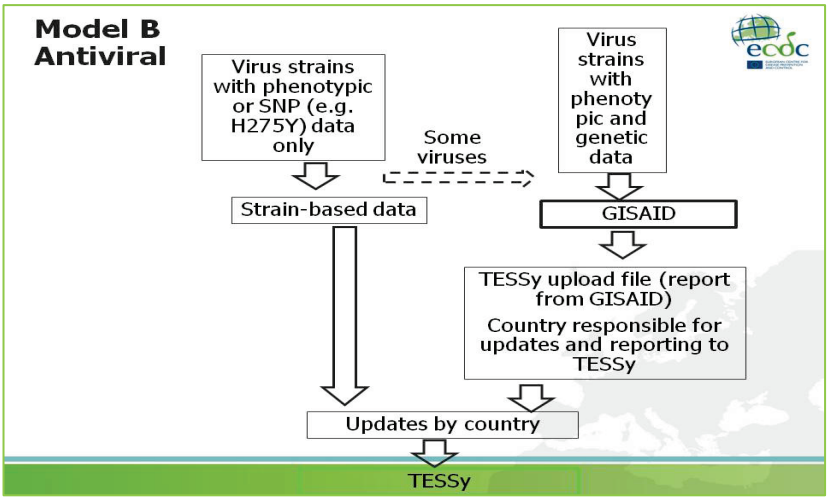

Figure 3. Model C for reporting molecular surveillance data on human influenza in Europe.

In this model, all data are reported to TESSy v3, generating reports suitable for upload to GISAID.

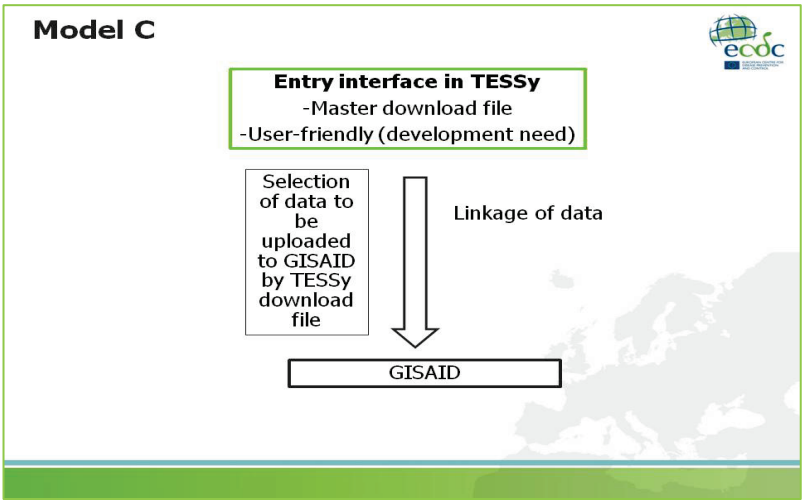

Table 3. Advantages and disadvantages of the different models.

Model and changes to current reporting scheme	Advantages	Disadvantages
Model A; data sent directly from TESSy to GISAID	• Countries have one entry and reporting interface for both clinical and virological data. • All virology data shared with GISAID. • Linkage possibilities between clinical and virological data.	• GISAID not accepting automatic upload from TESSy; user needs to enter data into GISAID. • Entry interface development required in TESSy.
Model B; antigenic; virus-based reporting to start in season 2013–2014	• Aggregated results reported by week until 2013–2014 (change from cumulative reporting to by week by season 2012–2013). • Virus-based reporting, to start in 2013–2014, allows linkage with the genetic data and with clinical case-based data.	• Changes in reporting scheme • Metadata set changes
Model B; genetic; virus-based reporting to start in season 2013–2014; entry interface in GISAID	• All genetic data reported to GISAID. • TESSy-upload file as a GISAID output file. • No double reporting of genetic data.	• Development need in GISAID for output file • Metadata set matching needed between GISAID and TESSy
Model B; antiviral; viruses with both genotypic and phenotypic data reported to GISAID	• TESSy-upload file as a GISAID output file. • No double reporting of genetic data.	• Development need in GISAID for output file. • Metadata set matching needed between GISAID and TESSy. • Viruses with solely phenotypic data can only be reported to TESSy.
Model C; molecular surveillance database and analysis platform, genetic data output file in GISAID-acceptable format.	• Countries have one entry and reporting interface for both clinical and virological data. • All analysis modules in TESSy. • No need for direct linkage to GISAID. • All virology data shared with GISAID. • Linkage possibilities between clinical and virological data.	• No automatic reporting to GISAID.

Table 4. Proposed major changes and target season

Description of proposed change	Target season	Required actions
Virus isolate-based reporting of AG and GEN characterisation data.	2013–2014	Countries to comment on feasibility Metadata set changes in TESSy TESSy development • Changes in reports • Changes in WISO.
Virus isolate-based reporting of AG and GEN characterisation data linkage with epidemiological data.	2013–2014	Countries to comment on feasibility Metadata set changes in TESSy TESSy development • Changes in reports • Changes in WISO.
All virological genetic and antiviral susceptibility data is uploaded to GISAID, generation of a .csv file output that the Member States upload to TESSy.	2013–2014	Agreement with GISAID[1] • Reporting of all this data to GISAID • Category assignment analysis tool development • TESSy-compatible .csv-output file development • Metadata set agreement Metadata set changes in TESSy TESSy development • Changes in reports • Changes in WISO.
Linkage of genetically and phenotypically reported antiviral susceptibility results between TESSy and GISAID by GISAID accession number.	2013–2014	TESSy v3 development for influenza.

[1] If GISAID does not agree with the development plan all changes will still be made in TESSy v3, including the development of the category assignment tool.

5.3 Knowledge transfer plan and timeline

Agreed outcomes:

- A meeting report and ECDC publication on "Strategic and functional requirements for EU molecular surveillance of human influenza viruses"
- The meeting report will be sent to the meeting experts for review and then to the EU Member State influenza reference laboratories (with the involvement of epidemiologists) for review.
- EU/EEA-wide preliminary decisions are expected from the EISN annual meeting, May 2012**.** These decisions will then be sent to the national contact points for review and approval.
- Metadata set revisions to be made in TESSy.
- Although beyond the scope of this meeting, it was agreed that the user-friendliness of TESSy needs to be further developed, regardless of molecular surveillance.

Suggested timeline:

- Draft report with recommendations from meeting experts, GISAID and TESSy review by 30 November 2012.
- Reviews by 16 December 2012.
  - Comments on feasibility by GISAID.
  - Comments on feasibility by TESSy.
  - Review the capability and capacity in Europe.

- Report and recommendations to be sent for review to the national influenza laboratory experts and epidemiologists, 20 January 2012.
- Comments by 20 February 2012.
- Changes to the document by end of February 2012.
- Teleconference at the end of March- before EISN annual meeting in May. Development plan needed for TESSy and GISAID.
- Documents for review to be sent to the Member States by April 2012 at the latest.
- Annual meeting as preliminary decision forum, May 2012
- Preliminary decisions to be reviewed by national contact points and ECDC Advisory Forum, summer 2012.
- Metadata set revisions by October 2012 at the latest.

5.4 Comments from GISAID after the meeting

The GISAID Foundation and its governing bodies are unequivocally supportive of the European network in their efforts to improve European surveillance on influenza. This is why GISAID is keen to help the ECDC explore ways to ease the submission of certain data that cannot be published in GISAID but must be published in the TESSy database. Further discussions on details of such data are dependent on technical feasibility and must remain compliant with the GISAID Database Access Agreement (DAA) that governs the use of the GISAID EpiFlu™ database.

While interconnectivity of servers between GISAID and TESSy is restricted due to GISAID's obligation to protect the rights of its submitters, as governed by its DAA, cooperation between ECDC and GISAID on the use of .csv files should be further explored. While the analysis of data from a TESSy perspective would be in favour of a download of GISAID data directly from TESSy, it would conflict with GISAID's user rights, since only individuals – not institutions – are granted access to GISAID per se.

ECDC has discussed with GISAID the need to develop new tools, but a discussion of new development issues requires a more precise characterisation of the needs of the CNRL/EISN community. Model A is problematic from GISAID's point of view as GISAID accepts data from individual submitters and protects the rights of submitters.

Submission of data to GISAID is dependent on the willingness of the user to submit data to GISAID because there is no obligation. Nevertheless, the network can be encouraged by ECDC to share data via GISAID. In contrast, member countries are obliged to report influenza surveillance data to ECDC, resulting in a need to streamline the molecular surveillance reporting. GISAID is not in a position to generate reports by default without the consent of the data submitters, as this would not be reconcilable with its mission. Further discussions are needed to define the eventual output file format. A direct machine-to-machine report from GISAID would also be dependent on submitter approval and must be technically feasible and consistent with the DAA.

5.5 Comments from TESSy after the meeting

The integration of influenza molecular surveillance within TESSy v3 and development needs for analysis tools should be agreed at the EISN annual meeting in collaboration with the relevant national contact points for surveillance. It must also be ensured that the agreed influenza molecular surveillance implementation is in line with the strategies and priorities of the molecular surveillance implementation roadmap being developed in 2012 by ECDC with the Member States and disease-specific networks. This concept paper may need to be revised following planned finalisation of the molecular surveillance roadmap in early 2013.

If the GISAID output report is uploaded to TESSy by a Member State in a TESSy-acceptable format, the changes to the reporting scheme on the TESSy side should be relatively minor. However, the overall plan for changes to reporting (Table 3) indicates several metadata set changes and development requirements. These will have to be prioritised at ECDC and will require substantial input from the TESSy development team.

Model A is unacceptable to GISAID and therefore cannot be implemented. Model B is complicated for the users, although technically feasible. **The TESSy team favours Model C for its simplicity.**

5.6 Proposals of the expert group

Despite the challenges in streamlining the molecular surveillance reporting, the expert group is committed to supporting GISAID as the influenza sequence database of choice. The EU/EEA Member States are obliged to report influenza virus data to ECDC and therefore a solution must be found to connect the data reported to GISAID as sequences and the surveillance data reported to TESSy. The expert group is proposing the following as the concept for influenza virus molecular surveillance in Europe:

- EISN will adopt the long-term goal (aim for season 2013–2014 if feasible, subject to decisions and approvals) of reporting more detail on virology (move towards isolate/strain-based reporting), enabling individual linkage with clinical data, especially for ICU/SARI cases where an influenza virus sequence accession number would be available.
- The CNRL laboratories will move towards virus isolate-based reporting of AG and GEN characterisation data to the extent possible by the 2013–2014 season.
- Model B flowcharts will be implemented for influenza virus molecular surveillance data (see below). This will mean that:
  - AG data is reported to TESSy in its current aggregated format. Later (target 2013–2014; subject to decisions and approvals) when antigenic data would be made available in virus isolate-based format, the TESSy data upload would be adapted accordingly. However, for the viruses with both AG and GEN data, the GEN data would be submitted to GISAID to generate a .csv file that the Member State would then upload to TESSy with the AG data.
  - All the viruses for which genetic data are available in a virus sequence-based format for TESSy upload would be adapted to virus isolate-based reporting by 2013–2014 (subject to decisions and approvals as well as development capacity). In this model, the data is uploaded to GISAID which would allow generation of a .csv file output that the Member State would upload to TESSy.
  - The viruses which are phenotypically characterised but not genetically characterised will be reported in a virus isolate-based manner to TESSy, as is currently the case with the INFLANTIVIR record type in TESSy. The viruses that have genetic data will be uploaded to GISAID to allow generation of a .csv file output that the Member State would upload to TESSy. In TESSy, phenotypically characterised viruses that are later characterised genetically are linked through their GISAID isolate IDs with the GISAID uploaded data.

6 Action plan

The following actions were suggested by the expert group at the meeting.

Table 3: Action plan

Actions to be taken	Responsible/deadline
Before the end of May 2012	
Report to be produced with recommendations from meeting experts, also for GISAID and TESSy review	ECDC and rapporteurs/30 November 2011
Review of the meeting report	All meeting participants/16 December 2011
Comments on feasibility by GISAID	Received and integrated
Comments on feasibility by TESSy	Received and integrated
Excel files containing the country-based virology and clinical data prepared for the WISO report will be saved on the EISN Extranet.	From now onwards
Pie charts showing antigenic and genetic data will be developed for WISO and/or as ECDC website TESSy reports	Under development
Review the capability and capacity in Europe. Capability maps to be added to the proposal.	Need support from GISAID (Anne Pohlmann) and CNRL (Olav Hungnes, Joanna Ellis) by 20 January 2012
Proposal and recommendations sent to EU/EEA Member State national influenza experts and epidemiologists for review.	ECDC/early January 2012
Revisions by national influenza experts and epidemiologists	Member States/ 20 February 2012
Changes to document	ECDC/29 February 2012
Teleconference of the meeting participants: plan development needs for TESSy and GISAID.	ECDC-TESSy-GISAID meeting participants/28 March 2012
The laboratory guidance concerning influenza virus sequencing should be reviewed and discussed with the EISN laboratory network, CNRL.	CNRL Task Group 2 members/April 2012
Documents for review to the Member States	Member States/30 April 2012
EISN annual meeting as decision forum	EISN members/May 2012
Before the beginning of the influenza season 2012–2013	
Decisions sent to national contact points for review	National contact points/August 2012
Metadata set revisions	ECDC and Member States/ October 2012
Before the beginning of the influenza season 2013/2014	
All required changes to TESSy	
GISAID to provide agreed tools and outputs, ECDC to support development.	

7 References

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Agenda

Meeting room: N514, ECDC, 5th floor, Granits väg 8, Solna, Stockholm

Thursday 17 November 2011, 09.00–17.00. Chair – Eeva Broberg			
Item			Time
1.0	Welcome and introduction	Eeva Broberg, Angus Nicoll	09.00
2.0	2.1 Public health value and scientific priorities for molecular surveillance for influenza	Olav Hungnes	09.10
	2.2 ECDC perspectives on molecular microbiology surveillance	Karin Johansson	09.30
	2.3 How can GISAID contribute?	Anne Pohlmann	09.50
	2.4 GISAID data analysis examples	Mia Brytting	10.10
	Coffee break		10.30
3.0	Strategic requirements of molecular flu surveillance at EU level • What do we want to achieve with molecular surveillance of influenza? • Which additional molecular surveillance tools are needed in Europe? • What is the current capability and capacity in the EU Member States? • Definition of goals for EU influenza molecular surveillance • Link between genotypic and phenotypic typing	All, Facilitator Bruno Lina Rapporteur (tbd)	11.00
	Lunch (SMI)		13.00
4.0	Functional requirements of molecular flu surveillance at EU level and the structure for linking TESSy v3 and external database • How do we reach the goals set in the strategic session? • What are the functional requirements for achieving the goals? • What are the needed end user outputs? • What are the structures to achieve the goals? • Outline of structure and roadmap for 2012	All, Facilitator Karin Johansson Rapporteur (tbd)	14.30
5.0	Closing remarks	Eeva Broberg	16.45
	Drinks at Angus' place		18.00
	ECDC hosted dinner at Da Peppe http://www.dapeppe.se/		19.30

Friday 18 November 2011, 09.00–14.00. Chair – Eeva Broberg			
6.0	Introduction, summary of Day 1	Eeva Broberg	09.00
7.0	Finalisation of the working group slides • Definition of goals • Outline of structure and roadmap	Rapporteurs and split of participants to support the rapporteurs	09.15
8.0	Outcomes 8.1 Strategic requirements of molecular flu surveillance at EU level 8.2 Functional requirements of molecular flu surveillance at EU level and the structure for linking TESSy v3 and external database	Rapporteurs, all	10.00
	Coffee break		11.00
9.0	Agreement on outputs; future plans	Chair: Angus Nicoll	11.30
10.0	AOB, closing of the meeting.	Angus Nicoll	12–12.15

Annex 2. List of participants

Name	Country/organisation
Besselaar, Terry	WHO
Bragstad, Karoline	Denmark
Brytting, Mia	Sweden
Daniels, Rod	WHO Collaborating Centre, London, UK
Ellis, Joanna	United Kingdom
Hungnes, Olav	Norway
Lina, Bruno	France
McCauley, John	WHO Collaborating Centre, London, UK
Pohlmann, Anne	Germany/GISAID
Schweiger, Brunhilde	Germany
Beauté, Julien	ECDC
Broberg, Eeva	ECDC
Erlman, Elina	ECDC
Johansson, Karin	ECDC
Nicoll, Angus	ECDC
Plata, Flaviu	ECDC

Apologies presented by: Jan Mark Pohlmann (BLE, Germany), Helena Rebelo de Andrade (Portugal), Immaculada Casas (Spain), Maria Zambon (UK), Ian Brown (VLA, UK), Caroline Brown (WHO-EURO), Dmitriy Pereyaslov (WHO-EURO).