European Influenza Surveillance Scheme (EISS) and its future
4th Joint EC/ECDC/WHO workshop
Pandemic Influenza Preparedness
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History

• WHO global network of National Influenza Centres (NIC) since 1949

• Eurosentinel Scheme 1987-1991
  – Collaboration of sentinel networks of GPs, epidemiologists and virologists in Europe
  – Integrated reporting of clinical and virological surveillance data

• WHO CARE Telematics project Europe 1992-1995

• European Influenza Surveillance Scheme (EISS) (1995- )
  – Started with 7 countries and includes since May 2007 all 27 EU Member States plus Croatia, Norway, Serbia, Switzerland, Turkey, Ukraine

• Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) (2003- )
Countries and Laboratories in EISS

33 countries (27 EU MS + Croatia, Norway, Serbia, Switzerland, Turkey and Ukraine)
- Sentinel physicians
- Epidemiological institutes
- Laboratories

EU Community Network of Reference Laboratories for Human Influenza (CNRL)
- 40 laboratories
  - 35 WHO NIC
  - no NIC in Cyprus, Estonia, Lithuania, Malta and Ukraine

Description CNRL in Journal of Clinical Virology, 2005;34:87-96
Flu surveillance in the community

National Influenza Surveillance Network

Other sources
- Hospitals, other GPs
- Etc.

Sentinel physicians (GPs, Pediatricians, other)
- 1-100% of total doctors
- median 2.2% (range 0.4-100%) of total population

Nose/throat swabs, blood

Other labs

Reference lab
NIC/CNRL

Virological data

Clinical data

Epidemiology institute

Epidemiological data

Central national hub

Special reports
- Members, EC, ECDC, EWRS, ESCON, Flu contact points

Weekly Electronic Bulletin
- Community, Members, ECDC, EC, etc

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NIC/CNRL – WHO / ECDC interactions

FluNet

Laboratories

Virological data

NIC

CNRL

Automated data transfer

GISN

Virus isolates

Reference reagents

Co-ordination CNRL

EISS-CC

Bulletins, reports, etc.

MRC

National Institute for Medical Research

World Influenza Centre

Sharing of information and experiences

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Core data collection

• Epidemiological data (weekly)
  – Consultation rate (ILI and/or ARI)
  – Intensity of influenza activity
  – Geographic spread of influenza (WHO indicator)

• Virological data
  Weekly:
  – Type, subtype, strain characterization virus detections
    • Swabs collected by sentinel physicians
    • Swabs from non-sentinel sources (e.g. hospitals)
  – Dominant type or subtype
  Seasonally (start, half-way, end):
  – Antiviral susceptibility
Antiviral susceptibility

Europe dataset (VIRGIL)

Set up by VIRGIL in collaboration with EISS CNRL

Three seasons data available

Technology transfer to national NIC/CNRL established (protocols, reagents, courses)

Starting 2007/2008 season, situation update at start, half-way, and end of season on EISS website

National dataset
Basic tasks CNRL

1. Direct virus detection
2. Culture of virus
3. Typing and subtyping of virus
4. Strain characterisation of virus isolates
5. Diagnostic influenza serology
6. Archiving of clinical specimens and virus isolates
7. Capacity to detect antiviral resistance

These tasks comply with WHO roles of NICs:

http://www.who.int/entity/csr/disease/avian_influenza/guidelines/RoleNICsMayf.pdf
Other core services

- Mailing/discussion lists
- Reagents database
- Who-is-who and resources database
- Laboratory protocol library
- Influenza Sequence Database
- Five Virology Task Groups working on harmonisation and improvement of quality of routine surveillance
Who-is-who and resources database
Capacity of labs (N=40)

- Direct virus detection
- Virus isolation (cell)
- Virus isolation (egg)
- Typing A/B
- Subtyping H1
- Subtyping H2
- Subtyping H3
- Subtyping H5
- Drift analysis Antigenic
- Drift analysis Genetic
- Serology
- Antiviral susceptibility (NI)
- Antiviral susceptibility (M2I)
- Antiviral susceptibility (sequencing)
- Work at BSL3
- Work at BSL4

Percentage of labs (N=40)  
Capable  Not capable

Extracted July 2007
Virology Task Groups

**Aim:** to facilitate consistent performance of all laboratories in the basic tasks

- **Virus isolation**
  - Sylvie van der Werf, NIC, Paris, France
- **Antibodies**
  - Brunhilde Schweiger, NIC, Berlin, Germany
- **Molecular virology**
  - Olav Hungnes, NIC, Oslo, Norway
- **Quality Control Assessment**
  - Martine Valette, NIC, Lyon, France
- **Antiviral Susceptibility Testing**
  - Maria Zambon, NIC, London, UK

Journal of Clinical Virology, 2005;34:87-96
Vaccine, 2006;24:6717-6723
Virus Isolation

SOPs
- Isolation of influenza virus
- Plaque reduction assay
- Microneutralisation assay
- Biosafety issues
Antibodies
Testing RBCs for use in HI assays

Percentage of viruses with the highest or the second highest titer using different RBCs:

- **H3N2**
  - Turkey: 30%
  - Guinea pig: 80%
  - Chicken: 40%
  - Human: 90%

- **H1N1**
  - Turkey: 40%
  - Guinea pig: 70%
  - Chicken: 50%
  - Human: 80%

- **B**
  - Turkey: 20%
  - Guinea pig: 60%
  - Chicken: 30%
  - Human: 90%
Antibodies

EISS antigenic characterization pie chart

Europe, week 16/2005
Cumulative influenza virus isolate antigenic strain characterisations* (Total N = 2041)

- A/Hong Kong/99/2003-like (B/B)
- A/Shanghai/45/2004-like (B/B)
- A/New Zealand/1/2006 (H3N2)-like [890]
- A/California/7/2004 (H3N2)-like [851]

* Sentinel and non-sentinel specimens combined
Characterisations are based on the hemagglutinin protein (antigenic characterisations).
Influenza A virus isolates include both neuraminidase not subtyped and neuraminidase subtyped isolates.
EISS also collects data on genetic characterisations; for detailed antigenic and genetic characterisations click on this graph.

Antigenic Cartography

Guus Rimmelzwaan et al. NTVG, 2006
Molecular Virology

In collaboration with many other NICs provided:
1) Controls for H5 molecular testing:
   - cDNA A/Vietnam/1203/04
   - A/Vietnam/1203/04 H5 plasmid
   - A/Chicken/Cambodia/7/04 H5 RNA
   - A/Duck/Vietnam/TG24-01/05 inactivated H5N1 virus
2) Validated molecular testing protocols for differential diagnosis influenza virus types and subtypes
ISD – EISS private compartment
basic phylogenetic trees

Molecular Virology

AIM: timely monitoring of evolution of the virus and relate this to possible impact on burden of disease.

Basic tree

Own sequence

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Quality Control Assessment

• Culture and identification
• Molecular, including avian viruses, in collaboration with QCMD
• Follow-up help for less performing labs

• Participation obligatory for labs participating in EISS
• Explore possibility for serology QCA

"THE QUALITY-CONTROL INSPECTORS ARE VERY GOOD, THEY'LL NOTICE"
External Quality Assessment

virus culture detection, typing, subtyping influenza virus and RSV

1 QCA
n = 14

2 QCAs
n = 9

3 QCAs
n = 14

≥90% correct
100% correct
External Quality Assessment
molecular detection, typing, subtyping influenza virus

Labs in EISS returning results for flu A and A(H5) pilot molecular EQA (N=32)

- flu A detection
- flu A(H5) detection

False positive

1 H1
1 H5 + H1
1 H3 + H3
1 H1
Comment: This country (X) scores good in the interpandemic period, however in case of a pandemic the country should pay attention to surge capacity. Tool will be available beginning of 2008.
Conclusions

• Well developed network with great commitment of members to exchange information and to improve methodologies to achieve high quality virological surveillance of influenza in all its aspects, i.e. from virus detection to analyse of evolution of the virus and insight in antiviral susceptibility.

• Current funding covers costs for the development and maintenance of databases and the EQA programme.

• Costs for preparation of standardised reagents and research on improvement of methodologies are covered by laboratories and responsible ministries of a number of countries.
Post 2008 Scenario

- Structure functions and responsibilities will change
- Set strict conditions for outsourcing
  - guarantee clin epi viro link and automatic datatransfer at EU and national level
  - guarantee group process / solidarity
  - guarantee links with partners
  - EU and non EU members
  - guarantee current strong link with WHO
  - coordinator should be neutral and pandemic proof
  - agreement on location of (special) databases
  - at least three years funding