

Influenza A(H1N1), public health approach – Report on the research seminar organised by the EHESP, Rennes, on 11 May 2009

Report drawn up collectively by the presenters



Agenda for influenza A(H1N1) seminar Public health approach

10.45-12.45

- Welcome and introduction, issues and objectives (A. Flahault, Dean of the EHESP)
- International situation (update) (J C Desenclos, InVS)
- WHO-CoPanFlu: international, multi-centre cohort survey of 1000 households over 2 years (F. Carrat, Inserm-UPMC, X de Lamballerie, UnivMed-IRD-EHESP and A. Flahault, EHESP)

13.00-14.00 – Lunch (in situ) / seminar for EHESP personnel

14.00-15.00

- Social, economic, behavioural and management sciences (M. Setbon, CNRS-EHESP, JP Moatti, UnivMed-IRD-Inserm, C. de Sinaly, EHESP, B. Parent, EHESP)

15.00-16.00

- Project to study and monitor hospitalised patients (C. Leport, APHP-EHESP and F. Carrat, APHP-Inserm-UPMC)
- Randomised test of combination therapy vs monotherapy (C. Leport, T. Hanslik and T. Blanchon, Inserm-UPMC)

16.00-17.00

- Importance of data for modelling (P Y Boëlle, Inserm-UPMC, E. Vergu, Inra, M. Béra, EHESP)
- Links between health watch, research / scientific watch and health authorities (J C Desenclos, M. Setbon)
- Sundry questions: other research required, general approach

17.00

- Conclusions, the future, methods and proposed work schedule (A. Flahault)

Participants: see list attached at appendix 2

Issues

- **Imminence of the pandemic** -> *rapidity* of reaction
- **Complexity of the issue**-> *interdisciplinarity* of the response
- **Globalisation: Pandemic**-> *internationalisation* of the problem (emphasis on third world countries)
- **Scientific challenge** -> *Rapidity+interdisciplinarity+internationalisation+excellence*

Historical flashback: *Annals of the Pasteur Institute, 1919, p.448*

“Action of Antipneumococcus serum during pneumonia and influenza complications

by Dr Louis CRUVEILHIER

It has been said with reason that ‘flu condemns and additional infection executes. It is increasingly apparent that the damage caused throughout the world by influenza is nearly always due to its complications which give the illness a special character and a particular gravity. Of the various complications, those that affect the respiratory system are by far the most common. Sometimes, there are simple cases of pulmonary congestion. At other times, one can observe the usual symptoms of pneumonia. More rarely normal auscultation reveals ganglia ...”

1. CoPanFlu, multi-centre, international cohort survey

- Principal Investigator: Fabrice Carrat, Inserm-UPMC (UMR-S 707)
- International co-ordination: EHESP (Dean Antoine Flahault)

Aims

Characterise the “natural” history of the infection and its variability, determine how it is transmitted
Describe the public health impact in terms of morbidity, complications and consumption of health resources by the S-OIV (swine ‘flu) infection
Study the individual, collective and environmental determinants of S-OIV ‘flu infection and the determinants of the clinical expression of the infection
Study changes in behaviour and evaluate the level of risk perception and its evolution over time
Evaluate the efficacy of the measures set up (treatment, vaccination, barriers)
Characterise the homeotypic, heterosubtypic and heterotypic immunity of participants, according to age – evaluate herd immunity
Characterise the viral diversity and ‘flu virus evolution mechanisms

A modular structure

module 0: epidemiologic platform / cohort of households

module 1: epidemiology: measure the incidence of infection by S-OIV and risk determinants, evaluate barriers

module 2: virology: viral diversity, evolution of ‘flu viruses, virus/immunity

module 3: immunology: explore the types of immunity and duration of immunity

module 4: human and social sciences: KABP (knowledge, attitude, behaviour and practices) and risk perception

module 5: mathematical modelling: measure natural history parameters of the disease. Medical-economic modelling.

module 6: international comparisons

CoPanFlu: modular survey – partners

France – EHESP

m1 Epidemiology Public health impact UMR-S707	m0 Prospective cohort 1,000 households monitoring for 2 years UMR-S707	m5 Modelling Environmental factors UMR-S707 INRA
m2 Virology Serology Virology lab	m3 Cellular immunology To be defined	m4 Human and social sciences (HSS) U912
		m6 International comparisons IRD-EHESP

Selection of households

Ideally: Representative of the French population

Sampling should cover representative areas, rural/urban – IRIS

Agreement by all members of the household

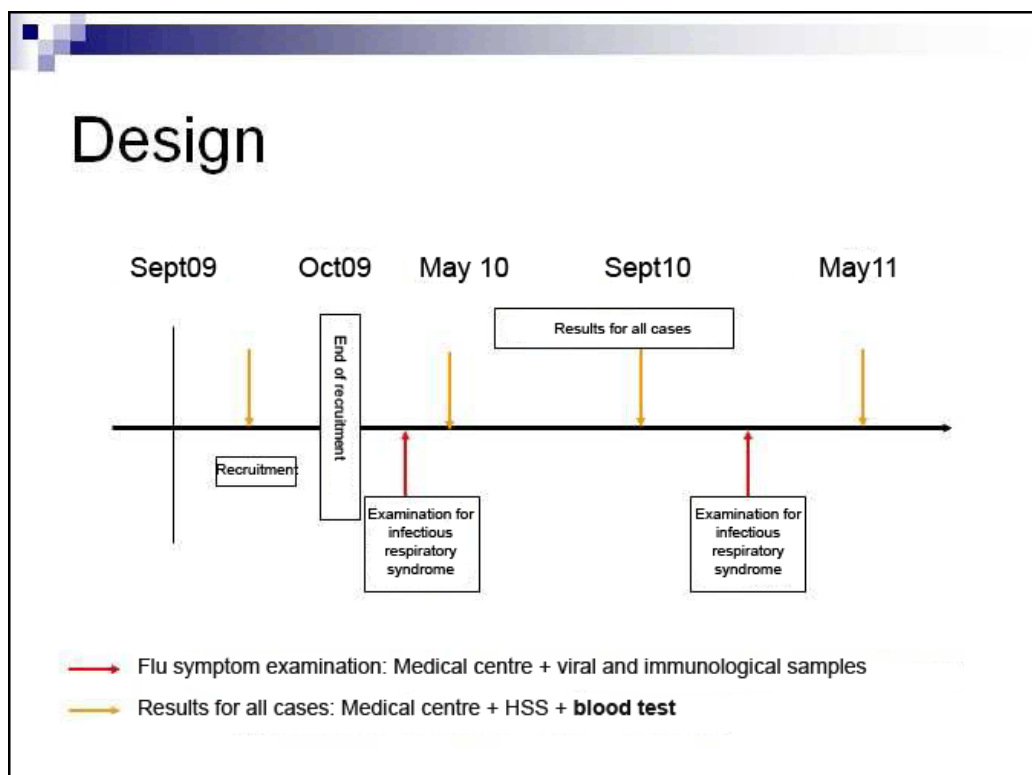
Recompense for taking part in project

Initial data

Clinical and vaccination records
Risk perception
Characterisation of environment and social contacts
Initial blood tests
Serum bank + evaluation of seroprevalence to the various 'flu viruses, including S-OIV
Study of immunity types in a sub-sample

Monitoring

Each year, between May and September
Clinical and serological report
Study of immunity types in the same sub-sample
Active monitoring of respiratory infections during periods of epidemics
Weekly contact with the households
Collection of clinical, epidemiological, therapeutic, preventive, immunological and virological data for ALL members of the household if one member has an infection; monitoring the household 5 times over 20 days taking samples



Information system

All samples will be centralised, creation of data banks
An electronic data collection platform will be set up
Regional or departmental organisation of handling and collecting data
Network of survey investigators (1 per 100 households) + research nurses

Provisional schedule

Scientific Committee->May 2009
Steering committee and scientific advisory board (for international)->May 2009
Core Protocol ->May 2009
Specific protocols (viro/immuno/HSS) -> June 2009
Kick Off Meeting->June 2009
CPP/CNIL (Data protection) ->June/July 2009

International partners (as at date of meeting)

WHO, Geneva (Sylvie Briand, Isabelle Nuttall)
European Union (ECDC, Angus Nicoll, ASPHER, Jacek Sitko)
USA (NIH-Fogarty, Mark Miller, *pending confirmation*)
UK, Andrew Hayward, *pending confirmation*
Germany, Ursula Schlipkötter
IRD network (Senegal, Benin, Cameroon, Gabon, CRVOI-La Réunion)
Fondation Mérieux network
EHESP network (Mali, Laos, Bolivia)

2. FluCo, cohort survey of patients infected by the influenza A(H1N1) virus

- Principal Investigator: Catherine Leport, EHESP-Paris Diderot-APHP
- Methodology: Fabrice Carrat, Inserm-UPMC, UMR-S 707, and JC Desenclos, InVS

Cohort targeted on the first cases (hospital and/or town), to collect clinical and epidemiological data on suspected patients, centred on contagiousness and gravity, the two essential characteristics for adapting the response strategy to a possible pandemic. At NATIONAL level: allow for international extension

A founding alliance bringing together clinicians, public health, epidemiologists and methodologists as well as virologists, immunologists, social sciences, etc
It is supported by Inserm, IMI and ISP and the EHESP.

Aims

- Main aim

Study the **determinants of exposure and the gravity** of the first suspect cases

- Secondary aims

Determine the clinical, epidemiological, biological and virological predictors

Epidemiological: classification of cases, incubation, contagiousness, evaluation of protection and prevention measures, etc

Clinical: clinical presentation and atypical forms, signs of gravity, evolution, death and cause of death, efficacy of treatment,

Human and Social Sciences: motivations and compliance with measures taken, etc

Microbiological: infectious agents, typing, sensitivity to anti-infective drugs, etc

Immunological: response modalities

Methods

Patients with suspected flu H1N1, treated in the first treatment structures set up

Collection of epidemiological, clinical and psycho-social data

Creation of a biotheque (blood and ad hoc biological fluids) to characterise the emergent infectious agent

Inclusion criteria: All patients with a possible S-OIV infection according to the InVS definition

- an acute respiratory febrile illness combining:
fever >38°C (100°F) or myalgia/stiffness or asthenia/fatigue

AND respiratory signs: cough or dyspnoea

- with illness onset

within 7 days of travelling to a community where S-OIV was circulating (according to the list of countries and regions kept by InVS), or within 7 days of close contact with a suspected, probable or confirmed case of S-OIV

infection during his/her/their own infectious period (starting one day before symptom onset)

A close contact is defined as

persons living in the same place approach within 1 meter, physical contact, immediate neighbour during a journey, or in a classroom or a workplace

Informed agreement is required.

Clinical

Patients will be monitored daily during the whole period of hospitalization until discharge, with a final visit after one month (Day 30). Data collection will be monitored by a trained survey supervisor dedicated to the survey. Each symptom will be classified daily on a predefined scale (see appendix).

Epidemiological

All possible cases will be investigated on admittance according to risk factors of S-OIV infection. In addition, data will be linked to epidemiological investigations of contacts performed by InVS.

Virological

Nasopharyngeal swabs (or other respiratory specimens, e.g., nasopharyngeal aspirates for children, bronchoalveolar lavage) will be collected daily until discharge and analysed using real-time quantitative PCR in accordance with the procedure defined by the National Reference Centres. (link: <http://...>). Supernatant from nasal swabs will be stored to create a dedicated databank for further virological and biological studies.

Immunological

Immunogenicity measurements will be performed on Day 1, Day 2, Day 5 (or on discharge if earlier) and on Day 30. Blood samples (30 ml) will be processed within 24 hours centrally after shipping (see list of laboratories taking part). PBMCs will be isolated by ficoll centrifugation and stored in liquid nitrogen in accordance with the procedure (link: <http://...>). Sera will be stored for further studies.

Flu - CO : Follow -up

<u>Assessment / Procedure</u>	D0	D1*	D2	D3**	D4**	D5	Dis***	D30
<i>Study days</i>	0	1	2	3	4	5		30
Informed consent, medical history	x							
Physical Examination	x	x	x	x	x	x	x	x
Laboratory tests	x					x		x
Treatment intake and adverse events	x	x	x	x	x	x	x	x
Virological specimens collection	x	x	x	x	x	x	x	
Serum sample collection	x					x		x
Blood collection for immunological analysis		x	x			x		x

3. BiVIR, a randomised clinical trial to compare a combined therapy of Oseltamivir + Zanamivir with each of the two drugs on their own in general practice

- Principal Investigator: Catherine Leport, EHESP-Paris Diderot-APHP
- Associated organisations: Réseau Sentinelles [French Communicable Diseases Computer Network] (Inserm-UPMC UMR-S 707), Grog, CNR Nord and Sud
- Methodology: France Mentré and Xavier Duval (APHP, Université Paris Diderot)

Background

In the advent of a 'flu pandemic, anti-viral drugs have a major role to play at the outbreak of the pandemic to reduce the impact of the emergent virus before vaccines are available. The BiVIR trial (Evaluation of Efficacy and Safety of Oseltamivir and Zanamivir) has been set up and has all the official permits required so that it can be activated rapidly should a pandemic occur in 2009-2010. The BiVIR trial would monitor patients infected by the virus and showing symptoms, with all the documentation associated with that of a randomised study.

Experimental plan

Randomised double-blind trial on the virological efficacy in three groups of 300 patients. The patients selected by the trial's general practitioners will be stratified depending on the time between the onset of the first symptoms and the time of the first anti-viral treatment at the practice (less than 12 hours, between 12 and 24 hours, between 24 and 36 hours). The trial will compare the virological efficacy of the association of oseltamivir and zanamivir with the use of oseltamivir with a placebo and zanamivir with a placebo in the curative treatment of suspected 'flu using a rapid positive diagnostic test for a type A influenza virus.

The trial will be carried out during an outbreak of seasonal 'flu on an ambulatory care basis.

Therapy 1: oseltamivir, 75 mg twice a day, *per os* for 5 days with zanamivir, two 5mg inhalations (i.e.10mg) morning and evening, i.e. 20 mg per day for 5 days.

Therapy 2: oseltamivir, 75 mg twice a day, *per os* for 5 days with a placebo instead of zanamivir, two 5mg inhalations (i.e.10mg) morning and evening, i.e. 20 mg per day for 5 days.

Therapy 3: zanamivir, two 5mg inhalations (i.e.10mg) morning and evening, i.e. 20 mg per day for 5 days with a placebo instead of oseltamivir (75 mg twice a day for 5 days)

Assessment criteria

The main criterion is the virological efficacy in terms of the percentage of patients with a negative RT-PCR for the type A Influenza virus at Day 2.

The secondary criteria are the duration and severity of the symptoms, the frequency of the onset of 'flu syndromes at Day 14 in members of the household with whom the patients have been in contact and who did not have any 'flu syndrome before or at the same time as the patients in the trial, the undesirable events recorded in the three arms of the study, therapeutic observation, the number of times and length of time members of the household were on sick leave, the frequency of complications of an infectious nature (ear infections, bronchitis, sinusitis and pneumonia), the consumption of antibiotics and the cost / efficacy ratio of the treatment. The frequency of resistance to anti-viral drugs will be studied later.

End of the first BiVIR campaign (May 2009)

Success of the 1st phase of inclusion: 542 patients (of 900 expected)

End of epidemic -> Suspension of inclusions

Target number of patients not fully met -> Continue trial: open centres

Opinion of independent committee

Continuous updates to those involved

Interim analysis in BiVIR: for and against

• For

- Stop the trial if no differences are recorded
- Stop the trial if the combined therapy is significantly more effective
- Save human and financial resources
- Results can be published more rapidly if the trial is stopped

• Against

- Not planned at the start
- Problem of changing the main criterion
- Analysis of virological results only
- Results would be more representative if trial were carried out over two campaigns
- Methodological problems
 - Two comparisons (what happens if one is stopped but not the other?)
 - Stratification according to timing? (requires CRF data)

4. Risk perception

- Principal investigator: Michel Setbon, CNRS-EHESP (interdisciplinary risk management centre)

Aims

Observe, understand and anticipate to be able to publicise this knowledge (publications) and guide public action

Interdisciplinary experience of the chikungunya (and dengue fever) epidemics: analogies?

But in this case it is possible to be operational before the “great wave” and have tools and knowledge that can be put to use during the pandemic (if there is one)

Opportunity to construct a bridge between monitoring and research

Research schedule

• Before and up to the time when the pandemic is established for all to see (phase 1)

Know, characterise, monitor and model the relationship between risk perception (of a pandemic and of falling victim to it), perceptions of protection measures and foreseeable behaviour of the general population

Analyse the identified cases of influenza A(H1N1r) in socio-behavioural terms

Model this data to draw up scenarios and adjust public communication on the pandemic risk

• During the pandemic (phase 2)

Determine the main factors of contamination by the new A(H1N1) virus

Measure, foresee and evaluate the health and socio-economic impact of the pandemic

Determine ways of adapting the health system (those involved and the system itself) and the consequences

Estimate the needs in countries in the southern hemisphere

Evaluate the implementation of the national plan for combating the pandemic

• Afterwards, when the pandemic is receding (has died out?) (phase 3)

This will depend in part on the treatments and vaccines used

Anti-viral drugs vs self-medication and traditional medicines

Availability of a vaccine? Willingness to be vaccinated?
The most affected social categories?
Political management of the pandemic?
Role of the media?

Basis

A priori, a cohort of 1,000 households is well suited to the multi-disciplinary aim and monitoring
Can be adapted easily to changing circumstances
Useful standardisation for international comparisons

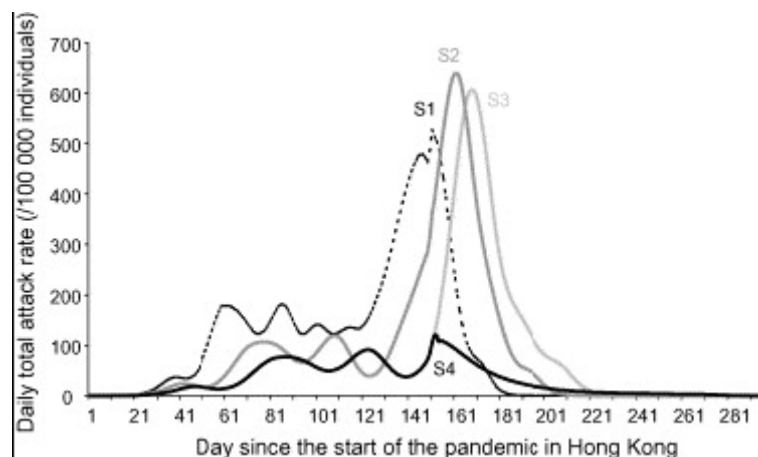
Ad hoc transverse surveys?
Specific groups? Doctors, nurses, migrant populations, etc.
Hospitals?
Groups at risk? Age, socio-cultural situations, etc.
Developing countries?
Other?

5. Centre for outbreak analysis and modelling

Principal Investigator: Pierre-Yves Boëlle, INSERM-UPMC (UMR-S 707)

Use of modelling:

- Pre-pandemic: Planning
 - Pandemic: Monitoring / Efficacy of actions
 - Post-pandemic: Analysis, etc
- What would happen if ...



What parameters are required?

Generation interval

From primary case to secondary case

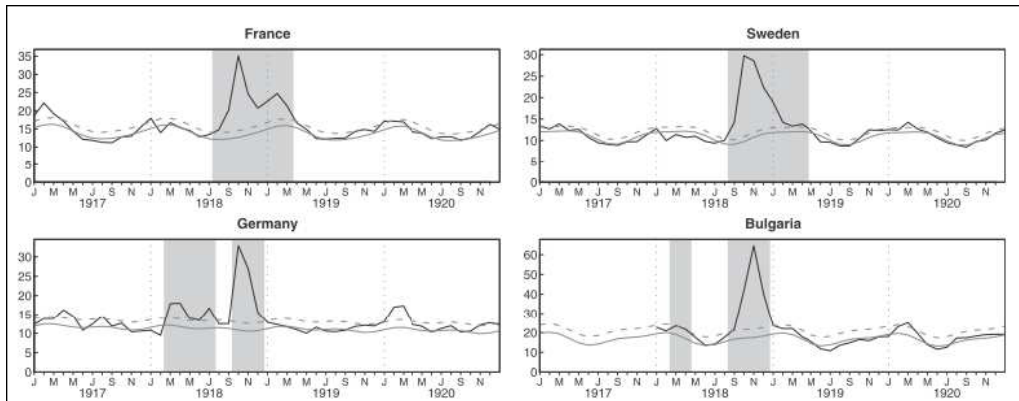
Reproduction rate

Number of descendants per case (R_0)

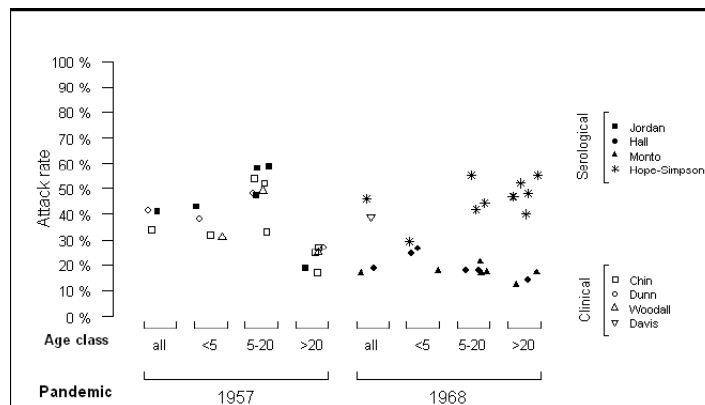
Attack rate

ppm of population affected

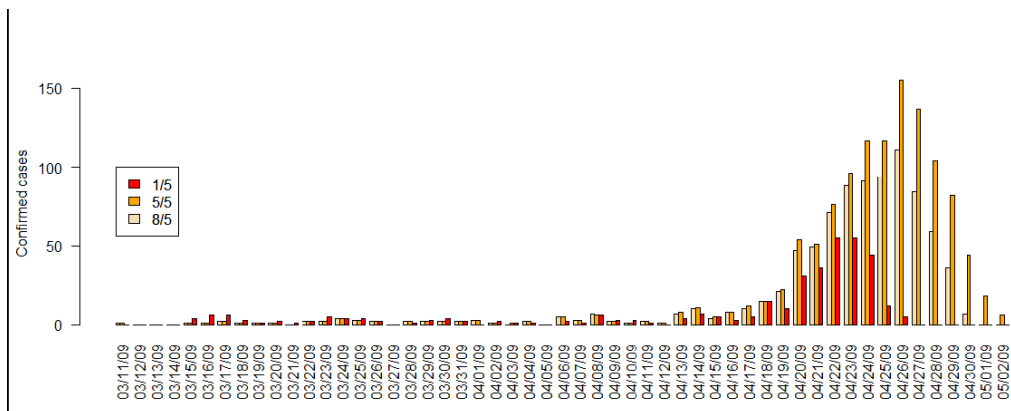
1889, 1918, 1957, 1968: Mortality all causes, specific, morbidity: used to estimate R/R_0



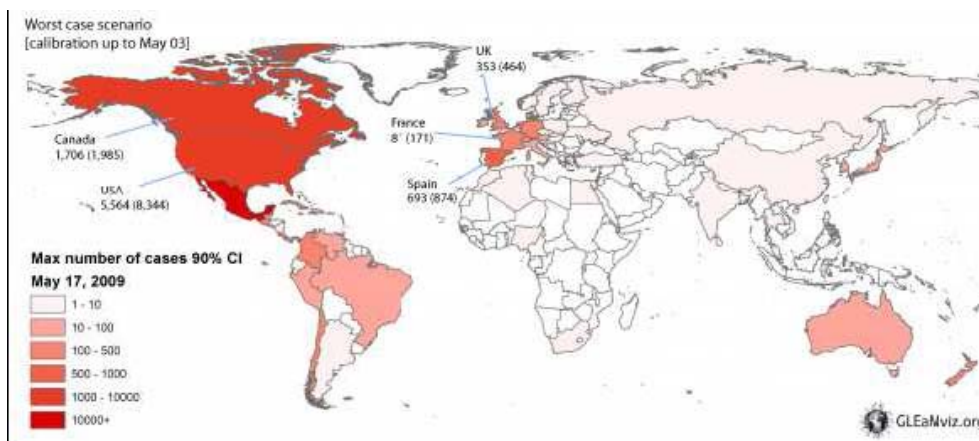
1957, 68: Study of households / Serological / Clinical: used to estimate the attack rate



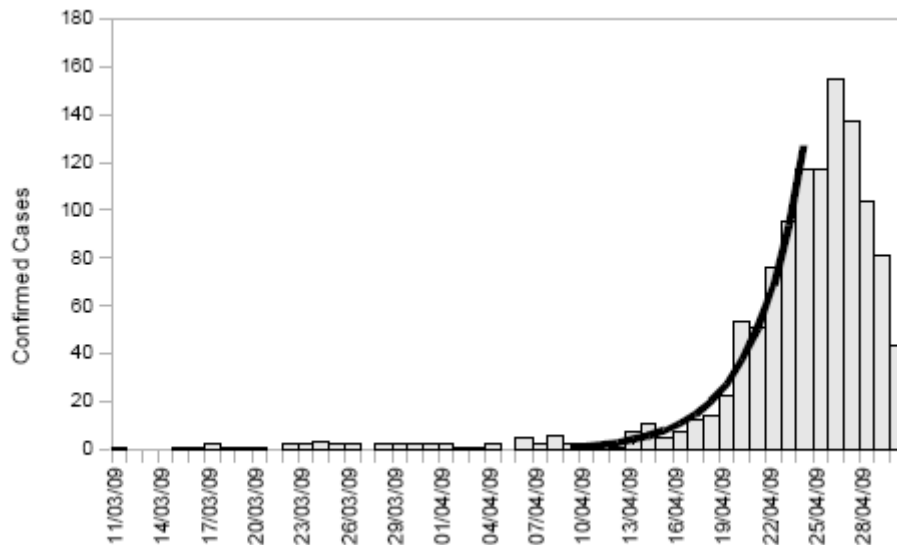
What is the current state of the epidemic?



How will the epidemic evolve?



Exponential growth of the epidemic in Mexico (~30% per day)



Depending on the generation interval:

R could be between 2.2 and 3.1

But overestimation is probable (under-declaration)

What is the value in the USA?

What is the generation interval?

The cases are younger than expected in comparison with the pyramid of ages in Mexico

The distribution of the 'flu may differ from country to country: it is therefore important to carry out new estimates for different localities

Can one create a *Centre for Outbreak Analysis and Modelling*

Adapt existing models for real time analysis of the epidemic

Data from laboratories, hospitalisation, monitoring network, etc

Adapt the models for measuring the efficacy of actions

After the pandemic

Analyse the natural experiences

6. Watch-Research interface

- Presenter: Jean-Claude Desenclos, InVS

To allow data collected by monitoring-watch to be used for research (modelling, etc)

To allow the observations of the watch to be used for drawing up hypotheses and for research guidelines

To optimise data collection systems so that they are as complementary as possible and can interact with any common tools

To support the implementation of epidemio-clinical data collection in institutions (and financially if necessary)

Benefits of research work as an aid for decision-making

• Phase 5A

- Identify imported cases

- Detect grouped cases (for corroboration)

Notification (>3 cases in an institution in <1 week)

Via DDASS/InVS-CIRE/InVS

Notification sources

health establishments, by health professionals (hospital doctors, or doctors responsible for notification of nosocomial infections, if the case is of nosocomial origin)

homes for the elderly: by the establishments' medical co-ordinators

schools: by school doctors or nurses

armed forces: the armed forces' doctors

general practitioners: by the health professionals who have identified the cases

businesses: by occupational doctors

more generally by any health professional

Virological confirmation

Epidemiological investigation

• Phase 5B

– Included cases

– Community monitoring

Networks for monitoring seasonal 'flu:

Networks for monitoring epidemics in the community (Réseau Sentinelles, Network of Regional Influenza Observation Groups (GROG), Réseau SOS médecins in mainland France; specific networks of general practitioners in overseas departments).

Virological monitoring by continuing the sampling operations of the GROG networks and RENAL hospital network to monitor the evolution of strains and their sensitivity to anti-viral drugs; included in the European Influenza Surveillance Scheme (EISS)

Monitoring severe forms:

Hospitalisation rate (Sentinelles)

Hospital emergency network (Oscour network) to monitor those admitted each day to emergency services and hospitalisation with 'flu + gravity score + hospitalisation rate

Network for studying and monitoring hospitalised cases (C Leport, F Carrat, UMR707-UMPC)

Monitoring specific deaths related to 'flu:

22 DDASS network which monitors the annual mortality related to flu will be extended to all DDASS.

Improve (accelerate) the electronic reporting of cause of death in hospitals.

Quantitative monitoring of deaths from all causes based on data provided by INSEE (network of 1042 communes):

analyses of mortality by age groups and geographical zones

• Phase 6

– Monitoring communities (cf above)

• Projects programmed at and with InVS (before a pandemic)

– GEA-IRA surveys

– seroprevalence vaccination surveys

Efficacy of vaccines in the framework of the European project (Sentinelles)

Watch tools to be developed?

Weekly consultation of panels via internet

Use of models as an aid to decision-making

Collaboration between InVS-UMR707

Estimating R (PY Boelle)

Simulation model (F Carrat)

Human and Social Sciences: advantage +++ for KABP (knowledge, attitude, behaviour and practices) (experience from Nicolle survey)