



# Global Influenza Hospital Surveillance Network

## GIHSN 2014 Annual Meeting



Anncy, 13-14 October 2014

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## Foreword

This is a comprehensive report of the 2014 GIHSN Annual Meeting; it is to be a companion of the slides of the presentations, which presenters generously accepted to share with the meeting attendees. We suggest that Annex 1 (meeting agenda) and Annex 2 (list of participants) are used when in doubt on who presented a certain topic.

As we did all along the meeting we strongly recommend that the manuscript *Hospitalizations with influenza during the 2013–2014 Northern Hemisphere influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network* be consulted to better understand and develop the methods of the GIHSN field work.

## Executive Summary

The Global Influenza Hospital-based Surveillance Network (GIHSN) is a public-private partnership constituted by FISABIO (*Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana*), Sanofi Pasteur, Fondation Mérieux and country sites affiliated with health authorities, each one supervising a network of hospitals following the same core protocol.

This hospital surveillance network focuses on estimating the burden of disease due to severe influenza and the burden of the disease attributable to each strain. In addition, when possible, it provides the framework for estimating effectiveness of seasonal influenza vaccines in prevention of severe cases in various age and risk groups. A yearly-pooled analysis of the data collected by the network is performed by the coordinating center (FISABIO) and presented during an annual meeting.

Last season (2012-2013), in the networks' first year, hospitals from Moscow, St. Petersburg, Turkey, France and Spain participated in the study. The GIHSN covered 4 countries and 21 hospitals, and collected a large set of laboratory-confirmed hospitalized cases of influenza for a single season (n=1,545).

This season (2013-2014), China and Brazil have joined the GIHSN that is intended to continue to expand globally and attract new partners. Through this broad geographical coverage, the standardization of data collection and its expected sustainability over sequential influenza seasons, this network will allow for a better understanding of influenza epidemiology.

In 2013–2014, the GIHSN included 24 hospitals (6 in Spain, 4 in the Russian Federation, 4 in China, 2 in Brazil and 7 in Turkey). It was a pilot year for Brazil and China. Among the 5,925 patients included with polymerase chain reaction results, 1,139 (19%) were positive for influenza.

The second annual meeting took place on 13-14 of October 2014 in the Fondation Mérieux conference center in Annecy, France.

This meeting was aimed to:

1. Discuss the different study sites fieldwork experiences and protocols to analyze and derive best methodological practices
2. Review the data and results generated by the study sites and from data pooling.
3. Discuss way to disseminate the information generated
4. Review the current framework of this global partnership, principles of collaboration and network future prospects.

Main points covered:

## **Influenza severe outcomes epidemiology**

Every participant of the meeting agreed that heterogeneity is an asset for the network as well as a challenge for an accurate analysis of the results. Indeed, it is difficult to consider all sites as a whole and a lot of effort is to be devoted to make procedures homogenous while being respectful to local needs and characteristics.

In the Northern Hemisphere influenza appeared around week 3 and slowly declined after week 12. H3N2 was dominant in the Russian Federation and Turkey whereas H1N1 circulated mainly in Valencia (Spain).

Influenza B Yamagata was more present in the Beijing province.

There were only 3 patients positive for B Victoria.

H1N1 appeared to be more present in those >50 years of age in contrast to H3N2 which was more present in younger population. Influenza B Yamagata appeared to be more present among children and teenagers (5<18yo).

Pregnancy and obesity were significant risk factors for being hospitalized with influenza:

- A/H1N1, A/H3N2 or B/Yamagata in pregnant women
- A/H1N1 in the obese

The strains' circulation by site observed in the GISHN might was related to the representation of the pediatric population on some sites (types of hospitals), of young people (considering the inclusion of a high number of pregnant women) in Moscow and the elderly in Valencia (Spain).

## **Influenza Vaccine Effectiveness (IVE)**

A preliminary estimate of IVE for the GISHN 2013/14 season (Zhejiang and Brazil sites excluded) was presented during the meeting (OR 0.61 (0.49-0.77)). GISHN IVE estimates were adjusted for age (years) and epidemiological week of admission (splines), and underlying chronic illnesses.

## **Study sites experiences**

Influenza vaccine uptake remains low in some countries.

Some investigators consider that it is difficult to ascertain the vaccination status of enrolled patients relying on self-reporting due to recall bias, in other sites recall and

registries information is used as previous work validating both and using capture-recapture methods showed that this minimized misclassification.

Protocol adaptations will be made in order to amend eligibility criteria that generated low numbers of screened patients; hence, for Fortaleza the area considered for residency will cover adjacent provinces and the 48 hours from admission criteria will be set to 72 hours; the inclusion criteria of seven days since symptoms onset to admission will be, however, maintained. Except for those two points, even if other exclusion criteria were discussed, application of the protocol are to be reinforced and definitions harmonized.

Although the GIHSN aim is to describe influenza epidemiology and influenza vaccine effectiveness, this should not be seen as a limitation to develop other particular research interests by sites or work on other topics (Other respiratory viruses, economic evaluation, or others) under GIHSN support.

New guidelines will be produced for data quality. The coordination Office plans to work on a protocol and if needed and funds are available to run a Data Management workshop aimed at site's data managers.

### **Opportunities for synergies**

It is advisable to study other hospital-based surveillance networks, in order to put GIHSN in a more global context and look for collaboration opportunities, as it seems possible to build bridges for cooperation and experience-share.

### **Publication strategy and network visibility**

As an important achievement, the GIHSN published data from the season 2012-2013 in order to present publicly the first year experience of the network, pilot, achieved goals and limitations found. A preliminary report of the 2013-2014 season results has been sent for publication.

A website has been conceived to promote the network, with an external component and a community platform for GIHSN partners.

### **Feedback and improvements**

The GIHSN is on track to provide a global picture of the epidemiology of severe disease due to influenza.

According to external experts and partners, points that are to be considered to improve the GIHSN operations and future outcomes are:



- Contact with the coordination team is essential when any sort of doubt arises, and to prevent any delays.
- Inclusion criteria can be tailored to the needs and characteristics of the specific sites, however, they are to be contemplated in the core protocol and any change or adaptation is to be written down and communicated with the coordination center, and needs to be consistent within the site and kept explicit.
- Influenza Vaccine Effectiveness (IVE) is a secondary objective for this network.
- As IVE estimated is compared to negative admissions it could be considered to compare IVE results from hospitalized patients to IVE results in patients that come for ambulatory care.
- It would be interesting to additionally study the serological serums and look for immunity and antibodies.
- Opportunity to study the effectiveness of different vaccines.
- Pooling across seasons would also be a good idea to increase sample size when looking at calculating IVE.

For the coming season, the network will expand, incorporating 6 hospitals from Mexico and 1 hospital from Czech Republic into the GIHSN.



## Meeting report

### Session 1: Setting the context

#### Current framework of GIHSN

##### Genesis

- Flu epidemiology is mainly about surveillance, even though there are still existing gaps in the knowledge of influenza epidemiology
- The countries and sites selected for the network are based on their motivation, geographic representativeness, ability to conduct epidemiological studies, availability of laboratory facilities and influenza surveillance experience.
- A hospital network is used, because severe cases of influenza requiring hospitalization are probably the most influential factors in term of flu vaccination advocacy and cost-benefit evaluation of vaccination.
- There are advantages towards applying a hospital surveillance network compared to a General Practitioner network. It is easier to standardize and coordinate.

##### GIHSN Objectives:

1. Document the burden of severe influenza (leading to hospitalization) and raise awareness about influenza morbidity
  2. Document the burden of disease attributable to types and subtypes
  3. Evaluate vaccine effectiveness against hospitalizations from influenza and related complications (only for a subset of sites)
- Such platform allows for yearly flu burden and vaccine effectiveness data for various populations
  - Additional piggy-back components can be added to respond to other scientific question if needed

##### Global Influenza Hospital Surveillance Network

- The network was initiated by Sanofi Pasteur in 2011
- The network is animated by FISABIO
- It is a network of country sites, each one coordinating 1 to 7 hospitals
- There is a standardized core protocol with local adaptation based on national priorities and feasibility

- All study sites are public partners, where part of the costs is usually supported by the partners
- The study sites have full ownership of their data
- One of the aims is to create a sustainable network, where long term initiatives are planned to be renewed every year depending on satisfactory outputs and budget availability
- Sites are encouraged to publish locally their data, and pooled analysis is presented and discussed annually by the FISABIO at the global meeting
- This 2013-2014 season 24 hospitals participated in the network, from Spain, Brazil, Turkey, Russia, and China. The coming season hospitals in Mexico and Czech Republic will join the network

#### **Added-value of the network**

- The network is an example of public and private partnership with transparency and mutual trust
- The network aims to estimate the global public health impact of flu vaccine, and the outcome that comes out of this platform over the year has most probably a better external reproducibility and a lower cost than a one shot efficacy study

#### **Expectations**

- In order to keep this platform and network sustainable, developing partnerships with similar networks would be an asset
- The platform can also be used for other related activities
- One of the aims for the network is to be more cost efficient and to come together and converge the methodological processes

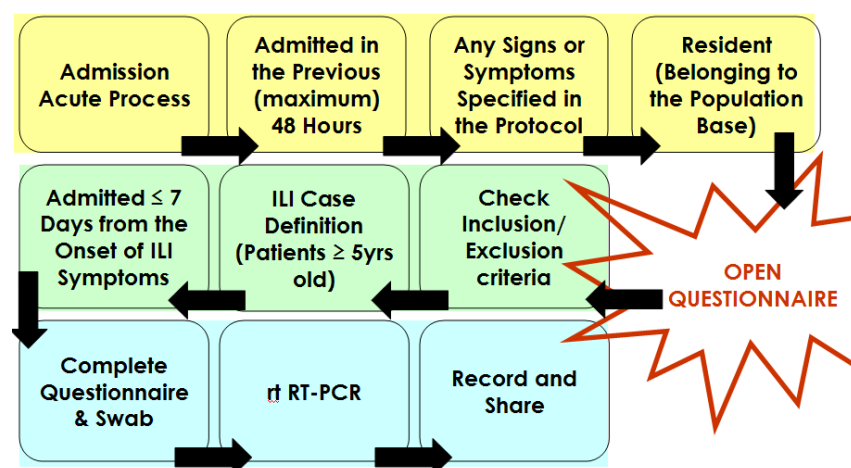
### **Outcomes and challenges of the GIHSN**

#### **Background**

- Influenza is a global public health problem. Worldwide, every year 10-18% of the population will have an influenza infection, 5% to 10% of the population will have clinical manifestations; influenza infection will be involved in 5,000,000 admissions and 700,000 deaths annually.
- There is, therefore, opportunity to generate high quality information on the epidemiology of influenza-related severe disease.
- Prospective studies with laboratory confirmed endpoints are required to better assess the contribution of influenza to severe morbidity
- Hospitals are the natural place to study severe influenza cases

## Outcomes

- An multinational network of hospitals coming from different countries has been established, where all sites follow a common approach based on:
  - Prospective hospital-based active surveillance study
  - Each site defines the beginning and the end of the influenza period according to their local aspects
  - All residents and eligible admissions are approached consecutively without previous knowledge of vaccination or influenza status
- Supporting documents have been generated and shared with sites in order to follow a common approach:
  - Core protocol
  - Core questionnaires (therefore a minimum set of common variables)
  - SOP (Standard Operating Procedures)
  - DMP (Data Management Protocol, planned)
  - SAP (Statistical Analysis Protocol, on going)
- The following sites participated during the 2013-2014 season:
  - 2 hospitals in Brazil
  - 5 hospitals in China
  - 4 hospitals in Russia
  - 7 hospitals in Turkey
  - 6 hospitals in Spain
    - In the 2014-2015 season 6 hospitals in Mexico and 1 hospital in Czech republic will join the network
- To summarize the common fieldwork processes at each site are as follow:



- The Coordination Office has been put in place in order to animate the network a provide support to all implementing sites:
  - Coordinator: Joan Puig-Barberà

- Epidemiologist: Angels Natividad-Sancho
- Epidemiologist: Anita Tormos
- Data manager and statistical support: Ainara Mira-Iglesias
- Research assistant: Amparo Buigues-Vila
- A summary of the methods and results from the network (preliminary results of the northern hemisphere sites) has been submitted for publication and the manuscript is shared with attendees: ***Hospitalizations with influenza during the 2013-2014 Northern Hemisphere Influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network; Supplement article, Influenza and Other Respiratory Viruses. IRV-2014-086***

### **Results (2012-2014)**

- In the past two seasons around 20,000 eligible admissions were reported to the Coordination Office, and around 12,000 were swabbed.
- The first season (2012-2013) of the GIHSN was more intense than the second season (2013-2014), whereas in the first season all influenza viruses were circulating, in the second season influenza A was predominant.
- The distribution of included patients in comparison to the distribution of patients positive for influenza was similar in all sites, indicating that there was no gross by site selection or misclassification bias for laboratory confirmed influenza.
- Across the northern sites of the GIHSN in the 2013-2014 season there was an average of 20% of influenza positives by site. It was also seen that there were differences in terms of the populations represented: elderly in Valencia, the young adults in Moscow, the pediatric population in St. Petersburg, but globally all ages are represented

### **Congresses, meetings and publications**

- The GIHSN results have been presented at different congresses, meetings and have also been published in different journals
- In 2012-2013:
  - Options for Control of Influenza
  - ISV
  - First GIHSN annual meeting (Valencia 17-18 June, 2013)
  - Puig-Barbera, J., Tormos, A., Sominina, A., Burtseva, E., Launay, O., Ciblak, M., Natividad-Sancho, A., Buigues-Vila, A., Martinez-Ubeda, S., Mahe, C., Group, on behalf of T.G., 2014. ***First-year results of the Global Influenza Hospital Surveillance Network: 2012-2013 Northern hemisphere influenza season***. BMC Public Health 14, 564.

Available at: <http://www.biomedcentral.com/1471-2458/14/564>

- Puig-Barberà, J., Natividad-Sancho, A., Launay, O., Burtseva, E., Ciblak, M.A., Tormos, A., Buigues-Vila, A., Martínez-Úbeda, S., Sominina, A., the GIHSN Group, 2014. **2012-2013 Seasonal Influenza Vaccine Effectiveness against Influenza Hospitalizations: Results from the Global Influenza Hospital Surveillance Network**. PLoS ONE 9, e100497.

Available at:

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0100497>

- In 2013-2104:
  - SEE
  - ESWI
  - ISV
  - Second GIHSN annual meeting (Annecy 13-14 October, 2014)
  - Joan Puig-Barberà, Anita Tormos, Svetlana Trushakova, Anna Sominina, Maria Pisareva, Meral A. Ciblak, Selim Badur, Hongjie Yu, Benjamin J. Cowling, Elena Burtseva, The GIHSN Group, 2014. **Hospitalizations with influenza during the 2013-2104 Northern hemisphere influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network**. Influenza and Other Respiratory Viruses.

### **Next steps**

For the coming season, the network will expand, incorporating 6 hospitals from Mexico and 1 hospital from Czech Republic into the GIHSN.

The outcomes and results of this season will be written in two different reports; 1) 2014 GIHSN Influenza epidemiology and 2) 2014 GIHSN overall influenza vaccine effectiveness.

Data management activities will also be put in place, in order to improve the quality and consistency of the data.

### **Limitations, strengths and challenges**

#### **Limitations:**

- Completeness of reported information of the "exclusion" criteria part of the questionnaire.
- Overwhelming the sites with excessive demands.
- Difficulty to define and enumerate the source population (denominators).

**Strengths:**

- Sites complying with the protocol
- Magnificent response from everyone
- Knowing much better the sites

**Challenges:**

- Developing a cumulative and comparative by site quality data management profile report along seasons
- Focus on other than incidence burden-of-disease parameters
- Heterogeneity
- Produce virology data (only some sites produce this sort of data, the challenge is how and what to share)

**Conclusion**

The GIHSN is on track to provide a global picture of the epidemiology of severe disease due to influenza.

**Plenary: Challenges and Opportunities**

- It is clear that the case definition is well defined and that we aim to focus on ILI cases in hospital. However in this area there are still challenges
- This network is based on teamwork, and it is based on good collaborations and constant contact with the sites. It is important to always stay in contact with the coordination team when any sort of doubt arises, and to delay on resolving doubts or queries.
- Another interesting aspect that can be looked at, something PAHO has already explored would be IVE in SARI cases compared to IVE in ILI cases.
- It is not possible to calculate GIHSN-IVE by brand of vaccine. It is known that there are several different brands of vaccines at each site, and in the GIHSN framework the information of which vaccine patients are receiving is collected only when a registry is available. With this it makes it hard to calculate IVE by brand, 1) because vaccination coverage is low in countries, 2) official registries are not available to know when and with what vaccine the patient was vaccinated, and 3) when looking at different brands sample size is even smaller
- It would be interesting to additionally study the serological serums and look for immunity and antibodies.
- Pooling across seasons would also be a good idea to increase sample size when looking at calculating IVE

- [Devil's advocate question]: If influenza morbidity is so important why are we having troubles with numbers, or impact measures?

## Session 2: Site field work experiences

### Moscow

#### Setting:

- Moscow has a population of about 12 million, where the majority (74%) of the population ranges in the ages 15 to 64 years old.
- 1 hospital in Moscow participated in the GIHSN. The hospital is specialized in infectious diseases.
- The number of beds that are present in the hospital is 806, of these 254 beds were used (included) to screen patients, where 120 beds covered the adult population, 53 beds the children, 69 the pregnant and 12 from the ICU.
- 7 doctors and 6 nurses worked in the frame of the study on Tuesdays, Wednesdays and Thursdays.

#### Methods:

1. Screening
  - Patients were screened on the basis of their clinical symptoms.
2. Recruitment (Inclusion/exclusion criteria)
  - Inclusion criteria:
    - Having an admission diagnosis as listed in the questionnaire
    - ILI within the last 7 days.
  - Exclusion criteria:
    - Not able to communicate
    - No given consent
    - Non-resident
    - Institutionalized
    - Hospitalized in the last 30 days (any reason)
3. Data collection
  - Interview of the patient
  - Paper-based questionnaires
  - The use of the GIHSN excel worksheet
4. Virological testing
  - 24-48hours after swabbing
  - rtRT/PCR



- PCR kits, Amplisens, looking for Influenza A and B, A(H1N1)pdm09, A(H3N2), B/Yamagata, B/Victoria
- Part sequencing for influenza A positive samples (non-typed by PCR)

**Study period:**

- The first patient was included and swabbed on week 51 2013.
- The last patient was included and swabbed on week 23 2014.
- Definition of study period: the start of the study begins when 1 or more lab confirmed influenza cases are detected for 2 consecutive weeks, and ends when no cases are detected for 2 consecutive weeks.
- The majority of the cases this year were positive for influenza A(H3N2).

**Vaccination:**

- There are several different vaccines used in Russia aimed at different age groups.
- GRIPPOL and GRIPPOL plus, are the most commonly used. These are inactivated, polymer-subunit vaccines.
- Vaccination is free of charge for the target groups, and since the end of May 2014 the pregnant and the obese have been added to the vaccination target groups.
- When looking at the effect of begin vaccinated against influenza infection in the past 2 seasons of the GIHSN in Moscow, it shows that in 2012-2013 the efficacy was at 17%, in 2013-2014 the efficacy was at 62%, and for the two seasons the efficacy is at 48%.

**St. Petersburg**

Study: Code FLU21-EXT: "Global Influenza Hospital-Based Surveillance Network – Branch: St. Petersburg, Russian Federation"

**Setting:**

- Infectious Hospitals serves the residents of the city regardless of where they live.
- 3 hospitals participated in the GIHSN:
  - City Infectious Diseases Hospital # 30 (code #1), the ward for adults aged ≥ 17 years (60 beds); covers about 7.6% of total number of adult ILI&ARI patients hospitalized in the city.
  - Children's Infectious Hospital # 5 (code # 2): two wards for children aged from 0 to 17 years (60 beds each);
  - Children's City Hospital # 4 (code # 3): two wards for children aged from 0 to 17 years (60 beds each) covers about 4.5% of total number of children hospitalized in the city for the season.

- Thus, all three hospitals covered about 276 540 (5.5%) residents of the city
- Doctors (scientists of the Influenza Institute) working in two hospital wards for children and in one ward for adults
- Specialists in molecular diagnosis and genetic analysis,
- Virologists, who conducted virus isolation and antigenic analysis,
- Epidemiologist, who presented data on morbidity and hospitalization in the city for the season 2013-2014 by age group,
- Specialist, responsible for internet presentation obtained clinical and laboratory data in GIHSN database and RII database development

#### **Ethical Considerations:**

- Approval by the local research ethics committee was obtained.
- Confidentiality legislation and requirements in the handling of personal information was strictly followed.
- Informed written consent was obtained for enrolment
- No intervention, apart from the nasopharyngeal sampling was associated with the study
- Good epidemiological practice procedures were implemented in all study processes.

#### **Methods:**

##### 1. Screening

- Patients were examined in the primary hospital emergency room from where they were directed according to the diagnosis to the relevant ward

##### 2. Recruitment (Inclusion/exclusion criteria)

- Inclusion criteria:
  - ILI within the last 7 days.
- Exclusion criteria:
  - Not able to communicate
  - No given consent
  - Hospitalization for less than 24hours
  - Institutionalized

#### **Study period:**

- **Beginning of the investigation:** week 4 starting January 20 (following detection in the city of 5 laboratory confirmed influenza cases)
- **End of the whole investigation:** week 22 ending 1 June when lab confirmed cases were not detected anymore in the study

Total of patients enrolled: 1713

Of the included patient 70% were children and 30% of the patients were adults.

There was simultaneous growth of RSV detections and influenza cases.

The season 2012-2013 seemed to be more intense than the 2013-2014 influenza season.

## Turkey

### Setting:

- 7 hospitals participated in the GIHSN
  - 2 located in Anakara
  - 4 in Istanbul
  - 1 in Bursa

Different wards or departments from each hospital participated in the study: acute medicine, emergency medicine, infectious disease, pediatrics ICU, allergy ward, pulmonary wards, cardiology department, coronary ICU

- Attending physicians or physicians in their residency training were the participating fieldworkers on the Turkey sites.

### Methods:

#### 1. Screening

- All centers had computerized admission system to screen for patients with ICD-10 codes on daily basis. However, some centers did not make use of the system accordingly
- All patients with proper ICD-10 codes who had been hospitalized in the past 48 hours were eligible for the study. These patients were recorded on an Excel sheet separate from the GIHSN shared excel sheet.

#### 2. Recruitment (Inclusion/exclusion criteria)

- Inclusion criteria:
  - ILI within the last 7 days (patients 5 years and older)
  - Admission diagnosis with the last 7 days
- Exclusion criteria:
  - Non-resident
  - Institutionalized
  - Discharged from the hospital within the past 30 days
  - No given consent

#### 3. Data collection

- Via face-to-face interview using paper questionnaires.

- Collected data was sent to the coordinating centre in Istanbul to be entered in to the GIHSN excel worksheet:
4. Virological testing
- FTD® Respiratory pathogens 21
  - Five tube multiplex PCR for detection of influenza A, H1N1, influenza B, rhinovirus, coronavirus NL63, 229E, OC43, HKU1, parainfluenza 1, 2, 3, 4, human metapneumovirus A/B, bocavirus, *Mycoplasma pneumoniae*, respiratory syncytial virus A/B, adenovirus, enterovirus, parechovirus and internal control

**Study period:**

- Beginning of the investigation: week 48 2013
- End of the whole investigation: week 16 2014
- Definition: the start and end of field work is defined according to annual influenza surveillance in Turkey, detection of any influenza virus for two consecutive weeks from samples send by general practitioners marks the start of the epidemic and no detection of an influenza virus for two consecutive weeks marks the end of influenza epidemics.

**Vaccination:**

- No vaccination record keeping is properly in place in Turkey
- NH, TIVs are used in Turkey
- Mainly two brands Vaxigrip and Fluarix

**Concerns and Challenges:**

- Exclusion if hospitalized within past 30 days
  - Some centers indicated that the patients might have several underlying conditions including cancer and these patients get hospitalized often. Because of this we are losing many patients for inclusion. This could be reduced to the incubation period of influenza (1-4) days
- 48 hour stay in the hospital
  - Can 48 hours be extended to 72 hours? Sometimes patients arrive at the weekends patients can be missed

**Valencia**

**Setting:**

- 6 general hospitals participated in the GIHSN
  - 2 located in Valencia

- 2 located in Castellón
- 1 located in Alicante
- Each hospital had a principal investigator, and one dedicated field researcher focusing on just applying the study
- Population covered: about 1.5 million inhabitants
  - Each hospital serves to a specific Health District which covers a defined population
  - Each patient has a unique identification number (SIP) which indicates the primary care center and the hospital where the patient will receive healthcare attention

### **Methods:**

#### 1. Screening

- Resident patients of all ages hospitalized through emergency doors in the previous 48hours and with any of the protocol admission diagnoses
- Field researchers propose the study to eligible patients, and request written informed consent

#### 2. Recruitment (Inclusion/exclusion criteria)

- Inclusion criteria:
  - ILI within the last 7 days (patients 5 years and older)
  - Admission diagnosis with the last 7 days
- Exclusion criteria:
  - Non-resident
  - Institutionalized
  - Discharged from the hospital within the past 30 days

If excluded all information is recorded, up until the point of exclusion

#### 3. Data collection

- Via face to face interviews with patients
- Completing the whole study questionnaire in the e-CRF

#### 4. Virological testing

- Two swabs are taken from the included patients whenever possible. A nasopharyngeal swab for all patients, and additionally for patients less than 14years old a nasal swab, and additional a pharyngeal swab for patients 14 years old or more
- Both samples are combined into 3ml vials with universal viral transport medium (UTM, Copan®) and kept on site from -20°C to -50°C. Temperatures are registered daily and monitored weekly

- Shipped to central laboratory once a week where they are processed and stored at -70°C

#### **Study period:**

- Beginning of the investigation: week 46 2013
- End of the whole investigation: week 13 2014
- Where during the week 46 to week 50 a pilot study was conducted, and from week 51 to week-to-week 11 the IVE study is conducted. And that the whole 20weeks (week 46 to week 13) encompasses the respiratory virus burden of disease study

#### **Vaccination:**

- Vaccination is offered free of charge to target groups
- For the general population a trivalent subunit vaccine was used
- For the 65 years old or older a trivalent MF59 adjuvanted subunit was used
- Vaccination status was obtained through face-to-face interview with the patients, and via the vaccine information system (an official Valencia region registry). If any of the both sources were positive the patients was considered vaccinated

#### **Data management:**

- Data and swabs are collected by study fully dedicated field researchers
- An **electronic CRF** is used to record all the data
- Data check: weekly data cleaning
- Our goal: **data completeness**. All queries must be solved before field work is finished

## **China**

#### **Setting:**

- 5 hospitals participated in the GIHSN
  - 2 located in the Beijing province
  - 3 located in the Zhejiang province
- Each hospital had different wards or departments used within the hospital screening patients; department of respiratory medicine, paediatrics, critical care medicine, infectious disease, internal medicine

#### **Methods:**

1. Screening
  - Admitted in study participating wards
  - Admitted in the previous 24 – 48 hours

- Admitted due to any diagnosis possibly associated with an influenza infection
2. Recruitment (Inclusion/exclusion criteria)
- Inclusion criteria:
    - ILI within the last 7 days (patients 5 years and older)
    - Admission diagnosis with the last 7 days
  - Exclusion criteria:
    - Not able to communicate
    - No given consent
    - Not resident of the districts that the hospital belongs to
    - Institutionalized
    - Hospitalized in the last previous 30 days
3. Data collection
- Via paper questionnaire by a combination of face-to-face interview of patients and attending physicians and by reviewing clinical records
4. Virological testing
- Two pharyngeal swabs per patient
  - Samples kept frozen at -20° C in each hospital if they are not sent straight away to a reference laboratory
  - A multiplex real time RT-PCR performed to all samples to detect the presence of: Influenza virus A (H1N1 / H3N2/ H1N1pdm/H5N1/H7N9) and B (Yamagata / Victoria)
  - Lab test were conducted in two batches a week during flu season; one batch a week in non-flu season. 30-40 samples represents' one batch.

**Study period:**

- Beijing: October to April
- Zhejiang: All year round
- All in all: the study in China ran from the 9<sup>th</sup> of December to the 28<sup>th</sup> of April

**Vaccination:**

- Vaccination coverage was very low compared to norms. Where in total in the patients included in the GIHSN study from china, there was a 4.7% vaccination coverage

**Concerns and challenges:**

- Completeness of data: Missing values for some variables, such as admission diagnosis codes, chronic conditions, and discharge diagnosis
- In Zhejiang:



- No positive specimen had been detected from Jan to Apr 2014 in one of the hospitals (Jianshang hospital), which is a community health center
  - The vaccination coverage rate in the hospital's catchment area of the First People's Hospital of Huzhou turned out to be very low
  - Only 1 in 9 self-reported flu vaccination in Ningbo Women and Children Hospital was verified in the local immunization registration system
  - Due to the low vaccination rate and unsatisfied quality, we are considering remove the 3 sites in Zhejiang
- In Beijing:
- The flu vaccination recording from the questionnaires have missed 75% vaccinated patients and 40% self-reported vaccinations were wrong. So crosscheck with the local immunization registration system is necessary.
  - Among persons who should be swabbed >80% were actually sampled in Respiratory Medicine and ICU. Only 24% were actually sampled in Pediatrics. (1. The definition of eligibility for under 5yrs might be too wide; 2. high refuse rate in newborns)
  - An online information system has been established and will be put to use in Oct 2014. It is expected to help improve the feedback efficiency and data quality
  - It might help raise the number of questionnaires if we could have someone helping busy clinical workers screen patients firstly
  - According to evaluation of the data of the first year, sample size of the two hospitals in Beijing is not enough for evaluate vaccination effectiveness. More hospitals might be included if possible

A total of 871 patients were enrolled, where 136 were positive for influenza.

The H7N9 outbreak halted the surveillance work in one of the hospitals (Huzhou hospital) of the Zhejiang province from Feb to Apr 2014.

## **Brazil**

### **Setting:**

- Brazil was invited to join the GIHSN in June 2013
- In September 2013, IRB submission was done for adults
- In October 2013, IRB submission was done for children
- In December 2013, IRB approval for adults
- In March 2014, IRB approval for children
- In April 2014, IRB approval from the hospitals for adults, site visits and training
- In May 2014, Beginning of inclusion of adults

- In July 2014, IRB approval from the hospitals for children, beginning of inclusion of children
- In October 2014, investigator meeting
- 2 hospitals in the end participated in the GIHSN study, as one of the hospitals was not able to obtain IRB approval
  - 1 located in Fortaleza, where 206 beds participate in the study for screening patients
  - 1 located in Rio de Janeiro, where 303 beds participate in the study for screening patients
- Fortaleza covers a population of about 2.5 million inhabitants, where around 700,000 of this population represent the children less than 18 years old
- Rio de Janeiro covers a population of about 6.5 million inhabitants

**Methods:**

5. Screening

- Admitted in study participating wards
- Admitted in the previous 24 – 48 hours
- Admitted due to any diagnosis possibly associated with an influenza infection

6. Recruitment (Inclusion/exclusion criteria)

- Inclusion criteria:
  - ILI within the last 7 days (patients 5 years and older)
  - Admission diagnosis with the last 7 days
- Exclusion criteria:
  - Not able to communicate
  - No given consent
  - Not resident of the districts that the hospital belongs to
  - Institutionalized
  - Hospitalized in the last previous 30 days

7. Data collection

- Via paper questionnaire by a combination of face-to-face interview of patients and attending physicians and by reviewing clinical records

8. Virological testing

- Two US CDC's real time RT-PCR (Influenza A, H1N1pdm, H3, Influenza B) and virus isolation in positive cases
- Non-influenza respiratory virus
- US CDC's real-time RT-PCR for non-influenza respiratory viruses was used: respiratory syncytial virus, parainfluenza virus 1–3, human metapneumovirus, rhinovirus and adenovirus 1,2

- Next step would be to implement the FTD 23 plus

### **Vaccination:**

- Vaccination campaign is conducted from April 22 – May 26 administered to 87.3% of the population
- The vaccine used in Brazil is the trivalent Instituto Butantan and the Sanofi Pasteur one

### **Strengths and challenges:**

- Strengths:
  - Tropical and subtropical areas
  - National influenza center
  - Vaccine registries
  - Centers with good track record
  - Capacity to include new centers
- Challenges:
  - Population-based studies
  - Heterogeneity in access
  - Heterogeneity in population
  - Seasonality not very clear in all regions
  - Low inclusion for the number of screened patients
  - Difficulties to management of sites in different cities and regions
  - Concurrent testing
  - Low capture of severe patients (MV)

### **The application of the common core protocol, heterogeneity and similarities**

Study site differences and similarities were compiled in order to assess heterogeneity.

#### **Similarities**

- Exclusion and inclusion criteria. All sites followed the protocol and stayed in consistence and explicit with the different exclusion and inclusion criteria.
- Definition of residency (residing for at least 6months). All sites defined what 'resident-status' each patient would need to have for screening purposes. And the residing status for all patients had to be for at least 6 months at all sites.

#### **Differences**

- Number of beds used for screening patients. This differed at each site, and therefore it is why the number of enrolled patients by site could vary, as in some hospitals only 20 beds participated compared to others where all the beds in the hospital participated for the use of screening patients.
- Populations (Pediatric, adults, elderly). Different sites have different population demographics, where for example some sites may have a higher population of elderly, as in others not at all. As well some sites may differ in the age range in terms of what kind of hospital or wards are used to screen patients, as some may for example catch more pregnant women than other sites.
- Type of hospitals. The type of hospitals differ from the sites, such as some sites may have participating hospitals that are entirely focused on infectious diseases, some hospitals are reference hospitals for respiratory viruses.
- Vaccination campaigns. This differs by site, as some sites may have no vaccination campaign per se, as others may have an effective vaccination campaign of just four weeks where million of doses are administered.
- Field workers. This differs by site, where at some sites there are dedicated field researchers, and where in others nurses or doctors are applying the fieldwork of the GIHSN study.
- Admission diagnosis list. Some sites may have used a minimized list of admission diagnosis when screening patients and others may have applied the full list of admission diagnosis as in the protocol.
- Swabs. This differed in one of the sites where different swabs were taken, compared to all other sites.

### **Room for improvement**

- There is room for improvement when it comes to data entry.
- The aim is to reach completeness and consistency in the data entry.
- At site level:
  - Focus on data management, and completeness of data.
- At the coordination level:
  - Will write up a data quality diagnostic report, in order to pin point the areas where each site is require more focus on.
  - A data management protocol will be written and shared with all the sites, in order to standardized keep the datasets consistent and complete throughout the sites, to make it easier to share and pool, and produce results.

- A Data Management Workshop will be launched and all the data managers from each site will be invited, in order to train and go over all the data management issues.

### **Plenary: Site related issues, protocol discussion, problems with protocol, screening and recruitment methods**

- When pooling data and looking at it completely there are differences between the countries, but also within the countries, where different hospitals and wards are participating.
- It would be wise to analyze IVE with regards to chronic conditions, in order to understand why some people get vaccinated and others do not. Or in general, to perform a sub-study in order to observe the reasons why some people get vaccinated or not, as it may be due not only to their status of chronic conditions.
- Another idea could be to analyze the health economic expenses in terms of severe influenza hospitalizations.
- Some of the sites have physicians doing the fieldwork for the GHSN study. They have most probably be overwhelmed with work, at on top of their normal physician duties, GHSN field work needed to be accomplished, such as screening patients, including the patients, interviewing the patients and swabbing them.
- In the end it is strengths to have differences between the sites.
- It is curious that in bigger countries, where higher vaccination coverage is expected is in fact much lower than smaller countries.
- For some countries (like Turkey), it would be good to include private hospitals as well as public, as some populations may use more the private system compared to the public.

### **Session 3: Prospective new sites**

#### **Mexico**

- A local influenza surveillance system has been in place since the pandemic.
- During this season 2013-2014, there was a high peak of influenza on week 4 of 2014.
- This year, according to the surveillance system in place where there were 6,714 influenza cases during the 1<sup>st</sup> of January to the 25<sup>th</sup> of March 2014, 704 have died with an influenza infection.
- Of the influenza cases, there were no significant differences between genders.
- The majority of influenza present was influenza A(H1N1), where the young adults were most affected.
- Of the ones that died, the majority had influenza A(H1N1) and were 50 years old or more.

- In April 2009 the A(H1N1)pdm09 pandemic began in Mexico. In September 2009 the Mexican Ministry of health requested the implementation of a hospital-based program to detect in a timely manner the emergency of new infectious diseases and to describe the clinical and epidemiologic characteristics of the new influenza A/H1N1pdm09 virus and other emerging respiratory viruses.
- This hospital surveillance network in Mexico is made up of 6 hospitals and has laboratory, biostatistics, pharmacy, call center and other (if needed) support in order to proceed. It is coordinated and supported in terms of logistics, regulatory, operations, database management, informatics, administration and monitoring.
- All viruses are studied, and virological data in terms of haemagglutinin sequencing is done.

## Czech Republic

- Vaccination recommendations in Czech for:
  - People aged 65 years old or older
  - People with chronic conditions
  - Pregnant women
  - Health care and social workers
- Vaccines mostly used in Czech Republic are Vaxigrip (Sanofi Pasteur) and Influvac (Abbott).
- Vaccination coverage rates have been stable for the past couple of years are around 5 to 7% of the total population.
- There is no vaccination registry in Czech Republic; however it is sometimes recorded in patient medical documentation.
- Proposed study design:
  - Department of infectious disease of hospital Na Bulovce, Prague will be participating in the GIHSN 2014-2015.
  - This center is a referral and tertiary care center serving Prague and Central Bohemian Region (catchment area of 2.5million population).
  - 170 beds will be included in the study for screening patients, of these 30 beds are dedicated to respiratory diseases. Reference area covers a population of 2 million.
  - Specific virological investigation to be done at the National Influenza Reference Laboratory (National Influenza Centre), national Institute of Public health, Prague.
- Methods:
  - A physician will be responsible for the fieldwork; will be supervised by the chief physician of the department.

- The study will be focused on patients 18 years old or older,
  - Patients will be screened following the core protocol
  - Results of patients in the course of clinical care (*i.e.* bronchoalveolar lavage on critical care patients) will be used for study purposes.
  - Data collection will be done on paper based questionnaires
  - The study will start from November to march, using the criteria for the beginning of fieldwork when at least one positive case during two consecutive weeks is detected.
  - Virological testing will be performed in the National reference laboratory by qPCR, basic results will be obtained such as flu positive and flu negative (these will usually be available the same day or the next day) in the influenza positives additional PCR will be done to identify influenza subtypes and lineages subsequently.
- Challenges or concerns:
- Identifying the details about the forthcoming influenza season
  - Manually entering data from paper questionnaire in the excel worksheets, and would like to know the experience from other sites on this aspects and also maybe if available to share a template for web-based data entry.

#### **Plenary: Comments & discussion on the planned expansion of the GIHSN**

- The question is; are these hospitals ready for the implementation of the GIHSN study?
- The protocol will need to be applied, and it is important to have discussion with the Coordination office in terms of how to apply the GIHSN study to the local context of the new sites, as all sites are different.

#### **Session 4: Test Negative Design (TND)**

##### **The Test-Negative Design for Estimating Effectiveness of Influenza Vaccine**

- The test negative design has been in use for a while. Several studies using the test-negative design for influenza vaccine effectiveness have been published as early as in 1980 in the New England Journal of Medicine.
- Recent studies which use the test-negative design to calculate influenza vaccine effectiveness have also published, such as I-MOVE, the GIHSN, the US FLU VE network, the SOS in Canada.
- Papers have also been published on the methodological aspects and validation of the TND influenza vaccine effectiveness estimates.
- The TND can:



- Provide unbiased, valid estimates of VE under a wide range of situations; if certain conditions are met, the VE estimate from the TND represents VE against symptomatic influenza
  - Reduce bias arising from differential care-seeking patterns by vaccination status
  - Provide rapid VE estimates/mid-season VE estimates
  - The TND can significantly reduce the cost of conducting a VE study due to the ease and convenience of drawing both cases and controls from a clinical population (which becomes especially important for sustainability when these studies are to be repeated annually)
- The TND cannot:
- Eliminate confounding due to differential risk of influenza among people who are vaccinated
  - Eliminate misclassification due to imperfect test specificity and sensitivity or eliminate bias if test characteristics differ by vaccination status
  - Eliminate bias if enrollees are not tested randomly in regard to vaccine status
  - Eliminate bias from differential rates of participation by case and vaccination status

### **Test negative IVE studies in different seasons and countries**

#### A brief history of Influenza Vaccine Effectiveness

- During the pre 1990, there were investigations during the outbreaks of influenza. It was common to study this in nursing home, looking for ILI symptoms or absenteeism of symptoms, ad immunogenicity.
- During the 1990s to 2004, investigations boomed looking at pneumonia patients, hospitalized patients and deaths in the elderly adults due to respiratory infections. Information systems were put in place, to make it easier to retrieve data, mainly studies of cost effectiveness were conducted, in order to asses the cost of hospitalization due to respiratory infections.
- In 2005, PCR machines caused a revolution in terms of identifying the virus present in the patients.
- In order to assess or evaluate the vaccine efficacy in the field, a clear definition of a case needs to be identifies, as well as a how to identify or find these patients, and how to identify their vaccination status.
  - For this cohort studies and case control studies are conducted
  - Case control studies however may raise sources of bias and misclassification. Matched and unmatched case control studies can be

conducted. Odds ratios are calculated to approximate the relative risk. And there are no discussions of using clinic or hospital controls.

- Danuta and Gaston had been searching for efficient way to measure VE as part of routine surveillance and program evaluation. In early 2004, Gaston heard about Roche database that included vaccination status and test results for patients with ARI from 2000-01 through 2003-04. This gave them the idea to try using these data in a case-control approach. Danuta was in charge of the BC Sentinel Physician Surveillance Network at that time. They decided to add a couple questions about vaccination status and other relevant covariates. PCR testing was already in place at BC reference laboratory.
- In fall 2004, Gaston and Danuta analyzed the Roche database, which used rapid tests rather than PCR. The manuscript was criticized by reviewers due to low sensitivity of rapid test and misclassification of case status. In early 2005, Gaston was on sabbatical at US CDC and he presented their analysis at a grand rounds attended by Walt Orenstein. This lead to a theoretical analysis that was eventually published in the International Journal of Epidemiology. This added to the growing interest in the TND.
- Now there are new studies estimating influenza vaccine effectiveness from routine surveillance data, and from multi-centric case-control studies. As well as studies calculating vaccine effectiveness for specific vaccines.
- Publications and knowledge and interest in influenza vaccine efficacy or effectiveness have been booming in the past couple of years, and it is continuously increasing in amount of information.
- A systematic review is being conducted on test-negative influenza vaccine effectiveness studies in outpatient settings. Studies have been included or excluded on the basis of:
  - Having original reports of flu vaccine effectiveness in the years 1990 to 2013
  - Having cases confirmed by RT-PCR or culture
  - Having test-negative comparison groups
  - Having prospectively defined recruitment
  - Having a model adjusted by age
  - Having vaccine effectiveness reported by type/or subtype and season
  - Having the military/institutional populations excluded and excluding as well the interim reports only using the final reports.
- 124 published articles were looked out, where 4 hospitalization VE studies and 43 outpatient VE studies were included in the systematic review. 14 studies based in USA, 19 in Europe, 2 in Asia, and 8 in Australia. Where these studies range from the years 2004 to 2013.

- 10 of the 13 studies had a significant VE with a median of 66% and a median of 67% in the Post pandemic TIV vs. the pH1N1 studies.
- 11 of the 21 studies had a significant VE with a median of 48% and a median of 52% in the TIV vs. the A/H3N2 studies.
- 14 of the 27 studies had a significant VE with a median of 64% and a median of 66% in the TIV vs. B studies.
- A more formal meta-analysis is under way where outpatient VE studies from 2004 to 2014 will be added, pub-med and EMBASE will also be screened for more studies, already 117 articles have been selected for review and new publications will be added, and pooled VE estimates by type/subtype and age group using random effects model with heterogeneity assessment will also be done.

## Test negative methods and confounders

### Background:

- During the pre 1990, there were investigations during the outbreaks of influenza. It was common to study this in nursing home, looking for ILI symptoms or absenteeism of symptoms, ad immunogenicity.
- Confounding, bias and chance are the three major threats to validity of casual inferences.
- Chance is handles through statistical analysis
- Random controlled trials should eliminate confounding by design, and other components of the randomized clinical trials can help minimize bias.
- There are two broad types of bias; 1) Information bias and 2) selection bias.
- Confounding and bias need to be addressed in order to make valid causal inferences in observational studies.

### Confounding (common causes):

- High-risk status could increase the chance a person is vaccinated, and also increase the chance they will have medically attended influenza, while vaccination reduces the risk of medically attended influenza.

### Selection bias (common effects):

- Vaccinated persons are at lower risk of influenza virus infection, but more likely to seek medical attention if infected with influenza or another virus. This is a type of selection bias. The TND accounts for this bias by design.

### Mediation

- If we are interested in determining the casual effect of influenza vaccination in reducing the risk of medically attended influenza virus infection, we might choose not to adjust for a variable because that variable is a factor on the causal pathway.

## **Potential of the test-negative design for measuring influenza vaccine effectiveness.**

### **How do we know which variables are potential confounders?**

- Baseline incomparability needs to be looked at.
- Change in estimate criteria (such as Rothman suggests)
- The goodness-of-fit of a regression model
- And looking at the theoretical framework

### **Aim and methods**

- The aim is to identify methodological similarities and variations in published TND studies of influenza vaccine effectiveness
- Studies have been searched for in PubMed on the 4<sup>th</sup> of septemeber2014. Studies that reported estimated for any type of influenza vaccine were considered, interim, mid-year analyses, re analyses, or abstracts were excluded.

### **Results**

- 1,192 articles were screened, where in the end 85 articles were included in the review.
- There has been an increasing rate of publications o TND studies in the past years and influenza seasons.
- There are variations across TND studies, where there are considerable variations in the VE estimates reported by the different studies. Heterogeneity has also been shown due to difference in influenza strains circulating, vaccines used, vaccine match, population structure, health care systems and others.
- The following features of interest when looking at the studies:
  - Study setting
  - Source population
  - Inclusion criteria
  - Exposure (vaccination) definition
  - Ascertainment of vaccination status
  - Study period
  - Duration of illness
  - Case definition

- Laboratory testing
- Test-negative definition
- And approach used to estimate IVE
- 58 of the 75 studies defined their vaccination status as vaccinated when the patients were vaccinated 14 days or more before the onset of symptoms.
- Most of the studies (30/85) used more than 7 or 8 days between onset of symptoms and admission as an exclusion criterion.
- Most of the studies (33%) did not have a clear definition of the influenza season.
- Most of the studies adjusted for Age, calendar time, high-risk status, gender and study site.

## **Discussion**

- 85 published test-negative studies were reviewed to determine the similarities and differences in methodological approaches to the TND.
- All studies recruited patients with respiratory symptoms either defined as ILI or ARI, although there was considerable variation and overlap in the case definitions.
- Confirmation of influenza infection was generally done by RT-PCR
- Vaccine status was classified in different ways, and misclassification bias could have affected some studies, particularly where vaccination status is obtained by self-report.
- For a single surveillance system, subtle changes to the restrictions placed on the data (e.g. the period of surveillance used) and the variables included in the statistical model and how they are treated can impact VE estimated
- General consensus that age and high-risk status or eligibility for free vaccination should be adjusted as potential confounders.
- Most studies also adjusted for calendar time, but it is still unclear how best to do this.
- Restriction of patients to only those presenting a short time after onset of illness may have limited impact on reducing disease misclassification and could harm precision if it results in the loss of cases.

Should there be a statement of consensus on the best strategy to adjust in IVE TND studies?

## **Plenary: Discussion, challenges and opportunities**

- Selection bias in the GHSN is a subject that is applied in the protocol, for example there is no bias in the PCR results, because all positives are detected by PCR and national influenza centers.
- The main thing is that we don't only need positives but also need the negatives for influenza in order to compare.

- An idea would be to assess the severity of the patients, currently in the GIHSN framework, ICU admission, length of stay in hospital and death in hospital are collected, the following seasons additionally to those, records on if patients are on mechanical ventilation or on ECMO will be recorded.

## Session 5: Global related projects

### SARI Programs

#### Background:

The International Health Regulations is an international legal instrument conceived by the Global Health Security concerning 194 countries of the world and whose aim is to help the international community to prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide. In 2005, a shift occurred in the International Health Regulations as compared to the last version of 1969: it increased the emphasis on early source control rather than closing borders, it became applicable to all hazards, it promoted adapted response based upon risk assessment facilitated by communication rather than mere preset measures facilitated by communication and finally it included an obligation to build national capacities to detect and respond to potential public health events.

Global surveillance is based on early detection, reporting and investigation of threats. Global outbreak and response are based on initial screening, verification, risk assessment, and adequate response (in terms of investigation, containment and control, clinical management, finances, logistics, communication, security).

A very well done website made by Canada Global Public Health Intelligence Networks (GPHIN) gathers relevant news concerning networks' programs.

#### Influenza surveillance:

- Virus surveillance for vaccine virus selection
- Epidemiological surveillance
  - o ILI
  - o SARI
- Disease burden
- Influenza at the human-animal interface
  - o Risk of pandemics?
  - o Emerging viruses
  - o Factors of amplification

## **Global Influenza Surveillance and Response System:**

Composition:

- 6 WHO Collaborating Centers (Australia, China, Japan, UK, USA)
- 136 NICs in 106 countries
- 4 WHO Essential Regulatory Laboratories
- 12 WHO H5 Reference Laboratories (Australia, China, Egypt, France, India, Japan, Russian Federation, UK, US)
- Ad-hoc working groups: PCR working group, Antiviral resistance surveillance working group, IVTM development working group ...

### **SARI Surveillance**

SARI and influenza-like illness ILI surveillance should be integrated into existing public health systems to efficiently use resources and to promote surveillance.

Incorporation of sentinel influenza surveillance with other healthcare-based surveillance systems can strengthen each system, allowing for efficiencies in data collection, laboratory transport, and other logistics. SARI sentinel surveillance systems can be integrated with pneumonia, bronchiolitis, meningitis, and severe diarrheal illness surveillance, depending on local disease priorities.

#### **Principal objectives of SARI surveillance:**

- Determine when and where influenza activity is occurring, and who is affected;
- Detect changes in the antigenic and genetic characteristics and antiviral sensitivity of influenza viruses;
- Determine and monitor underlying risk conditions that are associated with severe disease and use of healthcare resources. Describe the clinical patterns of disease;
- Assess and monitor relative severity of annual epidemics or an outbreak of a novel virus;
- Estimate contribution of influenza to severe respiratory illness or overall disease burden
- Detection of unusual events;
- Measure the impact of interventions.

It is worth noticing that even if not detailed in this present report, each principal objective is linked to a specific use of surveillance data in decision-making (e.g. information, policy-making assistance, alerting healthcare providers).

The SARI Surveillance data-base, called FLUID, was built to support the SARI network in estimating the ongoing risk assessment of human infection with influenza viruses with

pandemic potential with monthly web updates. FluID also provides disease surveillance and monitoring biweekly and biyearly updates.

Fluid moved to a new platform (fluid@who.int), in order to facilitate quick upload of data. At the moment, 84 countries have data in FluID.

Global influenza surveillance standards document are published on web.

The burden of disease manual is nearly completed.

A pandemic global burden project based on sero-survey meta-analysis has been submitted and is under revision.

## **CDC Hospital surveillance**

### **Background:**

In the United States, the burden of serious influenza disease is high with approximately 129,000 annual influenza hospitalizations. Moreover, it has been estimated that 4 to 25% of children and 10 to 30% of adults hospitalized for influenza require ICU admission. Morbidity and mortality are mainly concentrated in older adults.

In the US, annual vaccination is primary prevention strategy and is recommended for all people over 6 months of age.

Most influenza VE studies estimate VE against symptomatic infection or medically attended outpatient influenza. Nevertheless, most studies, in all eras shown, included very little study of VE against serious outcomes, except for the studies of all-cause mortality, now considered by most to be seriously flawed.

VE against influenza-associated hospitalization appears to be similar to estimates of outpatient VE, but evidence is limited.

Influenza vaccines may potentially reduce the risk of hospitalizations due to influenza by over half.

The US currently lacks a consistent platform for assessing VE against inpatient outcomes. More research is needed on VE against severe outcomes and hospitalization.

### **Hospital VE study for 2014-15 season: US Flu VE Network study**

Before starting to present, the US-CDC speaker reminded that they were at the start of their study and with no advanced results to present but the framework of their prospective 2014-2015 research program.



- Objective: Estimate VE for prevention of healthcare visits due to influenza, by age group and type/subtype. Not designed to develop product-specific estimates
- Sites: Two of 5 US Flu VE Network sites for 2014-15 season:
  - o University of Michigan (MI)
  - o University of Pittsburgh (PA)
- Enrollees: Adults (both sites) and children (Univ. of Pittsburgh only) hospitalized with acute respiratory illness with cough  $\leq 7$  days duration
- Methods: Prospective case-control study (test-negative design)

Enrolled hospital patients tested for influenza by RT-PCR

- o Cases: RT-PCR influenza
- o Controls: RT-PCR negative for influenza

Ascertainment of receipt of 2014-15 influenza vaccine and prior season's vaccine from medical records and registries

- Analysis:  $VE = (1 - \text{adjusted OR}) \times 100\%$

Adjustment for age, days from illness onset to enrollment, and presence of high risk conditions

Hospital VE study for future influenza pandemic

- Purpose: Estimate VE for prevention of laboratory-confirmed influenza-associated hospitalization by age group in the event of an influenza pandemic
- Sites: Four sites actively preparing protocols through IRB approval (Wave 1); 6 additional enrollment sites when pandemic occurs
  - o Baylor College of Medicine: Houston, TX
  - o Geisinger Health System: Danville, PA
  - o Children's Hospital of Philadelphia: Philadelphia, PA
  - o University of Utah/Intermountain: Salt Lake City, UT
- Enrollees: Adults and children hospitalized with acute illness  $\leq 7$  days duration with  $\geq 2$  qualifying symptoms.

Screening criteria was intentionally broad since it is not possible to know when and how new influenza variant will present; erring on side of increased sensitivity/case ascertainment ( $\rightarrow$  high control:case ratio)

- Methods: Prospective case-control study (test-negative design)

Enrolled hospital patients tested for influenza by RT-PCR

- o Cases: RT-PCR influenza

- Controls: RT-PCR negative for influenza

Ascertainment of receipt of pandemic vaccine from self-report, medical records and registries

- Analysis:  $VE = (1 - \text{adjusted OR}) \times 100\%$

Adjustment for age, days from illness onset to enrollment, presence of high risk conditions, calendar time, et al.

Challenges for hospital influenza VE studies

1. Sample size:

- Difficult to enroll sufficient cases especially if VE is low
- Underpowered for subgroup VE estimates

2. Sustainability:

- Participation rates will go up and costs will go down if routine clinical specimens can be used for VE
  - VE biased if systematic testing of patients is not standard of care
  - Under what conditions can we rely upon routinely collected clinical specimens?
- Trade-off between sensitivity and cost: broad/lenient screening criteria will ascertain more cases but increases cost and increases bias (VE underestimated) if test lacks perfect specificity.

3. Interpretation of VE estimates:

- Two recent studies have validated the Test Negative Design for influenza VE against outpatient medically-attended influenza (Foppa et al, Vaccine 2013; Jackson M, Vaccine 2013)
  - Unbiased VE estimates when risk of ARI due to noninfluenza respiratory pathogens not influenced by influenza vaccination
  - TND is less susceptible to confounding by health care-seeking behavior than traditional case-control studies
- Recent analysis of data from four double-blind, randomized clinical trials of LAIV vs. placebo showed test-negative case-control analysis produced unbiased estimates of vaccine efficacy (De Serres G, Eurosurveillance, 2013)

### **Subsequent interrogations**

“If vaccine reduces the risk of symptomatic influenza illness AND the risk of requiring hospitalization given symptomatic influenza illness, what exactly are we measuring VE against?”

“Is it a measure of VE against virus infection, hospitalization for severe influenza, or both?”

“What are the inherent biases?”

“Under what conditions is the Test-Negative Design valid in a hospital context?”

Those questions have to be fully explored in order to bring the most optimal accuracy for future findings.

Conclusion

VE against serious influenza outcomes is important to know, and studies of VE against hospital outcomes are needed to fill a gap in the VE evidence base.

Studies of VE against influenza-associated hospitalization have complexities beyond Test Negative Design studies in the outpatient setting.

Validity of the Test Negative Design in a hospital setting remains to be fully explored and specific components of hospital VE studies remain to be fully developed.

Communication and partnership between hospital VE study investigators will enhance use and acceptance of study results.

### **Other hospital surveillance based programs**

The purpose of this presentation was to explore the functioning of other influenza surveillance hospital-based programs. The choice was made to study synthetically three networks on three different continents: InHOVE in Europe, SHIVERS in New-Zealand and REVELAC-I in Latin America.

InHOVE – Influenza Network of Hospitals measuring Vaccine Effectiveness in Europe

InHOVE is a network gathering twelve hospitals from France, Italy and Spain, created in 2010 with the aim of measuring vaccine effectiveness in Europe. The first season was carried out on 2010-2011 and the study was coordinated by EPICONCEPT. The program was funded by SPMSD and GSK.

A common protocol, locally adapted from an ECDC generic protocol, was shared between sites enabling a pooled analysis of the results.

- Objectives:
  - Primary objective: to measure seasonal influenza VE against laboratory confirmed influenza hospitalization
  - Secondary objectives: to measure VE by age group and to measure specific VE by subtype
- Method:

- Study population: Community-dwelling adults (18 years and above) belonging to the target group for vaccination and admitted to one of the participating hospitals for an influenza related illness
- Study period: From the week of the first laboratory confirmed case until the week of the last case
- Data collection & laboratory analysis: Questionnaire completion (details relating to the ILI episode, demographics, chronic diseases, vaccination status in the last 2 seasons, number of GP visits in the past 3 month/hospitalization in the past 12 months, smoking status, Barthel index for 65+); Nasal swabs for RT-PCR testing (subtype and lineages)
- Study design: prospective case-control study using the test-negative design (Cases: RT-PCR +; Controls (RT-PCR -))
- Analysis: Pooled analysis on Vaccine effectiveness:  $VE = (1-OR) \times 100$   
Stratified Analysis by: Age group (+/- 75 years); Country; Risk groups; Time between onset of symptoms and swabbing; Delay between vaccination and ILI onset
- Outputs and publications:
  - Generation of VE data for 3 seasons in different at-risk groups
  - Limits:
    - o Heterogeneity and differences between countries
    - o Difference of positivity rate among ILI patients
    - o Low sample size to be able to interpret the results of different stratified analyses (ex: stratification by age group, co morbidities, time since vaccination ...)
  - Publications: 2012/13 results: Oral communication at ESCAIDE in November 2013; Manuscript submitted to Eurosurveillance June 2014

Because of the withdrawal of one of the funds, the program's sustainability is strongly questioned.

SHIVERS - Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance

SHIVERS is an influenza surveillance program in New-Zealand, established in 2012 for a 5-year period, resulting from a multiagency collaboration between ESR, Auckland District and Manukau District board, University of Otago, Auckland, WHO and US CDC.

The program relies on two surveillance structures: a GP sentinel network and a hospital-based network. Since the interest of the presentation was to explore other hospital-based programs, the GP sentinel network was not overly explained.

The hospital-based surveillance system was designed to detect the SARI cases.

Two regions of New Zealand are concerned by the study and four hospitals participate in the study. The covered population was estimated to 838,000 inhabitants, which represents about 20% of the total population of New Zealand.

- Objectives:
  - o To measure incidence, prevalence, risk factors, clinical spectrum and outcomes for SARI and associated influenza and other respiratory pathogen cases
  - o To understand influenza contribution to patients not meeting SARI case definition
- Study Population: Adults and Children residents from ADHB (central Auckland) and CMDHB (east and south Auckland). Cases reported from 4 hospitals serving all residents.
- Case definition: Overnight inpatients with suspected respiratory infections. Cases are further identified as SARI WHO case definition or non-SARI. All SARI cases and a subset of non-SARI cases are enrolled.
- Laboratory test: Standard RT – PCR for Influenza and other respiratory viruses
- Description of the initiative and first results:
  - o Publication of Dr Sue Huang et al: WPSAR 2014;5(2):23-30 <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113656/>
  - o Oral presentation of the network at the ESWI Conference Sept 2014
- There is a unique opportunity to define cases of influenza not captured by the SARI definition. Additionally, the SHIVERS SARI surveillance system offers an opportunity to evaluate the sensitivity and specificity of the WHO definition and predicting symptoms for capturing non-influenza respiratory viruses
- Results (April to September 2012):
  - o 59,124 acute admissions to hospitals. 4,417 (7.5%) patients with suspected respiratory infections were assessed. 2,023 (45.8%) met the SARI case definition with 324 (22.7%) had influenza viruses
  - o A small proportion of influenza-positive cases (7.1%, 21/294) were identified from patients with onset in the past seven to 10 days. The case definition was expanded to onset within the past 10 days for subsequent study years (2013–2016)
  - o A small proportion (8.8%, 37/419) of influenza-positive cases was from non-SARI cases tested for clinical purposes

REVELAC-i – Network for evaluation of vaccine effectiveness in Latin America and the Caribbean

REVELAC-I is a collaborative project between US-CDC, TEPHINET and PAHO. The pilot of the program was launched in 2012 with 4 countries using SARI surveillance system. The official date for the creation of the network is February 2013, based on the lessons learned from the pilot season. The same year, the study was implemented in additional countries (Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Honduras, Panama and Paraguay).

Objective: To measure IVE in preventing Severe Acute Respiratory Infections, laboratory-confirmed for influenza, among vaccination target groups (children and elderly) by age groups.

- Method:
  - o Test negative case control design (PAHO-CDC generic protocol for influenza surveillance)
  - o Laboratory testing: Real-time PCR for influenza; Indirect immunofluorescence for other respiratory viruses
  - o Data received and analyzed at regional level
  - o Standardized tools and PAHO reporting system
- First results as of March 2014 :
  - o 8 countries with 71 sentinel hospitals reported a total of 2,395 SARI cases (627 Flu cases). Greatest concentration of Flu cases was found in June and July and circulation was recorded until December.
  - o Adjusted VE in children: 52% (36-72); Elderly 59% (45-79%)

Considering potential synergies of action, there is an opportunity to systematically evaluate the vaccine effectiveness using existing sentinel hospitals in LATAM countries and to continue integration of epidemiological surveillance, laboratory and immunization programs

### **Plenary: Opportunities for synergies**

From the glimpse at other networks, it seems possible to build on bridges and share of experience between the multiple programs. Indeed, a close collaboration could enable the surveillance systems based on a similar study design to cover multiple locations and different seasonality of the viruses' circulation and it would be facilitated by the existence of already identified operational sites with experienced hospital staff and available laboratory facilities.

Prerequisites for networks collaboration:

- Ability to conduct epidemiological studies
- Influenza surveillance experience

- Independence and ownership of data
- Sustainability of partnership (minimum criteria of commitment)
- Conviction of the added-value for sharing experiences

Motivators:

- Improve knowledge on influenza
- Improve surveillance systems
- Include more diverse populations and regions
- Enlarge public private partnership
- Leverage of resources

How?

- By developing data sharing and pooling of results
- By promoting best practice for laboratory testing
- By sharing experience in terms of training
- Whilst moving towards greater homogeneity and consistency between surveillance studies

However, the InHOVE project was not reconducted due to a lack of funding and it seems premature to start sharing data with SHIVERS.

The idea to create a “network of networks” has to be further studied and solidly framed in order to build an effective collaboration in the near future.

## **Session 6: GIHSN's results by site**

### **Moscow**

A total of 1742 patients were screened in season 2013-2014 (W51-W23). Of those, 1335 were included in the study (77%). The main reasons for exclusions (n=407) were “Onset of ILI more than 7 days” (n=110), “No consent” (n=64) and “Not a resident” (n= 63). The peak of influenza cases was between week 9 and 11, 2014. At the end of season mainly Influenza B and H3N2 were present.

The dominant influenza strain was A(H3N2) (15%), the second most present strain was B(4%) and finally A(H1N1)pdm9 (2%).

Compared to the 2012-2013 season, the strain circulation is very different as (H1N1)pdm9 was the dominant strain and H3N2 represented only 5% of the influenza hospitalizations.

The age group of 15-64 years old and pregnant women were the group most affected.

There is an over representation of young adults and pregnant women in the hospital involved from the Moscow site. This hospital is a Severe Respiratory Infectious Diseases Hospital and the wards participating in the study were the wards for pregnant women, pediatrics and adults.

Among children 0-4 the dominant strain was A(H3N2)(7%) followed by strain B (2%) and A(H1N1)pdm9 (1%).

Among patients in regards to pregnancy status (n= 523), 44% of the pregnant women were positive for influenza with A(H3N2) being the dominant strain (29%) followed by B/Yam (10%), A(H1N1)pdm9 (4%) and B/Vic (1%).

The most frequent underlying chronic conditions in patients positive for influenza were COPD (53%), cirrhosis (47%) cardiovascular disease (39%) and renal impairment (43%). Among all positive patients have been hospitalized once in the last 12 months or/and have had at least one previous GP consultation.

There was no significant difference between the three groups of smokers, past smokers and never smokers.

Vaccination rate among patients was found to be 4.3%. One of the reasons for low vaccination rates is because the majority of patients included are young adults and pregnant woman and neither of them belongs to the vaccination target group.

### **St. Petersburg**

A total of 1713 patients were screened in season 2013-2014 (W3-W22). Of those, 1291 were included in the study and swabbed (75.4%). The main reasons for exclusions (n=422) were "The patient does not comply with ILI definition and 7 days criteria (for 5 years and more)" (n=178), "No consent" (n=82) and "The patient does not comply with any of the admission diagnosis" (n= 63).

Influenza activity in Russia, including St. Petersburg, was unusually low this season with late beginning of epidemic and maximum observed on epidemiological weeks 7-17.

During 2013-2014 epidemic season influenza A(H3N2) dominated in St. Petersburg (23% for adults and 9% for children). Circulation of influenza B was very low and only Yamagata lineage B viruses were detected.

Rate of influenza cases detection among adults was more than twice higher than in children (26.9% and 12.8%). Other respiratory viruses affected mostly children (54.7% and 11.8% of cases).

Among ARI agents RSV and rhinoviruses were the most often (20.3% and 9.7% of all cases). RSV detection in children reached 24.9 - 35.4%, rhinoviruses 10.8 - 11.5% in both



children's hospitals. Parainfluenza (4.3%), corona (3.1%), adeno (1.6%), metapneumo (1.4%), bocaviruses (0.4%) affected mostly children (14.5% in total) in comparison with adults (3%).

RSV infection burden was very high for the period from week 5 to week 17, especially among children. Rhinoviral infection was the third by significance with peaks on weeks 5-7, 12 and 17. It is interesting that period of influenza epidemic coincided with RSV increased activity.

Considering chronic co-morbidities, there was no significant difference between groups except cardiovascular disease where percent of cases was significantly higher in the influenza negative group compared to the positive one.

In adult patients with CVD and COPD, influenza A(H3N2) was the dominating agent causing 39.3% of all recognized cases. RSV was the main cause of infection in children with rheumatologic diseases, CVD and COPD. Adenovirus infection was also observed in children with autoimmune diseases.

No significant differences were detected among smoking, ex smoking and never smoking groups in analysis of all patients with exception of rhinovirus infection, which was higher among smokers. Such relations were detected also in age groups 0-2 and 7-14 (smoking parents) and adolescents.

Only one pregnant woman was reported among the 562 adult females. ILI was caused by influenza A(H3N2) virus. She had no concomitant conditions, wasn't vaccinated and didn't receive antivirals before hospitalization. She was discharged in satisfactory condition.

Totally 1274 from 1282 patients in this study were not vaccinated and influenza was diagnosed among them in 17.4%. Only 8 patients were vaccinated and hospitalized, two of them (25%) were confirmed by PCR as influenza cases.

The conclusions on the genetic analysis of strains and swabs are the following:

- HA sequences of strains isolated on MDCK cells do not differ from sequences of HA gene determined in swabs from which these strains were isolated.
- 20-25 HA sequences of each influenza A subtype and B lineage obtained from swabs taken in different sites and time of epidemic season are necessary to make phylogenetic and epidemiologic analyses.
- Sequencing from swabs reflects the overall phylogenetic tendencies and can accelerate obtaining of the results.

- Genetic and antigenic characteristic of influenza A(H1N1pdm09) viruses isolated in St.-Petersburg
- 13 H1N1pdm09 strains were isolated from specimens collected in the framework of GIHSN Project and then characterized. HA, NA and M genes of 8 strains were sequenced and analyzed. Besides HA gene isolated from 8 swabs was sequenced.
- Genetic and antigenic analyses illustrate slow antigenic drift of influenza A(H1N1)pdm09 virus despite gradual accumulation of point mutations in HA gene. All 2014 viruses belonged genetic subgroup 6B
- No substitution H275Y was detected in any strain tested and by genetic structure all strains were susceptible to oseltamivir and zanamivir. All sequences retained coding for the S31N substitution in the M2 ion-channel protein, known to confer resistance to adamantanes.
- Genetic and antigenic characteristic of influenza A(H3N2) viruses isolated in St.-Petersburg
- 5 H3N2 strains were isolated from specimens collected in the framework of GIHSN Project. Besides HA gene isolated from 8 swabs was sequenced.
- The analyzed influenza A(H3N2) viruses drifted essentially from reference strain A/Victoria/208/09. They had very low titers with antiserum to A/Victoria/361/11 reference strain but reacted up to 1/2-1/4 of homological titer with antiserum to the current WHO-recommended vaccine strain A/Texas/50/12. All sequenced viruses belonged to subgroup 3C.3, genetic subgroup 3C.3b which carries amino acid substitutions E62K, K83R, N122D (resulting in the loss of a potential glycosylation site), L157S and R261Q in HA1. However, viruses in this subgroup do not appear to be antigenic drift variants.
- All strains by their genetic structure were also susceptible to oseltamivir and zanamivir and resistant to adamantanes.
- Genetic and antigenic characteristic of influenza B viruses isolated in St.-Petersburg
- HA gene isolated from 6 swabs collected in the framework of GIHSN Project was sequenced.
- Influenza B viruses isolated in Saint Petersburg belonged to Yamagata lineage. They differed significantly in HI-test from the contemporary vaccine strain B/Massachusetts/2/12 with 8-fold reduction of titer in comparison with homologous virus.
- Isolated in St. Petersburg B/Yamagata viruses belonged to clade 3 (B/Wisconsin/01/2010-like) and bore 10 amino acid substitutions 4 of which were in antigenic sites N116K (BC), S150I (BA), N165Y (BB2), A181T (BD). These 4 substitutions were reverse to the old strains circulating in 2011-2012. So we can expect the change of B/Yamagata vaccine strain.

## Turkey

From week 48, 2013- week 16, 2014, a total of 1547 patients were screened. Of those, 594 were included in the study. The main reasons for exclusion (n= 953) were " No Ill Symptoms" (n=559), "Discharged from the hospital in the last 30 days" (n= 156) and "No resident" (n=132).

582 samples were tested and 379 (65%) were positive for a virus. Of these, 124 (32%) were positive for influenza, whereas, 255(68%) were positive for other respiratory viruses.

The peak of cases was in week 4, 2014 in patients under 5 yo and was in week 3, 2014 in patients over 5 yo.

Among the population under 5 yo, RSV top ranked the distribution of viruses (37.4%) followed by A(H3N2) (26%), mix infection (13.7%), hCOV (12.2%), adenovirus (10.7%), rhinovirus (7.6%), hMPV (7.6%) and influenza B/Yam (6.1%).

Among the population of 5 yo and more, the distribution of viruses was headed by influenza A(H3N2)(30%), hCOV(29.2%), adenovirus (18.2%), mix infection (13.9%), influenza B/Yam (9.1%). Rhinovirus and RSV were also common in the adult population.

The vaccination rate among those aged 5 years and positive for influenza (n=82) was 9.8%, and was 17.9 % among the negatives (n=301).

The vaccination rate among patients less than 5 yo and positive for influenza (n=42) was 4.8%, and was 1.9 % among the negatives (n=157).

## Valencia

Of the 4841 patients screened, 2,573 were included in the study (53%) and 2568 samples were processed. 368 samples resulted positive for influenza and 233 were positive for other respiratory viruses. The rest of samples had a negative result for any respiratory virus.

Considering the virus distribution, influenza A(H1N1)pdm9 was the most frequent virus identified (n=293) followed by RSV (n=85), coronavirus (n=75) and A(H3N2) (n=66).

Bocavirus, adenovirus and mixed infections were also common.

During the 2013-2014 season, the Hospital Dr. Pesset experience applied a narrow set of eligibility criteria, the other 5 hospitals followed the protocol. As a result, 6 cases per 100,000 less were identified in Dr. Pesset among 18 yo and over. Speculations for this age group are at least 20% of unnoticed admissions with flu in the hospital.

The admission rate per 100,000 with influenza A (H1N1) in children less than one yo was four times that experienced in persons aged  $\geq 65$  yo.

In children aged 1-4 years, admission rates with A(H1N1) were similar to those of over 65 years

Influenza vaccination prevented one in every two to three admissions due to influenza in vaccinated.

*Overall, prevented fraction* in those exposed was in a most plausible range of 35% to 45%.

Results give ample support to the 2012 WHO recommendation of including pregnant women and children 6 to 59 months of age as priority groups in vaccination programs against influenza

## China

China's geographic territory presents a great diversity of climates including temperate, subtropical and tropical zones. This characteristics influence the epidemic seasonal trends of flu over the country with a Northern hemisphere following winter season and the Southern part of China where cases can occur all year long.

The following results present the preliminary data collected in China, 2013-14.

By the end of April 2014, 871 inpatients were recruited from 5 hospitals in 3 cities (Beijing, Zhejiang and Houzhu). Unfortunately Houzhu had to quit the study due to national priority on A(H7N9) surveillance.

Among the 713 samples processed, 131 were tested positive for influenza.

In Beijing, A(H3N2) was the dominant strain followed by influenza B. In Zhejiang, the most important strain in circulation was A(H1N1)pdm9 and A(H3N2) with a few influenza B cases. However, in Zhejiang the sample size was not big enough to provide satisfactory results.

The point estimate of vaccine effectiveness was 62% and 40% for influenza A and B with wide confidence intervals.

Findings are consistent with previous studies.

More subjects and more years of data are needed to permit more precise estimates and subgroup analysis.

The next steps for the study are to include more data into the analysis (cases recruited in May-August 2014 soon ready for analysis), to recruit more patients in following

seasons, and to improve ascertainment of influenza vaccination history. Indeed, considering vaccination status, recall bias were strong when comparison with records.

## **Brazil**

For the 2013-2014 season, Brazil participated in a pilot study including 2 cities: Fortaleza and Rio de Janeiro. A third site in Porto Alegre should start the study in the next coming season.

Considering the active Brazilian sites, 546 patients were screened with a very high exclusion rate. Catchment area was the main problem with 160 exclusions for "No resident" on a total of 403 patients excluded of the study. This issue was deeply discussed and will be solved by enlarging the residency definition for the Fortaleza region.

143 patients were included and swabbed. Among the 107 samples tested, 7 were positive for influenza and 59 were positive for ORV. One patient was diagnosed positive for influenza and RSV.

49% of the viruses identified were RSV, which could be because a lot of young children were included in the study (age-bias) since 60% of the less than 5yo were less than 1 yo, and/or because the screening started late in the season.

33% of the study population under 5 yo (n=109) were vaccinated in 2014.

32% of the study population of 5 or more (n=34) were vaccinated in 2014. Vaccination coverage appears to be quite high.

There was no predominance of one virus among over 5yo.

Among the individuals aged less than 5yo, 46% were positive for RSV, 14% for adeno positive and only 6% for influenza.

These low numbers could be explained by different reasons:

- the too restrictive catchment area around Fortaleza resulting in a high number of excluded patients;
- the unusually low activity of influenza in Brazil last season;
- the sites participating in the study are not located in the most active part of the country in terms of influenza virus circulation, according to SARI surveillance numbers in Brazil.

## **Moscow: pregnant women as a group at risk for influenza infection and complications**

From the results of the surveillance of influenza, the Moscow team worked on the study of pregnant women as a group at risk for influenza infection and complications.

Most of the pregnant women who were hospitalized for flu were in their third trimester (whereas in their second trimester during the 2013-2013 season). They mainly reported that their relatives were infected. No pregnant women were vaccinated against flu at their admission.

The most prevalent strains were A(H3N2) and B, A(H1N1)pdm9 was also present but to a lesser extent.

A(H3N2) was found to be responsible for increased risk of urinary tract infection but A(H1N1)pdm9 was found to be responsible for a more elevated number of influenza complications (urinary tract infection, pneumonia, tonsillitis, sinusitis).

The frequency of obstetrical pathology among pregnant women with influenza was observed and it was found that "cesarean section" was present for 40% of pregnant women with influenza and "threatening miscarriage" was present for 27.2% of them.

A(H3N2) was found to be responsible for increased risk during pregnancy causing "threatening miscarriage" (28.6%), "threatening premature labor" (11.6%), "miscarriage" (0.9%) and "premature labor" (7.1%).

A(H1N1)pdm9 and influenza B were also found to be frequent among "threatening miscarriage" and A(H1N1)pdm9 for "threatening premature labor".

The physiological immune-depression of pregnancy could explain the increased morbidity among pregnant women.

The risk of being pregnant and admitted for flu is 3 times higher than in the general population.

## **Session 7 GIHSN's results**

### **Epidemiological results**

#### **Preliminary analysis of data reported by GIHSN sites.**

The number of records received was 10,204. 9,891 patients were recruited during the season and 8,444 were screened for inclusion.

5,963 samples were processed with a result of 1,139 positives for influenza and 75 positive for mixed influenza infection.

According to number of influenza cases, H3N2 was the strain with higher number of positives (n=539), followed by A(H1N1)pdm9 (n=341) and B Yamagata (n=137).

H3N2 was dominant in the Russian Federation and Turkey whereas H1N1 positives were found mainly in the Valencia region.

Influenza B Yamagata was more present in the Beijing province.

There were only 3 patients positive for B Victoria.

Those trends might result from the high representation of the paediatric population on some sites (types of hospitals), high representation of young people (considering the inclusion of a high number of pregnant women in Moscow) and the high representation of the elderly population in the Valencia Region.

The highest wave of infections started to appear around week 3 and slowly declined after week 12.

H1N1 appeared to be more present in the elderly population (>50 years of age) in contrast to H3N2, which was more present in younger population. Influenza B Yamagata appeared to be more present among children and teenagers (5<18 years of age).

In total there were 82 deaths & 182 ICU admissions. There were no significant differences between positives and negatives for influenza when looking at the patients that died during hospitalization and the ones that were admitted to the ICU.

Pregnancy and obesity are significant risk factors for being admitted in hospital with influenza:

- A/H1N1, A/H3N2 & B/Yamagata in the pregnant
- A/H1N1 in the obese

### **Influenza vaccine effectiveness results**

The advantages of pooling data are to increase the total size of the combined analysis and therefore study power and precision around the point estimate; to increased generalizability of the results.

It is necessary to assess statistical heterogeneity to verify if it is feasible or not to pool data.

Thanks to the use of a common core protocol, statistical heterogeneity across sites is minimized. Indeed, low statistical heterogeneity was seen between IVE in the different study sites suggesting pooling analysis of the GIHSN is feasible.

This is a preliminary estimate of IVE for the GIHSN 2013/14 season.

Only the results from the study were included (Zhejiang and Brazil sites excluded).

GIHSN IVE estimates were adjusted for: age (years) and epidemiological week of admission (splines), underlying chronic illnesses.

Adjusted OR (95%CI) results for:

Valencia.....	0.70 (0.53-0.94)
St. Petersburg.....	0.49 (0.06-4.13)
Moscow.....	0.69 (0.27-1.80)
Turkey.....	0.76 (0.31-1.84)
Beijing.....	0.44 (0.08-2.28)
Overall (Random effects model).....	0.61 (0.49-0.77)

### **Plenary: comments on methods and representativeness of results**

The comments on the special issue on pregnant women were the following:

- To the idea of comparing two strains (H1N1 and H3N2) in order to look for the correlation between the severity of the disease and virus, it was answered that it has already been established that pregnant women are at risk for both strains.
- According to WHO findings, there might be two groups of countries: one with a high impact of flu on pregnant women (e.g. US, UK) and one group showing no impact (e.g. Japan and Scandinavian countries). Thus, such research focusing on pregnant women is interesting in order to shine a light on further countries specificities, or in order to put them into question.
- An additional cohort study would be interesting to have a burden of illness study with a comparison group. However this could not be implemented within the network study design.

The points raised about preliminary results for the VE estimates were the following:

- Not sure to evaluate the potential effect of previous vaccination on the VE because of the low numbers (not able to detect differences).
- Is there a waning effect related to the date of being vaccinated? Difficult to validate the accurate vaccination date; no differences observed for the risk of hospitalization.

Other comments:

- There is the hypothesis that vaccination could be a risk factor for getting other viruses as the findings of the study of B. Cowling in Hong Kong have shown but was not confirmed by other studies. Perhaps one explanation could be that the



population of the study in Hong Kong is more prone to be infected. Need further research on the population's characteristics and vulnerability to infection.

## Session 8: Publication strategy and network visibility

### Web development and publications

#### Web development

Two websites were developed in order to promote the GIHSN:

- [www.gihnsn.org](http://www.gihnsn.org), an external Internet website designed to promote the network to the scientific community and international health representatives; develop the visibility of the public private partnership; communicate the results to the scientific community; attract new partners.

- <http://grupos.fisabio.san.gva.es/web/gihnsn>, a community platform within the FISABIO website designed to share information with associate partners participating in the GIHSN study. This website was conceived as a practical tool for the GIHSN members, who will be given soon logins to be able to connect and have access to news, calendar, results, members and contact information.

#### Publications

As an important achievement, the GIHSN published data from the season 2012-2013 in order to present publicly the first year experience of the network, pilot, achieved goals and limitations found.

Data from the season 2012-2013 were published in two scientific papers last June 2014:

Puig-Barbera, J., Tormos, A., Somnina, A., Burtseva, E., Launay, O., Ciblak, M., Natividad-Sancho, A., Buigues-Vila, A., Martinez-Ubeda, S., Mahe, C., Group, on behalf of T.G., 2014. ***First-year results of the Global Influenza Hospital Surveillance Network: 2012-2013 Northern hemisphere influenza season.*** BMC Public Health 14, 564.

<http://www.biomedcentral.com/1471-2458/14/564>

Puig-Barberà, J., Natividad-Sancho, A., Launay, O., Burtseva, E., Ciblak, M.A., Tormos, A., Buigues-Vila, A., Martínez-Úbeda, S., Somnina, A., the GIHSN Group, 2014. ***2012-2013 Seasonal Influenza Vaccine Effectiveness against Influenza Hospitalizations: Results from the Global Influenza Hospital Surveillance Network.*** PLoS ONE 9, e100497. doi:10.1371/journal.pone.0100497.

<http://www.ncbi.nlm.nih.gov/pubmed/24945510>

For the season 2013-2014, the following scientific paper has been submitted for publication:

**Hospitalizations with influenza during the 2013–2014 Northern Hemisphere influenza season: Preliminary results from the Global Influenza Hospital Surveillance Network.**

Joan Puig-Barberà, Anita Tormos, Svetlana Trushakova, Anna Somnina, Maria Pisareva, Meral A. Ciblak, Selim Badur, Hongjie Yu, Benjamin J. Cowling, Elena Burtseva, on behalf The GIHSN Group

GIHSN representatives also participated in two international conferences (OPTIONS VII Sept 2013 and ISV VII Oct 2013) disseminating the network results and experience through oral presentations and posters.

For the 2013-2014 season, GIHSN will be presented at ESWI Sept 2014, Primum Non Nocere Sept 2014 and ISV VIII Oct 2014 with the supporting poster: **Epidemiological analysis of a worldwide network of hospitals - "Global Influenza Hospital Surveillance Network" (GIHSN)**. J Puig- Barberà, A Tormos, A Nativity Sancho, A Mira Iglesias, A Buigues Vila.

Next goal for the GIHSN is to publish the 2013-2014 season results with two scientific papers (coordinated by FISABIO) covering the topics of "Global Burden of disease and Epidemiological results" and "Heterogeneity and Influenza Vaccine Effectiveness" with a submission planned for January, 2015.

In addition, it was proposed to publish two thematic papers coordinated by a group of investigators with specific focuses (e.g. influenza among pregnant women). Those papers will be written on a voluntary basis but with the insurance to be provided external medical writing support if needed. Submission is planned for June, 2015.

Finally, two sites committed in writing on two different topics: the Moscow team took the lead on pregnancy thematic and the Saint Petersburg team took the lead on virology issues with the support of FISABIO in Valencia.

### **Plenary: Comments, discussion and opportunities**

Guidelines for the website reviewing:

- GIHSN partners present at the meeting were asked to go on the external website to read and check the accuracy of the information related to their organization (description, logo, link, etc.). They were asked to do so not too late after the meeting so that the website could be launched with accurate content.
- Besides, participating partners could send their remarks and change request all year long directly asking the person in charge of the website maintenance or through the contact mail on the website.

Discussion on the thematic publications to come:

- Other ideas for topics were brought: burden of disease in <5yo ; antibiotic use in viral infections ; use of mechanical ventilation and severity; patients in ICU; hospitalization cost (health economics)-Turkey was especially interested-; virology issues; definition of severe disease;
- The Moscow team took the lead on pregnancy thematic for one of the thematic papers.
- The Saint Petersburg team took the lead on virology issues with the support of FISABIO in Valencia.
- First step is to evaluate how far ones can go, proceed to a draft proposal and work with the support of medical workers and the support of the coordination team in FISABIO.

## Annex 1: Agenda

### 2014 Annual Meeting Annecy, 13/10/2014 – 14/10/2014

#### Sunday 12<sup>th</sup> of October

20:00 Welcome Cocktail Dinner

#### Monday 13<sup>th</sup> of October

8:30-9:00 Registration

9:00-9:15 Introduction and goals of the meeting  
(F Pradel, J Puig-Barberà, C Mahé)

9:15-10:30 Setting the context  
(mod: N Shindo, B Cowling)

9:15-9:35 Current framework of GIHSN (C Mahé)

9:35-9:55 Outcomes and challenges of the GIHSN (J Puig-Barberà)

9:55-10:30 Plenary: Challenges and Opportunities

10:30-11:00 Break

11:00-13:00 Summary of Site Field work experiences  
(mod: J Puig-Barberà, V Picot)

11:00-11:10 Moscow (E Burtseva)

11:10-11:20 St. Petersburg (A Sominina)

11:20-11:30 Turkey (M Ciblak)

11:30-11:40 Valencia (A Buigues-Vila)

11:40-11:50 China (Y Qin)

11:50-12:00 Brazil (F Bozza)

12:00-12:20 Coordination Office: The application of the common core protocol, heterogeneity and similarities (A Tormos)

12:20-13:00 Plenary: Site related issues, protocol discussion, problems with the protocol, screening and recruitment methods

13:00-14:00 Lunch

14:00- 14:40 Prospective new sites  
(mod: C El Guerche Seblain, A Sominina)

14:00-14:10 Mexico (L Guerrero)

14:10-14:20 Czech Republic (J Kyncl)

14:20-14:40 Plenary: Comments & discussion on the planned expansion of the GIHSN

14:40-15:40 Test negative design  
(mod: J Ferdinands, Angels Natividad)

14:40-14:55 Test negative methods and confounders (B Cowling)

14:55-15:10 Test negative IVE studies in different seasons and countries (E Belongia)

15:10-15:40 Plenary: Discussion, challenges and opportunities

15:40-16:00 Break

16:00-17:50 Global Related projects (mod: G Baccalà, E Burtseva)

- 16:00-16:20 SARI program (N Shindo)
- 16:20-16:40 CDC hospital surveillance (J Ferdinands)
- 16:40-17:00 Other hospital surveillance based programs (C El Guerche Seblain)
- 17:00-17:50 Plenary: Opportunities for synergies
- 19:30-22:00 Group Dinner

## **Tuesday 14<sup>th</sup> of October**

- 8:00-8:15 Reviewing second days' agenda
- 8:15-10:15 GIHSN's results by site  
(mod: M Thompson, X. López-Labrador)
  - 8:15-8:25 Moscow (S Trushakova)
  - 8:25-8:35 St. Petersburg (M Pisareva)
  - 8:35-8:45 Turkey (M Ciblak)
  - 8:45-8:55 Valencia (J Puig-Barberà)
  - 8:55-9:05 China (P Wu)
  - 9:05-9:15 Brazil (F Bozza)
  - 9:15-9:25 Special issues – Moscow (Lidia Kisteneva)
  - 9:25-10:25 Plenary: Results discussion and comments
- 10:25-10:55 Break
- 10:55-11:55 GIHSN's results  
(mod: E Belongia, Y Qin)
  - 10:55-11:10 Epidemiological results (A Tormos)
  - 11:10-11:25 Influenza vaccine effectiveness results (A Natividad-Sancho)
  - 11:25-11:55 Plenary: Comments on methods, analysis, results and representativeness of results
- 11:55-12:15 Coffee Break
- 12:15-13:10 Publication strategy and network visibility  
(mod: J Puig-Barberà, M Ciblak)
  - 12:15-12:30 Web development and publications (C El Guerche Seblain, A Tormos)
  - 12:30-13:10 Plenary: Comments, discussion and opportunities
- 13:10-13:30 Meeting Wrap-Up
  - 13:10-13:20 Summary of the meeting: main points and expectations (J Puig Barberà)
  - 13:20-13:30 Closing of the meeting (F Pradel, J Puig-Barberà, C El Guerche Seblain)
- 13:30-14:30 Group Lunch and Departure

## Annex 2: List of Participants

### 2014 Annual meeting

Annecy, 13/10/2014 – 14/10/2014

LAST NAME	FIRST NAME	AFFILIATIONS
Ackay Ciblak	Meral	NIR Laboratory Capa - <i>Istanbul, Turkey</i>
Afanasieva	Veronika	Research Institute of Influenza - <i>St. Petersburg, Russia</i>
Baccala	Glaucia	Fondation Mérieux - <i>Lyon, France</i>
Belongia	Edward	Marshfield Clinic Research Foundation - <i>Eau Claire WI, USA</i>
Booza	Fernando	Fiocruz - <i>Rio de Janeiro, Brazil</i>
Bricout	Hélène	Sanofi Pasteur MSD - <i>Lyon, France</i>
Buigues-Vila	Amparo	FISABIO - <i>Valencia, Spain</i>
Burtseva	Elena	D.I. Ivanovsky Institute of Virology - <i>Moscow, Russia</i>
Cakir	Banu	NIR Laboratory Capa - <i>Istanbul, Turkey</i>
Cowling	Ben	School of Public health, University of Hong Kong, <i>China</i>
El Guerche-Séblain	Clotilde	Sanofi Pasteur - <i>Lyon, France</i>
Fareau	Natacha	Sanofi Pasteur - <i>Lyon, France</i>
Ferdinands	Jill	CDC USA - <i>Atlanta GA, USA</i>
Flannery	Brendan	CDC USA - <i>Atlanta GA, USA</i>
Goldstein	Alexander	Sanofi Pasteur - <i>Moscow, Russia</i>
Guerrero	Lourdes	Instituto Nacional de Salud y Hospital – <i>Mexico City, Mexico</i>
Kisteneva	Lidia	D.I. Ivanovsky Institute of Virology - <i>Moscow, Russia</i>
Kyncl	Jan	National Institute of Public Health - <i>Prague, Czech Republic</i>
López-Labrador	Xavier	FISABIO - <i>Valencia, Spain</i>
Mahé	Cédric	Sanofi Pasteur - <i>Lyon, France</i>
Mira-Iglesias	Ainara	FISABIO - <i>Valencia, Spain</i>
Moura	Fernanda Edna	Universidade Federal do Ceará – <i>Fortaleza, Brazil</i>
Natividad-Sancho	Angels	FISABIO - <i>Valencia, Spain</i>
Picot	Valentina	Fondation Mérieux - <i>Lyon, France</i>
Pisareva	Maria	Research Institute of Influenza - <i>St. Petersburg, Russia</i>
Pradel	Florence	Fondation Mérieux - <i>Lyon, France</i>
Puig-Barberá	Joan	FISABIO - <i>Valencia, Spain</i>
Qin	Ying	CDC China - <i>Beijing, China</i>
Shindo	Nahoko	WHO - <i>Geneva, Switzerland</i>

Sominina	Anna	Research Institute of Influenza - <i>St. Petersburg, Russia</i>
Sondey	Juliette	FISABIO/Sanofi Pasteur - <i>Valencia, Spain</i>
Thompson	Mark	CDC USA - Atlanta GA, USA
Tormos	Anita	FISABIO/Sanofi Pasteur - <i>Valencia, Spain</i>
Trushakova	Svetlana	D.I. Ivanovsky Institute of Virology - <i>Moscow, Russia</i>
Vernet	Marie	l'Institut Pasteur, Centre Pasteur – <i>Yaoundé, Cameroun</i>
Wu	Peng	School of Public health, University of <i>Hong Kong, China</i>
Zheng	Jiandong	CDC China - Beijing, China