GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

WELCOME & INTRODUCTION

Cédric Mahé, Catherine Commaille-Chapus
• 55 participants, 25 countries

• A growing network:
  - 18 sites, 60 hospitals this season
  - 21 sites, 90 hospitals for the upcoming season

• An operational platform for data generation, capacity building and data sharing/valuation:
  - More than 3,500 documented cases of hospitalizations from influenza per season
  - Already up to 7 seasons of data generated including NH and SH data (>74,000 patients records available)

• Stronger scientific oversight
OBJECTIVES OF THE MEETING

• Review the individual and global results of the 2018-2019 season

• Exchange around the new GIHSN protocol and the evolution of the Network

• Present the new sites for the 2019-2020 season

• Discuss the strain sequencing process in order to optimize the GIHSN contribution to the WHO Strain Selection meetings

• Discuss how to value and communicate the generated data
# AGENDA: MONDAY 14TH OCTOBER

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>8:30 – 8:45</td>
<td>Welcome &amp; Introduction to the meeting</td>
<td>C Mahé (FIE)</td>
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<td>C Commaille (OpenHealth)</td>
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<td>8:45 – 10:30</td>
<td>Site results 1 (Poster Session with question-and-answer session) Sites 1 - 10</td>
<td>Site Investigators</td>
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<td><em>Moderated by: Elena Burteva, member of ISC</em></td>
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<td>10:30 – 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 – 12:30</td>
<td>Site results 2 (Poster Session with question-and-answer session) Sites 11 - 19</td>
<td>Site Investigators</td>
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<td><em>Moderated by: Marta Nunes, member of ISC</em></td>
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<td>12:30 – 14:00</td>
<td>Buffet Lunch</td>
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<td>14:00 – 14:40</td>
<td>GIHSN Results Season 2018-2019 (presentation followed by discussions)</td>
<td>Dr M Andrew (ISC)</td>
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</table>
| 14:40 – 16:00 | Round Table Discussion – Strain Selection Process: Current & Future Challenges | Dr W Zhang (WHO)  
                        |                                                     | Dr P Bogner (GISAID)  
                        |                                                     | Pr J McCauley (WHO CC)  
                        |                                                     | Pr B Lina (Lyon University) |
| 16:00 – 16:30 | Coffee break                                        |                                                  |
| 16:30 – 17:00 | Contribution of the GIHSN to the Strain Selection Meeting – Feedback on the 2018-2019 Season & Prospects for the Next Season | Pr B Lina (Lyon University)                       |
| 17:00 – 17:45 | GIHSN Implementation for the Next Season            | C Mahé (FIE)                                    |
|               | -Evolution of the Governance of the Foundation     |                                                  |
|               | -New Design of the GIHSN Implementation             |                                                  |
|               | -Participating sites for the 2019-2020 Season      |                                                  |
| 17:45 – 18:00 | Discussion & closure of Day 1                       |                                                  |
# AGENDA: TUESDAY 15TH OCT

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<tr>
<th>Time</th>
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<tr>
<td>8:30 – 8:45</td>
<td>First day wrap-up &amp; objectives of Day 2</td>
<td>C Commaille (OpenHealth)</td>
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<tr>
<td>8:45 – 10:15</td>
<td>Workshop Session 1: New Protocol Implementation</td>
<td>All sites</td>
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<td>- Implementation of the new questionnaire</td>
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<td><em>Moderated by: Sandra Chaves (FIE)</em></td>
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<td>10:15 – 10:45</td>
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<td>10:45 – 12:00</td>
<td>Workshop Session 2: Strain Sequencing Process</td>
<td>All sites</td>
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<td>- Timing of sequencing</td>
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<td>- Strain selection</td>
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<td>- Strain logistics between sites &amp; Lyon</td>
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<td><em>Moderated by: Bruno Lina (ISC)</em></td>
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<td>12:00 – 12:45</td>
<td>Dissemination &amp; Publications (Globally and Locally)</td>
<td>Pr B Lina (ISC)</td>
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<td>- Update on current manuscript development</td>
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<td>- Posters presented at Options X</td>
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<td>- Publication plan &amp; International conferences 2019-2020</td>
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<td>- Manuscript writing process 2018-2019 season &amp;</td>
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<td>12:45 – 13:00</td>
<td>Closing</td>
<td>C Mahé (FIE)</td>
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<td>13:00 – 14:00</td>
<td>Buffet lunch</td>
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SEASON 2018-2019: 18 SITES, 60 HOSPITALS

Included = 16,424
LCI+ = 3,505
GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

POSTER SESSIONS: SITES RESULTS

All Site Investigators
POSTER SESSION 1

Moderator: Dr. Elena Burtseva (Scientific Committee)

Sites: South America – Africa - Asia
Argentina
Peru
Brazil
Columbia
China - Shanghai
India
Ivory Coast
South Africa
Kenya
Tunisia

35 min poster round
60 min short presentation by each site investigator & questions and answers
POSTER SESSION 2

Moderator: Dr. Marta Nunes (Scientific Committee)

Sites: North America - Middle East - Europe
Mexico
Canada
Lebanon
France – Lyon
Romania
Russia – Moscow
Russia – St Peters burg
Serbia
Spain

35 min poster round
55 min short presentation by each site investigator
& questions and answers
GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

GIHSN RESULTS SEASON 2018-2019

Dr Melissa K. Andrew (Scientific Committee)
Study objectives and protocol
- Modifications for 2018-2019 season
GIHSN STUDY OBJECTIVES

Primary objectives

1. To evaluate the burden of severe influenza disease, defined as hospitalization related to community acquired influenza or complications following an influenza infection
2. To quantify the distribution of the different influenza strains (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) among these severe cases

Secondary objectives

1. Notice: the GIHSN goals are related to influenza epidemiology [Optional: If testing for other respiratory viruses is performed] To estimate the relative incidence of influenza compared to other respiratory viruses
2. [Optional: If vaccine coverage is sufficient for some age group] To measure the effectiveness of influenza seasonal vaccines to prevent these hospitalizations using a case control design
GIHSN DATA BASE 2018 – 2019: 19 SITES ARE SHARING THEIR DATA

2 sites in North America: Canada and Mexico

6 sites in Europe: France, Spain, Romania, Serbia, and Russia x 2

4 sites in Latin America: Columbia, Peru, Brazil and Argentina

3 sites in Africa:* Ivory Coast, Kenya and South Africa

1 site in the Middle East: Lebanon

2 sites in Asia: India and China

*The Tunisian site which was not a part of the Network this year has also shared data
Changes were implemented for the season 2018-2019 in order to simplify the protocol:

✓ A few historical exclusion criteria were removed such as:
  - Resident
  - Hospitalization in the last 30 days
  - Patient living in an institution

✓ Variables that were not relevant for analysis were removed and the section « laboratory results » was also simplified

✓ Adding the answer « Do not know » for many questions in order to allow for more data collection

✓ « Education levels » were replaced by « occupation »

✓ Adding of a Severity section – allowing for analysis on severity
NEW SEVERITY SECTION

Severity

26) Hypoxia at admission
27) Confusion at admission
28) Lethargy at admission
29) Oxygen saturation value on ambient air (%)
30) Blood pressure (systolic/diastolic)
31) Respiratory rate at admission (breaths per minute)
32) Blood Urea Nitrogen (mmol/L units)
33) Supplemental oxygen without mechanical ventilation
34) Vasopressor support
PROTOCOL 2018-2019

Eligible patients

- Admitted through emergency doors or study participating wards for an acute condition.
- Admitted in the previous 48 hours and having stayed in hospital for at least 1 night.
- Main complaint for admission possibly related to influenza infection.

Included population

- GIHSN ILI onset within the last 7 days for patients >=5 years of age
- Onset of symptoms for patients <5 years of age

Sample submitted to the lab

- Confirmed Influenza
- Negative
- Positive for other respiratory viruses

Exclusions

- No communication
- No consent
CURRENT ELIGIBILITY CRITERIA

Eligibility criteria

Enrolment is based on:

- Patients with an acute process
- Patients whose indication for admission was any of a predefined set of conditions, described as possibly associated with a recent influenza infection*
- In this case, [a study nurse, doctor...] will identify by hospital admission registries, chart review or available records, all eligible patients hospitalized in the previous 48 hours and has stayed in hospital for at least 1 night (therefore a patient admitted before midnight of the previous day).

*Admission diagnoses possibly associated with an influenza infection. International Classification of Diseases Code version 9 and 10. Codes are listed in the protocol and in annex of the questionnaire
CURRENT INCLUSION CRITERIA

Inclusion criteria

Patients 5 years old and older will be included in the study if they refer to a seven days or less antecedent of a community onset influenza like-illness (see definition in table 2).

Table 2. Modified European Centre for Diseases Control definition of influenza like-illness (ILI)

Combination of:
- at least one of the following four systemic symptoms (ICD-9-CM code): Fever or feverishness (780.6), headache (784.0), myalgia, (729.1) or malaise (780.79);
- at least one of the following three respiratory symptoms (ICD-9-CM code): b) Cough (786.2), sore throat (787.2) or shortness of breath (786.05).

Patients less than 5 years will be included if indications for admission, occurred within seven days or less between the beginning of symptoms and admission to hospital.
PROTOCOL SWABBING PROCEDURES

Swabbing procedures:
A nasopharyngeal swab for all patients and a pharyngeal swab for adults (14 years of age or older) and a nasal sample for children (less than 14 years old) will be obtained from each patient in case they comply with inclusion criteria and give consent.

Nasopharyngeal swab

Pharyngeal swab
Data Analysis –
Descriptive analysis and outcomes

(Data as of 25/9)
GLOBAL PATIENT INCLUSION
EVOLUTION OVER 7 YEARS

N= 67 026

*data from Colombia and Peru are not included
CONTRIBUTION PER ZONE 2018-2019

NORTHERN:
- #Included with valid lab result: 11,936
- #LCI+: 3,080
- #ORV+: 3,196
- 26% of incl patients

SOUTHERN:
- #Included with valid lab result: 2,938
- #LCI+: 156
- #ORV+: 946
- 5,3% of incl patients

INTERTROPICAL:
- #Included with valid lab result: 1,519
- #LCI+: 269
- #ORV+: 149
- 18% of incl patients

# SITES
- NORTHERN: 10
- SOUTHERN: 4
- INTERTROPICAL: 2

# SITES
- CANADA
- CHINA
- LYON (FR)
- ROMANIA
- MOSCOW (RU)
- ST PETERSBURG (RU)
- SERBIA
- SPAIN
- LEBANON
- MEXICO

- BRAZIL
- SOUTH AFRICA
- KENYA
- ARGENTINA

- INDIA
- IVORY COAST
- (PERU COLOMBIA)

N= 16,424
NORTHERN HEMISPHERE – 16 SITES SINCE 2013

# SITES

4  5  6  6  8  11  8

# Included with valid lab result  #LCI+  #ORV+

12_13  13_14  14_15  15_16  16_17  17_18  18_19

N = 56,524

EVOLUTION OF LCI+ & ORV+ RATIO

28%  21%  24%  36%  26%  33%  26%  27%

7%  19%  23%  22%  23%  24%
SOUTHERN HEMISPHERE – 5 SITES SINCE 2013

# SITES

1
3
4

Included with valid lab result
#LCI+
#ORV+

N= 6,665
INTERTROPICAL HEMISPHERE – 4 SITES SINCE 2013

PERU & COLOMBIA data not yet integrated in 2018-2019 data set

# SITES

1

2

3

2

Included with valid lab result

#LCI+

#ORV+

N= 3,837

Evolution of LCI+ & ORV+ ratio:

- 11% (15_16)
- 9% (16_17)
- 18% (17_18)
- 10% (18_19)

- 29% (15_16)
- 19% (16_17)
- 18% (17_18)
- 18% (18_19)
GLOBAL AGE & GENDER DISTRIBUTION
PATIENTS INCLUDED (W/ VALID RESULTS) 2018-2019

- 51% males
- 49% females

N = 16,424
VACCINATION RATE EVOLUTION
VACCINATION RATE VS INCLUDED PATIENTS
VACCINATION STATUS BY AGE GROUP
INCLUDED PATIENTS 2018-2019

GLOBAL VACCINATION STATUS

VACCINATION STATUS PER AGE GROUP

N= 16 401
VACCINATION STATUS BY AGE GROUP
LCI+ PATIENTS 2018-2019

GLOBAL VACCINATION STATUS

VACCINATION STATUS PER AGE GROUP

N= 3 499
INFLUENZA POSITIVES PER AGE GROUP
LCI+ 2018-2019

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>&lt; 5</td>
<td>36%</td>
<td>29%</td>
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<tr>
<td>5 - &lt; 18</td>
<td>12%</td>
<td>9%</td>
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<tr>
<td>18 - &lt; 45</td>
<td>14%</td>
<td>24%</td>
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<tr>
<td>45 - &lt; 65</td>
<td>15%</td>
<td>16%</td>
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<tr>
<td>65 - &lt; 80</td>
<td>15%</td>
<td>13%</td>
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<tr>
<td>80+</td>
<td>7%</td>
<td>9%</td>
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N = 3,512
INFLUENZA STATUS PER CHRONIC CONDITION PATIENTS <5

N= 7 343
INFLUENZA STATUS PER CHRONIC CONDITION PATIENTS >=5

- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Other
- Obesity
- Neoplasmin
- Renal impairment
- Asthma
- Neuromuscular disease
- Rheumatologic autoimmune disease
- Immunodeficiency/organ transplant
- Cirrhosis/liver disease
- HIV infection
- Active tuberculosis

N=9091

#Patient LCI+  #Patient LCI-
CHRONIC CONDITIONS IN OLDER AGE GROUPS
LCI+ VACCINATED VS NON VACCINATED

80+

- Cirrhosis/ liver disease
- Immunodeficiency/organ transplant
- Other
- Rheumatologic autoimmune disease
- Asthma
- Neoplasm
- Neuromuscular disease
- Renal impairment
- Obesity
- Diabetes
- Chronic obstructive pulmonary disease
- Cardiovascular disease

N=1763

65-<80

- HIV infection
- Cirrhosis/ liver disease
- Immunodeficiency/organ transplant
- Rheumatologic autoimmune disease
- Neuromuscular disease
- Asthma
- Other
- Renal impairment
- Neoplasm
- Obesity
- Diabetes
- Chronic obstructive pulmonary disease
- Cardiovascular disease

N=2057
LENGTH OF HOSPITAL STAY
LCI+ VS LCI-

Hospital stay in number of days

N=16 434

#Patient LCI+  #Patient LCI-
OUTCOME SEVERITY BY AGE GROUP

INCLUDED PATIENTS

INCLUDED VACCINATED PATIENTS

N=16 434

N=1 696
VIRUS DISTRIBUTION NORTHERN HEMISPHERE

N = 3,244

NB PATIENTS

Russia St Petersburg
Romania
Spain - Valencia
Serbia
China - Shangai
Canada
Russia Moscow
Mexico
Lebanon
France Lyon
VIRUS DISTRIBUTION SOUTHERN HEMISPHERE

N=156

NB PATIENTS
VIRUS DISTRIBUTION INTERTROPICAL HEMISPHERE

N=269

NB PATIENTS
VIRUS DISTRIBUTION OVER 4 SEASONS SITES IN NORTHERN HEMISPHERE

SPAIN

2018-2019
N=1 604

2017-2018

2016-2017

2015-2016

MEXICO

2018-2019
N=480

2017-2018

2016-2017

2015-2016

MOSCOW

2018-2019
N=2 159

2017-2018

2016-2017

2015-2016

Legend:
- A/H1N1
- A/H3N2
- Adenovirus
- A-Not Subtyped
- B/Victoria
- B/Yamagata
- B-Not Subtyped
VIRUS DISTRIBUTION OVER 3 SEASONS
SITES IN SOUTHERN & INTERTROPICAL HEMISPHERES

INDIA

2016-2017

2017-2018

2018-2019

SOUTH AFRICA

2016-2017

2017-2018

2018-2019

N=438

N=320
SEVERITY INDICATORS
INCLUDED PATIENTS

<5 YEARS
N=7,332

>-5 YEARS
N=9,080

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<th>Indicator</th>
<th>&lt;5 Years</th>
<th>&gt;-5 Years</th>
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<tr>
<td>Fever</td>
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<td>Supplemental oxygen</td>
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<td>Lethargy</td>
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<td>Hypoxia</td>
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<td>Vasopressor support</td>
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SEVERITY INDICATORS
PATIENTS >-5 YEARS

LCI+ N=2 362

LCI+ VACCINATED N= 265

Supplemental oxygen
Hypoxia
Confusion
Lethargy
Vasopressor support

% Patient

Yes
No
Do not know

Global Influenza
Hospital Surveillance
Network
6th Global Annual Meeting
SEVERITY INDICATORS
OLDER PATIENTS 65+

LCI+ VACCINATED

N=783
N=190
GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

STRAIN SELECTION PROCESS: CURRENT & FUTURE CHALLENGES
ROUND TABLE:

- Dr. Wenqing ZHANG (WHO)
- Dr. Peter BOGNER (GISAID)
- Pr. John McCAULEY (WHO CC)
- Pr. Bruno LINA (Lyon University)

Moderated by: Cédric MAHE (FIE)
CONTRIBUTION OF THE GIHSN TO THE STRAIN SELECTION MEETING – FEEDBACK ON THE 2018-2019 SEASON & PROSPECTS FOR NEXT SEASON

Pr. Bruno LINA
Influenza surveillance: diversity
The evolutive trend of the Influenza viruses is type/sub-type/lineage dependant

Neher RA et al, PNAS 2016
As a consequence:
Annual changes in the influenza vaccine composition

### NH vaccine composition

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- 2nd B strain for quadrivalent vaccine if needed
- 2nd B strain for quadrivalent vaccine OMS recommendation
H3N2 current evolution: multiple clades and sub-clades

Courtesy of DJ Smith
Project:
Use GIHSN to provide WGS real-time data to analyse strain variation and evolution. 2018-19 phase 1 feasibility study
Results for the 2018-2019 feasibility study

Summary:

1. 6 sites provided data
2. Overall, approx 200 whole genome sequences have been obtained
3. Shipments have been difficult to organize
4. Difficulty to provide real-time data by the GIHSN sequencing lab
   - For the sequence fasta files
   - For the GISAID upload
   - For the feedback to the originating labs
Results for the 2018-2019 feasibility study

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<th>Nb non tested specimens Ct&gt;31</th>
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| total seq failure |            |                    |              |                        |                               |                                           | 14      | 4
H1N1pdm09

112/115 with S183P
H1N1pdm09

112/115 with S183P
H3N2 HA
H3N2 clade evolution 2017-2019

North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Kansas 2018
Singapore 2016
Switzerland 2017

Courtesy of Derek Smith
University of Cambridge

Copyright GIHSN 2018
Discrepancies between GIHSN and WHO A(H3N2) clade evolution 2017-2019 (as of Feb 2019)

But, the extent of the GIHSN data is limited...
H3N2 NA

HA 3C.3a/NA 3C.2a1

HA&NA 3C.3a
Sequence variability and severity: H1N1pdm09
Sequence variability and severity: H3N2
Conclusions

This first year confirmed the potential of GIHSN to provide a complementary set of data for WHO and other stakeholders.

- consensus sequence
- minority variants

Need for better organisation (see project)

- better integration into GISRS
- define the reporting procedure (who does what)
Acknowledgements

NIC & Hospital Lyon:
- Bruno Simon
- Marine Jourdain
- Gwendolyne Burfin
- Estelle Gallice
- Rolf Kramer
- Alexandre Gaymard
- Gregory Destras
- Laurence Josset
- Florence Morfin
- Martine Valette

GIHSN sites and ISC:
- John Paget
- Melissa Andrew
- Luzhao Feng
- Justin Ortiz
- Daria Danilenko
- Xavier Lopez-Labrador
- Robert Steiner
- Marta Numes
- Christine Commaille-Chapus
- Clothilde El Guerche-Seblain

WHOcc Crick Institute:
- John McCauley
- Rod Daniels

WHO cc in Cambridge (Institute of Zoology)
- Derek Smith
- Sarah James
GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

GIHSN IMPLEMENTATION FOR THE NEXT SEASON

Cédric Mahé
Dedicated fund created in 2015 under the Fondation de France aegis: Fondation for Influenza Epidemiology

Mandate: Support the epidemiological and virological research on influenza

Governance
- Funding to the GIHSN is allocated through a yearly call for tender
- Selection is made by an Executive Committee

Key principles
- Applicants must be non-for-profit institutions
- Data generated through the projects is owned by sites but contributes to Foundation related projects (yearly pooled analysis)
- Coordination and technical support is provided Open Health Company
THE INDEPENDENT SCIENTIFIC COMMITTEE

9 experts with an increased decision-making ability since last season

- Review and advise on the scientific deliverables such as the protocol, analyses, interpretation of results, report(s), scientific communication and publications
- Advises on technical and scientific topics and provides specific recommendations
- Grading of the proposal to the tender  **NEW**
- 3 designated representatives at the Executive Committee  **NEW**

<table>
<thead>
<tr>
<th>Independent experts</th>
<th>Investigators</th>
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<tbody>
<tr>
<td>Jill Ferdinand (CDC, USA)</td>
<td>Elena Burtseva (Moscow)</td>
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<tr>
<td>Feng Luzhao (CDC, China)</td>
<td>Marta Nunes (South Africa)</td>
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<tr>
<td>Bobby Reiner (IHME, USA)</td>
<td>Melissa Andrew (Canada)</td>
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<td>Bruno Lina (Univ of Lyon, France)</td>
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<td>Justin Ortiz (Univ of Maryland, USA)</td>
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<td>John Paget (NIVEL, Nederland)</td>
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- Secretariat is managed by OpenHealth Company
• **GIHSN network:** 60 hospitals in 18 countries in 2018-2019
  - More than 3,500 documented cases of hospitalizations from influenza per season
  - Already up to 7 seasons of data generated including NH and SH data (>74,000 patients records available)

• **Diversification of funding:** small funding from IFPMA/IVS. Discussion ongoing with Seqirus

• **Expansion of the sequencing activities:** strain sequencing platform, GISAID partnership

• **Formal dialog with WHO GIP** and provision of data for the annual vaccine strain selection (NGS + clinical data)
GIHSN TIMELINES

DATA SHARING during NORTHERN & SOUTHERN HEMISPHERE SEASONS

ANNUAL MEETING
Onboarding of new sites

May → July
New Call Publication

Sept
EXECUTIVE COMMITTEE

ANNUAL MEETING
Presentation of the results of the season

ISC meeting (2 per year): Protocol review, Publication plan validation, ...

October

October Y+1
MAP OF GIHSN SITES FOR THE SEASON 2019-2020
(21 SITES - 6 NEW)

North America
Canada
Mexico

South America
Brazil
Argentina
Peru

Eurasia
Romania
Serbia
France (2)
Ukraine
Spain
Russia (2)

Africa
Ivory-Coast
South Africa
Kenya

Middle East
Lebanon
Turkey

Asia/Pacific
China (2)
India
Nepal
Bangladesh

New sites
Already existing sites
NEXT STEPS

Administrative aspects & funding allocations

Contacts: Foundation for Influenza Epidemiology (Sandra Chaves)
Fondation de France (Charlotte Von Thienen Bardinet)

• After acceptation of the grant, a letter of engagement including a description of milestones and payment terms is prepared for the site.
• When needed, a contract can be prepared by the institution to be signed by the Foundation

Study implementation & Kick-off TC

Contacts: Open Health Company (Catherine Commaille-Chapus, Maria Morizet)

• Sites are invited to start the seasonal active surveillance in accordance with national surveillance
• Open Health is planning to set individual Kick-off TC to review the study implementation, data collection
• Sites are encouraged to share data on the data web tool, once a week.
EVOLUTION OF THE STRATEGY AND RELATED DATA COLLECTION

• Stronger focus on strain circulation and their clinical significance (disease severity, vaccine failure) – burden and vaccine effectiveness not always feasible in most countries

• Stronger focus on timeliness, geographical representativeness

• Need to reduce cost per sites (for sustainability)

• Engagement of NICs and WHO CCs

Operational considerations

• Data collection for LCI only (with a lower number of variables)

• Linkage between clinical data and virus sequencing

• Timely availability of data (e-crf + GISAID)

• Offer of support for sequencing
DISCUSSION & CLOSING OF DAY 1

• Feedback from sites on the discussed results
• “First reactions” on the new protocol
• Important points to take “home”
GIHSN 7TH ANNUAL MEETING, PARIS, OCTOBER 13-15TH 2019

OPENING DAY 2

Catherine Commaille-Chapus
OBJECTIVES DAY 2

• Discussion on the implementation of the new protocole – exchange on the site organization and individual challenges

• Practical discussion on the strain sequencing process: sites doing their own sequencing vs sites needing to coordinate with Lyon for sequencing

• Present local and global publications and start discussing the publication plan relating to the 2019-2020 season data
# AGENDA: TUESDAY 15TH OCT

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
<th>Moderator/Source</th>
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<tbody>
<tr>
<td>8:30 – 8:45</td>
<td>First day wrap-up &amp; objectives of Day 2</td>
<td>C Commaille (OpenHealth)</td>
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<tr>
<td>8:45 – 10:15</td>
<td>Workshop Session 1: New Protocol Implementation</td>
<td>All sites</td>
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<td>- Implementation of the new questionnaire</td>
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<td>- Data Entry</td>
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<td>- Need for support</td>
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<td><em>Moderated by: Sandra Chaves (FIE)</em></td>
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<td>10:15 – 10:45</td>
<td>Coffee break</td>
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<td>10:45 – 12:00</td>
<td>Workshop Session 2: Strain Sequencing Process</td>
<td>All sites</td>
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<td>- Timing of sequencing</td>
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<td>- Strain selection</td>
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<td>- Strain logistics between sites &amp; Lyon</td>
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<td><em>Moderated by: Bruno Lina (ISC)</em></td>
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<td>12:00 – 12:45</td>
<td>Dissemination &amp; Publications (Globally and Locally)</td>
<td>Pr B Lina (ISC)</td>
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<td>- Update on current manuscript development</td>
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<td>- Posters presented at Options X</td>
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<td>- Publication plan &amp; International conferences 2019-2020</td>
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<td>- Manuscript writing process 2018-2019 season &amp; rules of authorship</td>
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<tr>
<td>12:45 – 13:00</td>
<td>Closing</td>
<td>C Mahé (FIE)</td>
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<td>13:00 – 14:00</td>
<td>Buffet lunch</td>
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WORKSHOP SESSION 1:
NEW PROTOCOL IMPLEMENTATION

Dr. Sandra CHAVES
RESEARCH OBJECTIVE 2019-2020

I. Support international capacities developed through the Global Influenza Surveillance and Response System (GISRS) of laboratories to increase the availability of clinical information linked with genetic sequencing of influenza virus strains

II. Support the biannual vaccine strain selection process of the WHO’s formal recommendation for the composition of human influenza vaccines
SIMPLIFIED DATA COLLECTION

✓ Data collection for laboratory-confirmed influenza (LCI) cases only
  ✓ 50 to 100 cases/site

✓ Timely upload of data (e-crf + GISAID)
  ✓ Weekly uploads of clinical and lab data
  ✓ Linkage between clinical data and virus sequencing

✓ Support for sequencing capacities – GIHSN center in Lyon, coordination by Open Health company (OHC)
## CLINICAL DATA

### EPI and CLINICAL VARIABLES TO BE COLLECTED

<table>
<thead>
<tr>
<th>Smoking habits</th>
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<tr>
<td>Pregnancy status</td>
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<td>Chronic medical conditions</td>
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<td>Prescriptions of antiviral for the current episode</td>
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<td>Influenza vaccination for the current and previous season (self-reported y/n)</td>
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<td>Supplemental oxygen without mechanical ventilation</td>
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<td>Vasopressor support</td>
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<td>ICU admission</td>
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<tr>
<td>Mechanical ventilation</td>
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<tr>
<td>Death while hospitalized</td>
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<td>Discharge/death date (yyyy-mm-dd)</td>
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<tr>
<td>GISAID Accession Number (EPI_ISL)</td>
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Workshop:

• Group discussion (6 groups) ~20 min followed by presentations: Only « key » challenges and opportunities

• Plenary discussion on identified key issues ~30 min

• Live demo of on-line questionnaire ~5 min
1. **How these changes would affect your site (pros and cons)?**
   - Reduce workload? No change in case finding strategy? Easy to manage?
   - Can leverage on other sites in the country?

2. **TIMELY is key!**
   - How feasible is to commit to weekly reporting?

3. **Capacity for FGS**
   - Available in site? Interested in sequencing in-house? Batches _ weekly ?

4. **Questionnaire – any thoughts?**
WORKSHOP SESSION 2:
STRAIN SEQUENCING PROCESS

Pr. Bruno LINA
Sample target: 50 – 100 per site

Sample selection criteria for sequencing:

1. All early season samples (before Jan 15), vaccine failure or severe case (ICU admission/ventilation/death)

2. A subset of the other samples collected across the season: 15-25 per months depending on the total number expected (50-100)
Process of influenza vaccine virus selection and development

Seasonal
- Collection of specimens and disease/epidemiological data (all year round)
- Diagnosis, virus isolation in MDCK, preliminary analysis
- Ferret antisera production
- Thorough antigenic and genetic analysis
- Review and selection of candidate viruses for vaccine use
- Classical reassortment of high-growth viruses for H1N1 & H3N2
- Reassortment of high-growth viruses using reverse genetics (and full safety testing)
- Antigenic and genetic characterization of reassortants

Availability of vaccine viruses and standardized reagents
GIHSN strain sequencing perspectives for 2019-2020

### SITES WITH ONSITE SEQUENCING

- Mexico*
- Brazil
- Canada
- Spain*
- Lebanon
- Ivory Coast
- South Africa
- Turkey
- Argentina
- China X 2
- Russia–St Petersburg*
- Romania

### SITES USING VIRPATH LAB FOR SEQUENCING

- India
- Bangladesh
- Nepal
- France - Lyon
- France - Paris
- Russia - Moscow
- Serbia
- Ukraine
- Argentina
- Peru
- Kenya
GIHSN strain sequencing perspectives for 2019-2020

Better link between the sites and the sequencing platform

Clarification on the circulation of the Data and the specimens from the sites (WHO/GISRS requirements)

Predefine for each site the dates of shipment of material to the GIHSN platform

Use a standardised data set for the shipment
GISAID batch upload facility

GISAID epiflu Uploader: the communication tool

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<th>Health_Status</th>
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| Submitting_Sample_Id | Authors | Originating_Lab_Id | Originating_Sample_Id | Collectio_n_Date | Collectio_n_Month | Collectio_n_Year | Antigen_Character | Adamantanes_Resistance_geno | Oseltamivir_Resistance_geno | Zanamivir_Resistance_genotype | Peramivir_Resistance_genotype | Other_Resistance_genotype | Host_Age | Host_Gender | Health_Status | Note | PMID |
|----------------------|---------|-------------------|-----------------------|------------------|------------------|-------------------|------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------------|-----------------|-----------|---------------|------|------|
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Better link between the sites and the sequencing platform

Clarification on the circulation of the Data and the specimens from the sites (WHO/GISRS requirements)

Predefine for each site the dates of shipment of material to the GIHSN platform

Use a standardised data set for the shipment

Predefine who is responsible for the upload of sequences (fasta files) in the GISAID database
Prepare 2019-2020 calendar for shipments/data sharing
Conclusions

The GIHSN sequencing platform will provide sequence data for 11 sites

This needs to be organized

- number of specimens per site
- date of shipments
- reporting procedure
- sharing with members (GIHSN/NIC /WHO)

Integration of the data obtained from the other sequencing sites

Work with different stakeholders to address unmet needs
Acknowledgements

NIC & Hospital Lyon:
- Bruno Simon
- Marine Jourdain
- Gwendolyne Burfin
- Estelle Gallice
- Rolf Kramer
- Alexandre Gaymard
- Gregory Destras
- Laurence Josset
- Florence Morfin
- Martine Valette

GIHSN sites and ISC:
- John Paget
- Melissa Andrew
- Luzhao Feng
- Justin Ortiz
- Daria Danilenko
- Xavier Lopez-Labrador
- Robert Steiner
- Marta Numes
- Christine Commaille-Chapus
- Clothilde El Guerche-Seblain

WHOcc Crick Institute:
- John McCauley
- Rod Daniels

WHO cc in Cambridge (Institute of Zoology)
- Derek Smith
- Sarah James
DATA OWNERSHIP & ACCESS TO THE DATA

▪ Data collected at site level remains the proprietary of the site.

▪ Each contributing site has full access to the data through a secured platform managed by Open Health Company.

▪ Open Health Company has access to the raw data for epidemiological research fulfilling the following conditions:
  ▪ Analyses are performed for research purposes in line with the mandate of the Foundation (i.e. surveillance and monitoring of influenza and other respiratory viruses)
  ▪ Analyses are exclusively performed with strictly anonymous and aggregated data
  ▪ Any analyses plan need to be approved beforehand by the Independent Scientific Committee (ISC) of the Foundation
GIHSN PUBLICATION RULES

- All analyzed results need to be submitted to ISC before publication.

- Scientific publications and conference communications mention GIHSN contributing sites with main investigators names in the authorship in line with the ICJME rules.

- Sites will be informed upfront for any additional planned data analysis beyond the annual pooled analysis.

- Sites have the possibility to opt-out.
**Seasonal pooled analysis**

- 1 manuscript in peer reviewed journal, and conferences, research question to be proposed/defined by the ISC
- **Authors:** ISC & GIHSN group of authors (volunteering GIHSN principal site investigators can be included in the list of authors provided they commit to the ICJME rules and the manuscript development timeframe)
- **Analyses:** OpenHealth

**Specific topics publications**

- 1 manuscript per year
- **Topics proposed by GIHSN members and validated by the ISC**
  - i.e severity analyses, Burden of disease in specific populations
- **Authors:** Group of authors including volunteers GIHSN investigators and led by one member of the ISC
- **Analyses:** OpenHealth

Medical Writing supported by the Foundation
The research proposal includes:

- a detailed description of a proposed study designed to investigate a specific question
- Should explain: rationale to develop the analyses, research questions, identification of variables, data period extraction
- Organisation of work: who will be part of the authors group, roles and responsibilities

The proposal is presented to the ISC for approval and must be led by a member of this Committee.
Complicated hospitalization due to influenza: Results from the Global Hospital Influenza Network for the 2017–2018 season

Bruno Lina\textsuperscript{1-3,*}, Alexandre Georges\textsuperscript{4}, Elena Burtseva\textsuperscript{5}, Marta C. Nunes\textsuperscript{6,7}, Melissa K. Andrew\textsuperscript{8}, Guillermo M. Ruiz-Palacios\textsuperscript{9}, Luzhao Feng\textsuperscript{10}, Jan Kyncl\textsuperscript{11}, Philippe Vanhems\textsuperscript{12-14}, Justin R. Ortiz\textsuperscript{15}, John Paget\textsuperscript{16}, and Robert C. Reiner\textsuperscript{17} on behalf of the GIHSN 2017–2018 study group†

Authorship:

• The main manuscript is developed by the Scientific Committee with Chairman Bruno Lina and sites who have volunteered to write (Czech Republic, Lyon and Mexico)
• In the group authorship are mentioned: main investigators of all sites
• Other investigators or research staff can be mentioned in the acknowledgements

✓ 1st outline June 14th
✓ Draft 1 July 16th
✓ Draft 2 September 13th
Final version expected for end of November
INTERNATIONAL CONFERENCES IN 2020

• IDWeek, 02-06 Oct 20 (abstract deadline 01 May 20; LB abstract deadline 08-Aug-20)

• ECCMID Paris, France 18-21 Apr 20 (abstract deadline 27 Nov 19; LB abstract deadline 20 Feb 20)

• ESPID 06-11 May 20 (abstract deadline 15 Jan 20)

• ISPOR, Orlando, FL, USA 16-20 May 20

• American Diabetes Association 12-16 Jun 20 (abstract deadline 12 Jan 20; LB abstract deadline 16 Mar 20)

• 7th ESWI Valencia, Spain 13-16 September 2020 (abstract deadline 15-May-2020; LB abstract deadline 15-Aug-20)

• International Society for Pharmacoepidemiology (36 ICPE) Berlin, Germany 26-30 Aug 20 (abstract deadline 13 Feb 20)

• AAFP – Family Medicine Experience (FMX 2020) Chicago, IL, USA 13-17 Oct 20 (abstract deadline 03 Apr 20)

• ISPOR-AP, Seoul, S. Korea 12-15 Nov 20 (abstract deadline 18 Mar 20)

• ISPOR-EU, Milan, IT 14-18 Nov 20 (abstract deadline 24 Jun 20)
During the **OPTIONS X** (Singapore, August 2019) a poster of the GIHSN network was presented (Scientific Committee represented by Pr Bruno Lina)

Local posters was also presented.
Developments of the global influenza hospital surveillance network to support better monitoring of influenza virus genetic evolution: The GIHSN-SevVIR network

Bruno Lina, John Page, Melissa T Andrew, Lutao Fang, Justin R Ortíz, Darío Dominik, Xavier Lopez-Lobrador, Robert B Beilin Jr., Marta C Nunes, Carolina Comattei-Chopin, Clotilde El Cucho-Subiela

INTRODUCTION
- After seven seasons of active influenza surveillance, the Global Influenza Hospital Surveillance Network (GIHSN) is leveraging capacity to link clinical and virological data.

OBJECTIVE
- The main objective is to analyze and monitor influenza virus character from hospitalized cases, and to provide this information to WHO for vaccine strain composition decisions.

METHODS
- During the 2015-2016 season, a coordinated approach was developed by the French National Reference Laboratory for Respiratory Viruses and Influenza (LIRAD). GIHSN surveillance sites and associated laboratories were mapped for their sequencing capabilities.
- A standardized method was proposed using Whole Genome Sequencing and the sites were invited to share information from sequenced strains or vials for sequencing by LIRAD. This sequencing data was linked to detailed epidemiological and clinical information on hospitalized patients collected by GIHSN.

RESULTS

Countries mapping
- All nine countries participating in GIHSN have laboratory capacity for influenza typing and subtyping (Figure 1).
- Sixteen laboratories participated in the sequencing data survey, eleven (including nine national reference laboratories) perform strain sequencing and share their sequence data with WHO's GISSN network via the GISAID platform.
- Three laboratories (Aberdeen, St. Petersburg, Lyon) shared reports with the WHO ahead of the February Vaccine composition meeting.

Strain sequencing results
- GIHSN surveillance sites provided the following data:
  - 73 A(H1N1)pdm09 and 4 B strains were sequenced by these laboratories.
  - 70 A(H3N2) belonged to subclade 3C.2a, while only 2 viruses were from subclade 3C.3a, and 1 from subclade 3C.2a (Figure 2).
  - All 105 A(H1N1)pdm09 belonged to the B/Sw1/3/2013 lineage and 100/2013 had the H1N1pdm substitution as described in the A/Brisbane/02/2008 reference strain. (Figure 3).

- Only 5 Yamanaka influenza viruses have been sequenced by the GIHSN lab, close to the B/Phuket/03/2013 virus.

CONCLUSIONS
- The development of a coordinated approach to link clinical and virological information is key to get a better picture of influenza strain circulation and associated clinical characteristics of patients.
- The first year of the GIHSN sequencing platform development has been promising in terms of capacity building and partnerships developments with GISAID and the WHO GISSN and Vaccine composition meeting.
- As compared to the GISSN data, GISSN reports a similar distribution of the viruses, with limited B viruses. However, due to the lack of recent strains, the GIHSN failed to detect the recent A(H1N1)pdm.
- An improved sampling strategy for sequencing (focusing on populations at risk, geographic diversity, and rapidity for sequencing viruses) will enable the use of the influenza surveillance and strain selection.

FUNDING STATEMENT
- The sequencing data platform is supported by the Foundation of Influenza Epidemiology (FIE), which is partly funded by Sanofi Pasteur.

CONTACT AUTHOR
- brunolina@influenza-lyon.fr
“Recommendations intended to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.”

The ICMJE recommends that authorship be based on the following 4 criteria:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

• Drafting the work or revising it critically for important intellectual content; AND

• Final approval of the version to be published; AND

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
CLOSING OF THE MEETING

Thank You All!