GIHSN-site’s experience &
Results of season 2015-2016

Saint Petersburg, Russian Federation

Research Institute of Influenza
Three participating hospitals
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Study management summary

• Name of coordinating institution: FGBU «Research Institute of Influenza” under Ministry of Healthcare of Russian Federation;
• Number of participating hospitals: Three hospitals;
• Specific demographic features: High proportion of young children, low proportion of elderly patients and adolescents;
• Specific regions covered: Number of patients in GIHSN study (2247 patients) was estimated as 15.2% of total number of hospitalized patients in St. Petersburg (14 785 patients);
• Differences with the core protocol: No differences in order to compare the data obtained in all study seasons;
• Study period: from 14 December 2015 to 26 April 2016.
Russian Federation: incidence rate and hospitalization in the for seven years period

Last epidemic was severe for the country: simultaneous start of an epidemic in a number of cities in the country have been reported. ILI and ARI morbidity were the highest for the last 5 years. Hospitalization ratio exceeded even indices registered during pandemic 2009.
Burden of disease in St. Petersburg: incidence rate and hospitalization for three consecutive seasons

Last season the highest incidence rate was registered in the city compared to the seasons 2013-2014 and 2014-2015. It reached 187 cases per 10,000 of population on the peak of epidemic and was higher than those registered during the first wave of pandemic in November 2009.

Hospitalization was also the highest in the season 2015-2016 and was estimated as 2788 patients per week on the peak of epidemic.

Site experience and results of season 2015-2016 – [St. Petersburg, Russia]
A total 14785 patients were hospitalized in the city and 2 247 (15.2%) of them passed initial examination in 3 hospitals involved in the study.
Season 2015-2016 results summary: flowchart of patients included in GIHSN study

Initially 2247

Included:
2081 (92.6%)
Adults = 460, children = 1621

Excluded
166 (7.4%)

Influenza and ARI positive
1438 (69.1%)

Flu positive 746 (35.8%)

Adults 162
Children 583

ARI positive 692 (33.3%)

Adults 65
Children 627
Distribution of different agents among positives: percentage of patients infected by influenza pandemic virus was the highest in adults. Influenza A(H1N1)pdm09 and RSV dominated in children. Influenza B and rhinoviruses were the following agents by significance in adults and children.
Etiological monitoring of ILI & ARI in the season 2015-2016 compared to 2014-2015, GIHSN study

Peak of hospitalization registered on week 5.2016 was associated mainly with pandemic virus, it was much higher compared to 2015 when mostly co-circulation of A(H3N2) and B (Yamagata lineage) viruses was observed. Last season influenza B (Victorian lineage) activity was much lower and registered mainly at the end of epidemic.

RSV activity was observed earlier than in the previous season. It was registered during the whole study period with decrease to its end. Last season rhinovirus detection was less than in 2014-2015 season.
Influenza A(H1N1)pdm09, A(H3N2) and B infection in patients with different co-morbidities (2014-2015 and 2015-2016)

Unlike 2014-2015 season when influenza A(H3N2), B and partly A(H1N1)pdm09 infections were registered in various combinations with different co-morbidities, influenza A(H1N1)pdm09 dominated regardless of comorbidity type during 2015-2016 season.
Last season percentage of patients hospitalized mostly with influenza A(H1N1)pdm09 infection regardless of co-morbidity type was much higher than in previous season when influenza A(H3N2) and B viruses co-circulated. Thus, pandemic virus can be evaluated as risk factor for hospitalization.
Burden of influenza: duration of stay in the hospital depending on age of patients

Last season duration of stay in the hospital was higher than in 2014-2015 season regardless of patient age (except adolescents). It was higher among influenza positive patients compared to influenza negative ones although these differences were not significant. As reported previously duration of hospitalization was the highest among elderly.
A total 22 patients (1.1%) were placed in ICU. Proportion of adults placed in ICU this season increased from 3.9% to 40.9%. Etiological agents were determined in 63.6% cases, most of cases were caused by influenza A(H1N1)pdm09 virus. RSV and metapneumovirus were detected less often.

The main reasons for ICU admission were convulsions, hyperthermia, heart or breath failure.

Seven deaths (2 children and 5 adults) were registered in GIHSN study. Most of them (5 deaths) were caused by influenza A(H1N1)pdm09, in two other cases the etiologic agent was not revealed. Comorbidity was not detected in three influenza associated death cases.

Influenza A(H1N1)pdm09 in combination with cardiovascular disease was recognized as risk factor for hospitalization of adults.

In children chronic obstructive pulmonary disease in combination with influenza A(H1N1)pdm09, RSV and rhinovirus was the main reason for hospitalization.
Strain characteristics by antigenic cartography (viruses isolated in two Russian NICs)

620 influenza viruses were characterized in 2015-2016 season:

- 512 strains of influenza A(H1N1) pdm09,
- 24 strains of influenza A(H3N2),
- 85 strains of influenza B viruses

Influenza viruses A (H1N1) pdm09 were antigenically related to the vaccine virus A / California / 07/09 included in the vaccine for the season 2015-2016;

The antigenic map based on HI test demonstrates that antigenic distance between the vaccine strain and the strains tested does not exceed the four-fold difference in homologous titer.

84 studied influenza B viruses belonged to the Victorian lineage and were similar to the reference virus B/ Brisbane/60/2008, only one influenza B virus belonged to Yamagata lineage

All 24 strains of influenza A(H3N2) virus were related antigenically to the virus A / Hong Kong/4801/2014

Site experience and results of season 2015-2016 – [St.Petersburg, Russia]
Phylogenetic analysis of HA gene of influenza A(H1N1)pdm09 viruses from the patients in GInSN study

All H1N1pdm09 viruses of the last epidemic season belonged to 6B.1 subgroup bearing amino acid substitutions S84N, S162N (+CHO), I216T (e.g. A/Slovenia/2903/2015) in HA1.

No substitutions was detected in known antigenic sites.

Substitution D222G was observed in some sequences from autopsy samples.
INFLUENZA A(H1N1)pdm09 VIRUSES ISOLATED IN 2015 - 2016 EPIDEMIC SEASON ACQUIRED SPECIFIC MUTATIONS IN INTERNAL GENES (IN ACCORDANCE WITH Epiflu GISAID DATABASE)

NS: AA substitutions D2E and E125D responsible for shut-down of host RNA transport and host adaptation of the virus drastically increased in less than 1 year from 10% to 74% in NS1 protein of the viruses. Substitution N48S was revealed in 39% of sequenced viruses;

NEP: In NEP protein the same phenomenon was observed for substitution M83I flanking nuclear export signal (NES), the frequency of which has increased from 13% in 2014/2015 to 83% in 2015/2016 epidemic season.

NP: Amino acid substitution M105T found in NP protein raised from 6% in 2013/2014 epidemic season to 86% in 2015/2016 epidemic season;

M1: Amino acid substitution Q208K in M1 first registered in 2014/2015 reached 83% frequency in 2015/2016 epidemic season.

PA-X (involved in host antiviral response shut-off) All sequenced strains encode substitution N204S in PA-X. The frequency of this substitution increased from 14.8% in 2014/2015 to 81.2% in 2015/2016 season. Possible link of pathogenicity with described internal gene constellation first revealed in influenza A/New York/61/2015 virus awaits further experimental proof.

Geographic distribution of influenza A(H1N1)pdm09 virus with specific mutations in internal genes (IG) according to EpiFlu GISAID database (June 2016)

Influenza A(H1N1)pdm09 strains with set of mutations in internal genes registered often in European region (85%), North America (86%) and Asia (57%), but rarely in South America and Africa (4-5%):

Distribution of viruses with set of mutation in IG by countries of European Region:

- Bulgaria - 100%
- France – 88.5%
- Kazakhstan – 100%
- Kyrgyzstan – 77.5%
- Russia – 97.9%
- Sweden -84.3%
- UK – 76.6%
- Ukraine -33.3%
Differences with past seasons (improvements)

In study managerial terms
the work of doctors in primary input of patient data into RII electronic database was simplified

In study findings: this season full genome NGS analysis was introduced for characterization of virus surface and internal genes

Strain circulation: More cost and time saving approach was used for virus isolation and strain characterization: only PCR-positive samples were used
Challenges

- **Room for improvement**: risk factor determination could be more accurate if immunological criteria are introduced in the study.
- **Perspectives**: identification of viral pathogenicity genetic determinants, circulated viruses’ matching to vaccine strains control.
- **Strengths**: full genome sequencing and antigenic cartography of influenza viruses from hospitalized patients.
- **Weaknesses**: decrease of support can lead to introduction of selection system for patient to be investigated by PCR for influenza and other respiratory viruses.

Site experience and results of season 2015-2016

Saint Petersburg, Russia
CONCLUSIONS

1. Severe influenza epidemic registered in St. Petersburg in 2015-2016 season was caused by influenza A(H1N1)pdm09. Influenza B circulation increased towards the end of the season. The change of the Yamagata to Victoria lineage was revealed. Influenza A(H3N2) activity was very low;

2. Antigenically influenza A (H1N1)pdm09 virus was related to the vaccine strain A/California/07/09;

3. Influenza A (H1N1)pdm09 viruses belonged to the subgroup 6B.1 with a number of specific mutations S84N, S162N (+ CHO) and I216T in the HA1 molecule; no mutations in the antigenic sites of HA were detected;

4. A dramatic increase of viruses with specific mutations in the internal genes NS, NEP, NP, M1, PA-X was registered;

5. Risk factors for hospitalization of adults with influenza was cardiovascular disease. In children chronic obstructive pulmonary disease in combination with influenza A(H1N1)pdm09, RSV and rhinovirus was the main reason for hospitalization;

6. Increase of lethality during influenza epidemic was registered in St. Petersburg last season. Hypertoxic form of influenza A(H1N1)pdm09 with acute respiratory distress syndrome was the cause of death in patients without comorbidity;

7. Percentage of vaccinated people among hospitalized patients positive for influenza was low.
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