Global Influenza Hospital Surveillance Network

The results of GIHSN study in Saint Petersburg and Ekaterinburg (Russia) in 2017-2018 season

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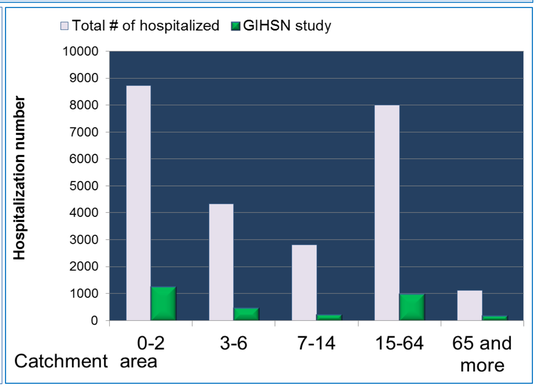
Site presentation: Expanding the geography of St. Petersburg site research by inclusion in the GIHSN study Ekaterinburg city from the Ural Federal District

Six Hospitals participated in the study:

St.Petersburg: The population of St. Petersburg includes 5 281 579 inhabitants. Three Hospitals, one for the adults (60 beds; code # 1) and two for the children (284 and 120 beds; code # 2 and 3) were included in the study. Three ICU are designed for 39 beds. 2707 patients were included in the study.

Ekaterinburg: The population of Ekaterinburg includes 1 432 thousands people. Three Hospitals, one for adults (60 beds; code # 4) and two for the children (100 and 105 beds; code # 5 and 6); Three ICU are designed for 33 beds. 403 patients were included.

A total **3110 patients** were included in the study and swabbed (**12.4%** from total number of patients admitted with ILI&ARI in all hospitals of two cities).

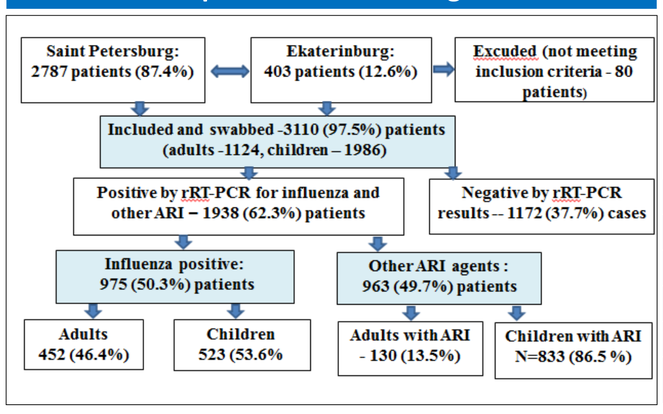


Methods

SARI patients of all age groups were selected by the GIHSN criteria of inclusion/exclusion in study. All procedures were performed according to GIHSN standardized protocol, Version 6.0, October 2016. Core questionnaires for patients less than 5 years and for patients 5 years or more were applied across all hospital sites; Investigation was conducted in accordance with the principles of GCP. The study was approved by the Local Ethics Committee. Nasopharyngeal swabs collected in UTM (Copan) were tested by RT-PCR using “AmpliSense” kits (Interlabservice, Russia) for influenza A&B as well as for subtyping of H1N1pdm09 and H3N2 viruses; Influenza B viruses belonging to Yamagata or Victoria lineage was specified using CDC&P (USA) primers & probes. RSV, MpV, PIV, CoV, RhV, AdV and BoV were recognized by “AmpliSense ARVI screen” kits. Virus isolation, genetic and antigenic analysis was performed for the matching of the vaccine and circulated in Russia influenza strains.

Results

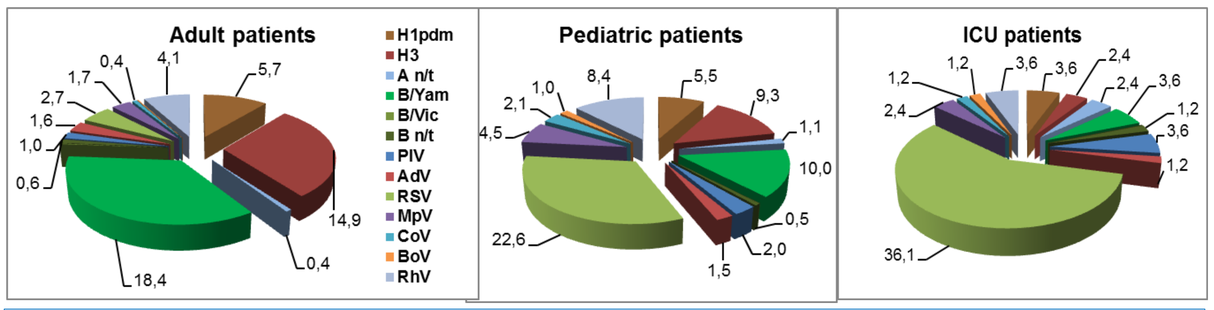
Relative burden of influenza viruses compared to other ARI agents



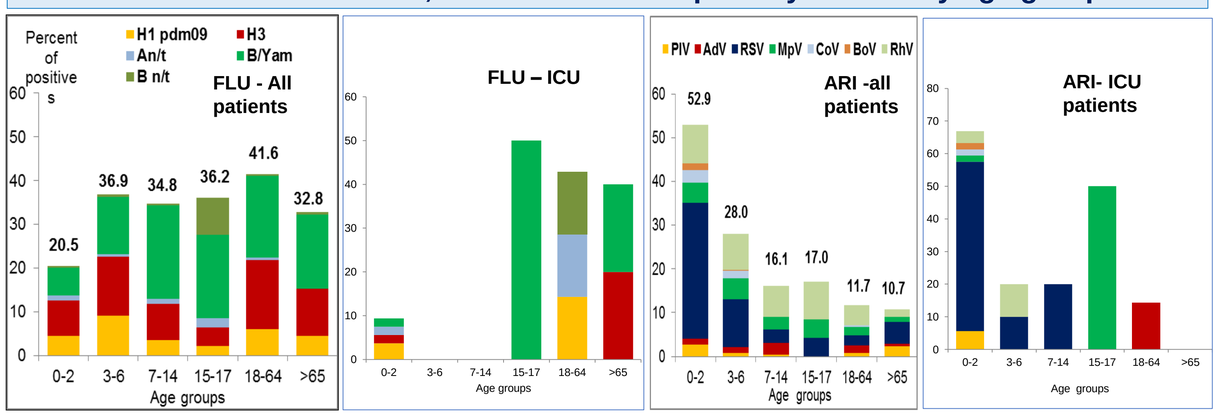
Age distribution of the patients

Age group (years)	Number of patients included in the study	Percentage of patients by age groups (%)
0-2	1245	40,0
3-6	464	14,9
7-17	277	8.9
18 - 64	947	30,5
65 and more	177	5,7
Total	3110	100,0%

Determination of age specific dominating etiological agents of SARI by results of detection of influenza and other respiratory viruses. Influenza A(H1N1)pdm09, A(H3N2) and B/Yamagata viruses co-circulated in 2017-2018 season. The burden of influenza viruses was higher in adult patients compared to pediatric patients (40.2% and 26.3%, respectively); The ARI agents prevailed in children (42.1% against 11.6%). RSV was the dominating causative agent of admission in pediatric patients (22.6%) reaching 31.1% in age group 0-2 years. A total 83 (4.3%) patients were placed in ICU and most of them were children aged 0-2 years The dominating agent (36,1%) was RSV. Influenza viruses caused 13,3% of investigated cases.

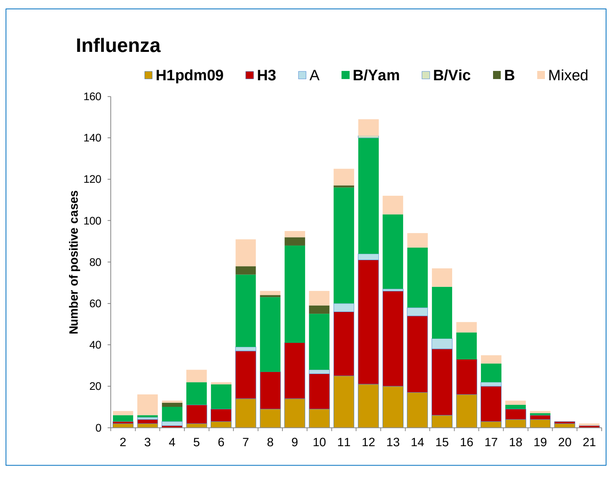


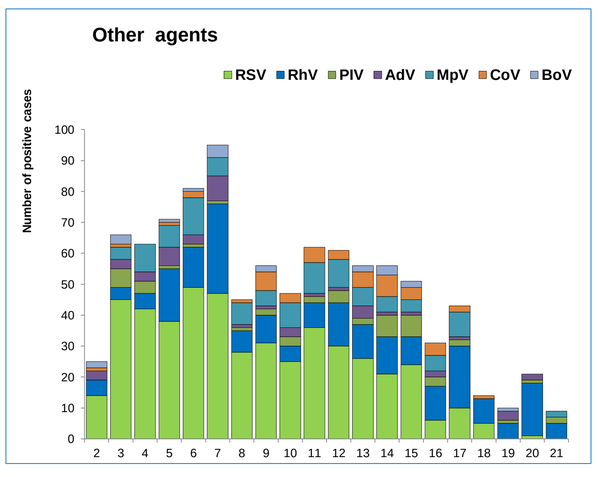
The burden of influenza, RSV and other respiratory viruses by age groups



RSV was the reason for hospitalization mainly of young children aged 0-2 yrs (p=0.002) in contrast to influenza viruses which were detected more often in older age groups (mostly in socially active adult patients aged 18-64 years). RhV and MpV affected more pediatric patients.

Monitoring of influenza and other respiratory viruses activity in 2017-2018

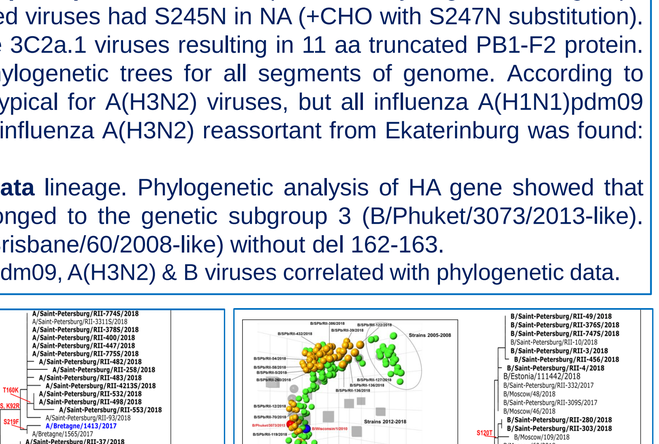




Pregnancy as a risk factor. A total of 106 pregnant women were included in GIHSN study in 2018. No significant differences in the rate of influenza were registered this season among pregnant women compared to the control group of not pregnant women. However ARI agents and co-morbidity was more often in pregnant women.

Index	Pregnant woman	Not pregnant (adjusted control)
Number of women	106	88
Influenza positives:	55 (51.9%)	44 (50.0%)
A(H1N1)pdm09	12 (11.3%)	8 (9.1%)
A(H3N2)	24 (22.6%)	17 (19.3%)
B/ Yamagata	18 (17.0%)	17 (19.3%)
ARI agents positives:	17 (16.0%)	6 (6.8%)
Parainfluenza virus	2 (1.9%)	0
Adenovirus	1 (0.9%)	1 (1.1%)
RSV	4 (3.8%)	3 (3.4%)
Metapneumovirus	3 (2.8%)	1 (1.1%)
Boca	1 (0.9%)	0
Rhinovirus	6 (5.7%)	1 (1.1%)
Co-morbidity cases:	27 (25.5%)	9 (10.2%)
Co-morbidity cases + FLU	8 (7.5%)	2 (2.3%)
Co-morbidity cases + ARI	7(6.6%)	3 (3.4%)

Identification of risk groups for influenza. Percentage of total influenza positive patients with chronic co-morbidity in 2018 was comparable with previous seasons except 2015-2016 season when influenza A(H1N1)pdm09 dominated. CVD, COPD, asthma and diabetes were the most often.

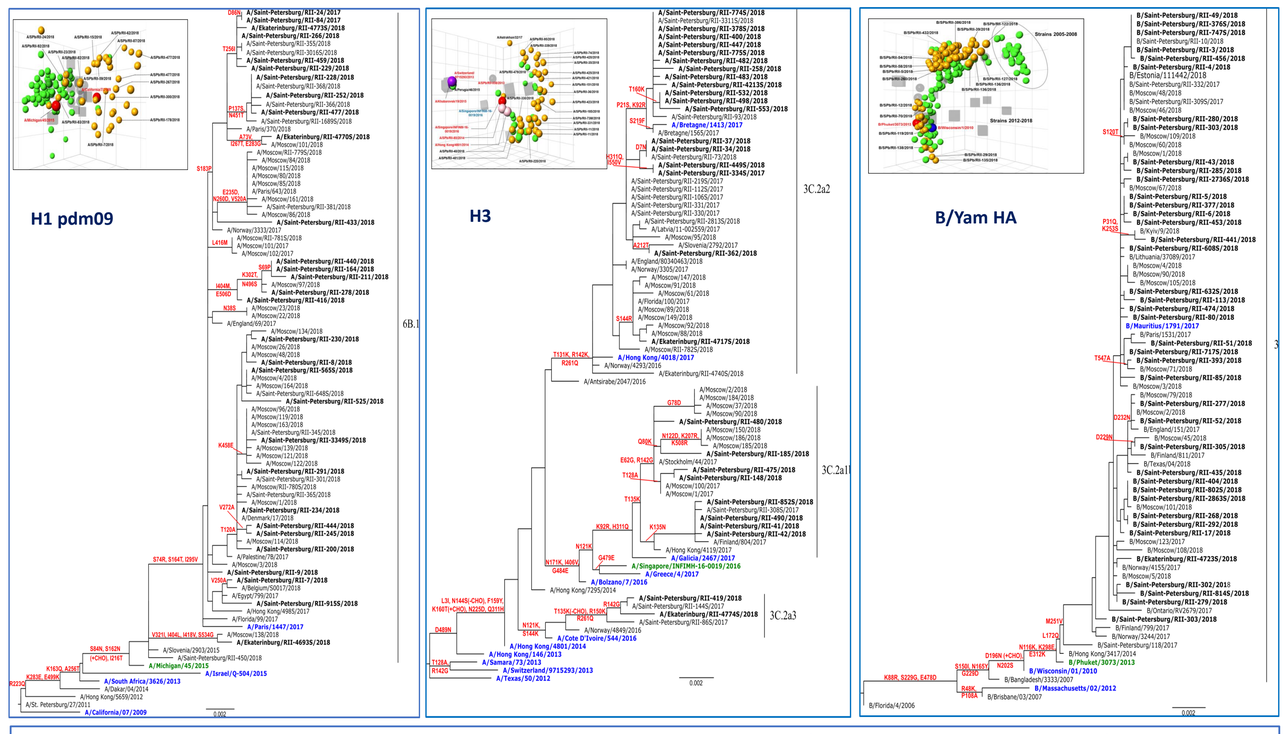


Phylogenetic analysis and antigenic cartography of influenza viruses from the patients included in GIHSN study. A slow antigenic drift of influenza **A(H1N1)pdm09 viruses** with the accumulation of point mutations in the HA gene was observed. All sequenced viruses (except 1 Saint-Petersburg and 1 Ekaterinburg viruses) belong to one cluster with amino acid substitutions in antigenic sites Cb (S74R, I295V) and Sa (S164T) of 6B.1 clade (A/Michigan/45/2015-like). Some viruses contain S183P substitution in HA1 which increases recognition of host cell receptors and possibly changes viral fitness or immune escape. A(H1N1)pdm09 viruses showed rather high rate of mutations in internal genes PB1, PB2, PA, M and NS.

According to HA gene phylogenetic analysis influenza **A(H3N2) viruses** were represented by 3 genetic subgroups 3C2a.2(64%), 3C2a.1b(29%) & 3C2a.3(7%). All sequenced viruses had S245N in NA (+CHO with S247N substitution). NGS sequencing revealed deletion in segment 2 of some 3C2a.1 viruses resulting in 11 aa truncated PB1-F2 protein. The PB1-F2 truncated viruses clustered together on phylogenetic trees for all segments of genome. According to EpiFlu GISAID database 11 aa PB1-F2 truncation is untypical for A(H3N2) viruses, but all influenza A(H1N1)pdm09 viruses have truncated PB1-F2. Singleton inter-subclade influenza A(H3N2) reassortant from Ekaterinburg was found: HA - 3C2a.2, other genes - 3C2a.3.

All influenza **B** viruses (except two) belonged to **Yamagata** lineage. Phylogenetic analysis of HA gene showed that influenza B(Yam) viruses isolated in St. Petersburg belonged to the genetic subgroup 3 (B/Phuket/3073/2013-like). Two viruses of **Victoria** lineage belonged to clade 1A (B/Brisbane/60/2008-like) without del 162-163.

The results of **antigenic cartography** of influenza A(H1N1)pdm09, A(H3N2) & B viruses correlated with phylogenetic data.



IVE against admission by age groups and virus subtypes. Trivalent inactivated subunit influenza vaccine (TIV) “Sovigrip” paid from the Federal Budget was used mainly for population immunization in Russia in 2017. Other vaccines available in the country: “Vaxigrip” “Begrivac”, “Fluarix”, “Influvac” were paid by patients themselves. A total 58.4 mln doses were used for population immunization in Russia, including 2.6 mln doses in St. Petersburg (for 49.7% of population). In GIHSN study of 1863 enrollees with complete data, 116 patients were positive for influenza A(H1N1)pdm09, 253 for influenza A(H3N2), 326 for influenza B/Yamagata. The overall IVE was 9%, adjusted IVE - 7 %. TIV offered little protection against influenza A(H3N2) and B components (as a result of mismatching vaccine strains and circulated H3N2 and B viruses) but was effective against influenza A(H1N1)pdm09 virus (IVE was 77%).

Age group (years)	Number of vacci-nated patients	Vaccinated #		Not vaccinated#		Risk flu+ in vacci nated	Risk flu+ in not vacci nated	IVE Crude	IVE adjust ed
		Flu (+)	Flu (-)	Flu (+)	Flu (-)				
3-6	21	6	15	165	278	28,6%	37,2%	23,3%	28,6%
7-14	42	16	26	64	124	38,1%	34,0%	-11,9%	-1,6%
15-17	5	1	4	16	26	20,0%	38,1%	47,5%	30,0%
Adults	62	23	39	429	631	37,1%	40,5%	8,3%	3.9%
Total	130	46	84	674	1059	35,4%	38,9%	9,0%	6,7%

Virus subtype	Vaccinated		Not vaccinated		Risk flu+ in vacci nated	Risk flu+ in not vacci nated	IVE
	Flu (+)	Flu (-)	Flu (+)	Flu (-)			
A(H1N1)pdm09	2	128	114	1621	2%	7%	77%
A(H3N2)	16	114	237	1498	12%	14%	10%
B/Yam	25	105	301	1434	19%	17%	-11%

** - age group 0-2 years was excluded from analysis due to low percent of vaccinated*

Key aspects:

1. The last epidemic caused by co-circulation of A(H1N1)pdm09, A(H3N2) and B/Yamagata viruses was characterized by late start, moderate intensity and shorter duration compared to previous one;
2. RSV was dominating agent of SARI among young patients. It circulated actively during all epidemic period along with influenza viruses;
3. Influenza A(H3N2) and B/Yamagata lineage viruses mismatched the vaccine strains by results of genetic and antigenic analysis in difference from A(H1N1)pdm09 virus, that determined the greatest effectiveness of vaccine against the last virus (77%);
4. CVD, COPD, asthma and diabetes were risk factors for SARI admission with influenza; ARI agents and co-morbidity was more often in admission of pregnant women compared to not pregnant ones.

Challenges: Further expansion of geography of GIHSN study in the country is important to obtain accurate indicators of influenza and ARI impact and to evaluate influenza vaccine effectiveness. Full genome analysis of viruses using NGS is important for the recognition of pathogenicity determinants of influenza viruses.

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Acknowledgements: We would like to thank Clotilde El Guerche-Séblain, Víctor Baselga Moreno, Javier Díez-Domingo, Maria Morizet and all GIHSN and Open Health Co. staff for close cooperation as well as all the doctors participating in the study for their dedicated work. We thank the Foundation for Influenza Epidemiology for catalytic financial support of St. Petersburg site.