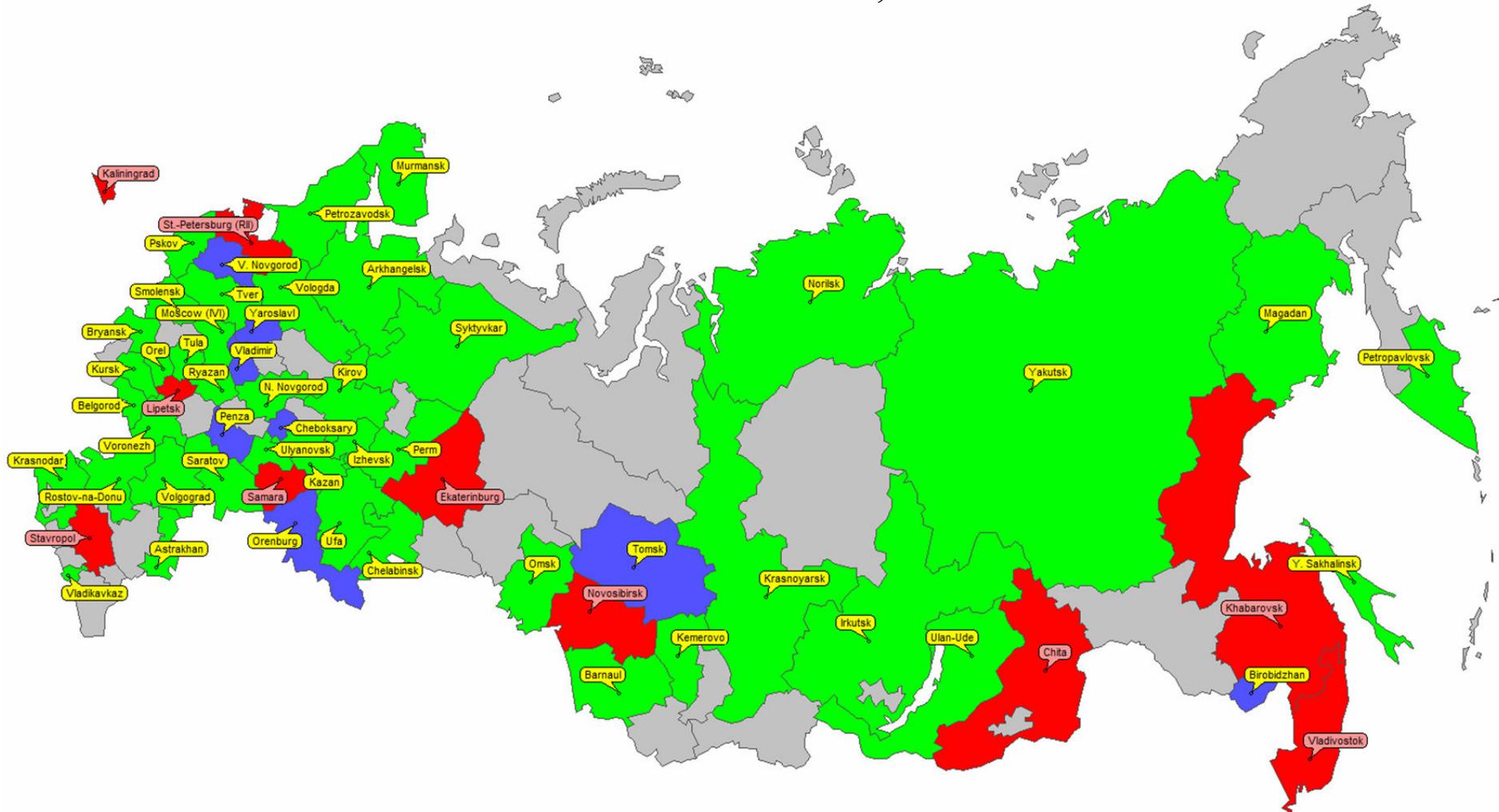




## Digest of Influenza Surveillance in Russia, Seasons 2009–2013



Russian Ministry of Healthcare  
Research Institute of Influenza  
WHO National Influenza Centre

**Digest**  
of Influenza Surveillance in Russia, Seasons 2009–2013

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[www.influenza.spb.ru](http://www.influenza.spb.ru)



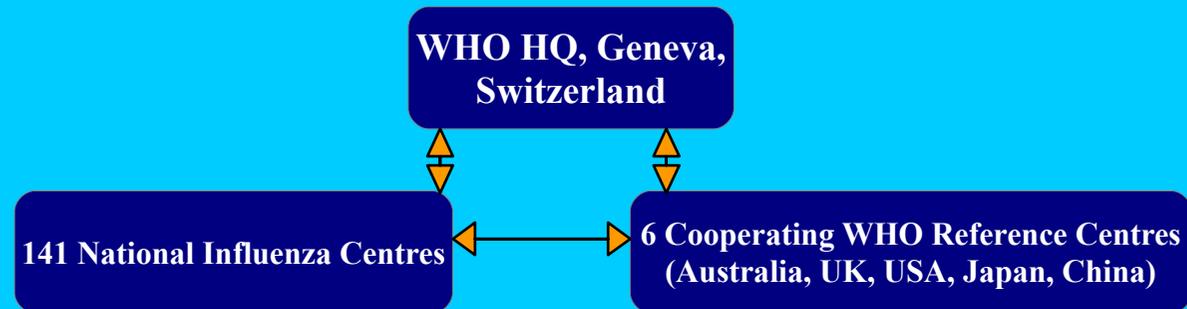
## Global System for Influenza Surveillance

113 countries are supporting the system introduced in 1952

The aim of the system is to diminish influenza morbidity & mortality.

Major tasks to cope with:

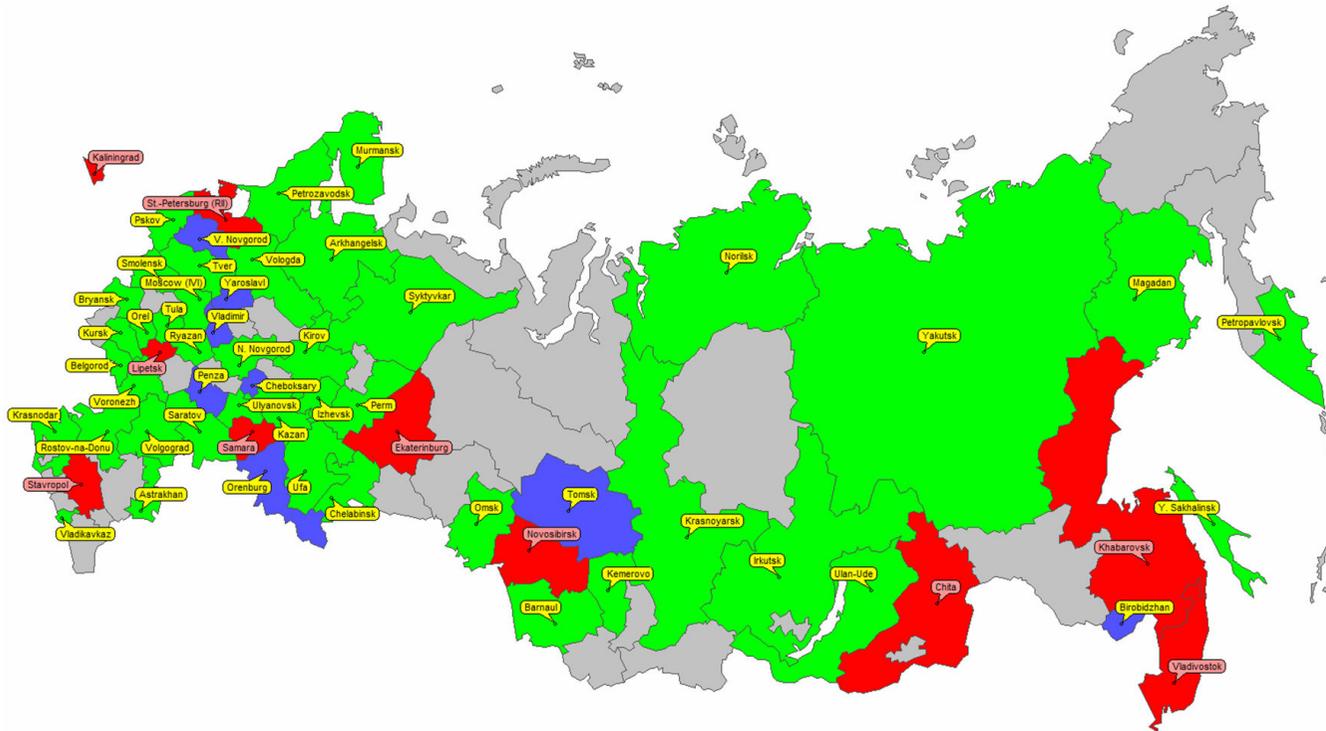
- Early identification of pandemic viruses
- Predicting the etiology of epidemics in various regions of the world
- Recommendations on strain composition of influenza vaccines



Russia joined the Global System of Influenza Surveillance in 1956, a year before the pandemic caused by A/Singapore/H2N2 virus. After the establishment of the Research Institute of Influenza (RII) in 1967, a National Influenza Centre was organized at the RII in 1971, linking national and international influenza surveillance. Currently, 2 authorized WHO National Influenza Centres are operating in Russia:

- Research Institute of Influenza (RII), St. Petersburg
- Ivanovsky Institute of Virology(IIV), Moscow

## Influenza Surveillance System in Russia



**Two National Influenza Centres:**  
 —Research Institute of Influenza (St. Petersburg), also Federal Influenza and ARI Centre;  
 —Ivanovsky Institute of Virology (Moscow), also Centre of Ecology and Epidemiology.

**59 Regional Base Laboratories (RBLs)** comprising national surveillance network. 49 are assigned to RII, 10 are assigned to IIV. RBLs collect and report all the surveillance data to NICs. RII manages an electronic surveillance database.

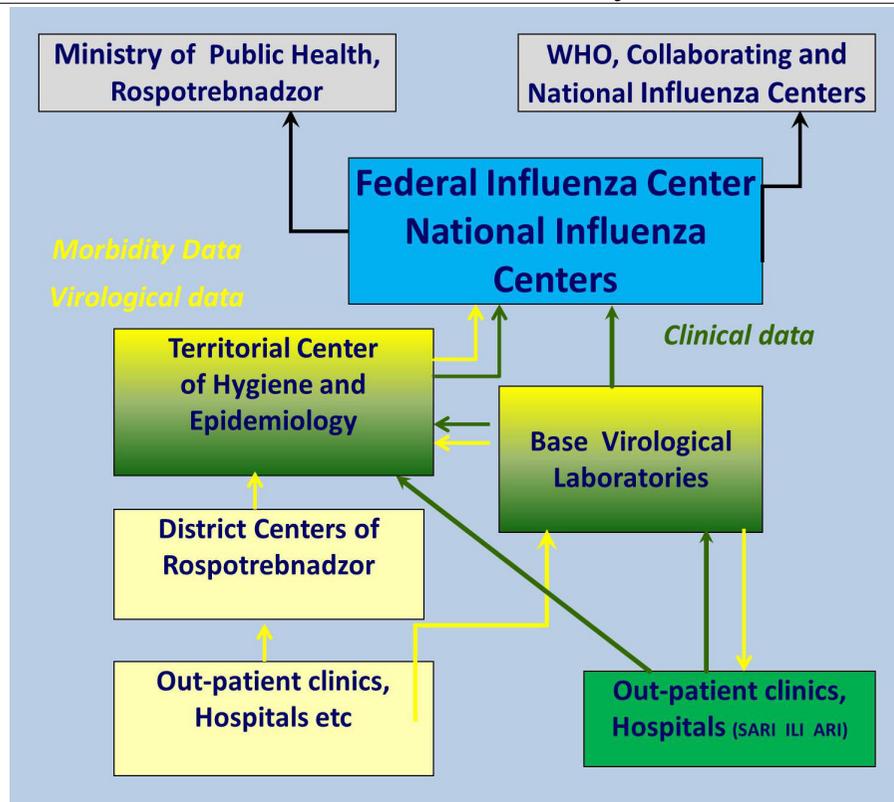
Regional Base Laboratories participating in influenza surveillance in Russia: Research Institute of Influenza: traditional surveillance (green); traditional and sentinel surveillance (red). Ivanovsky Institute of Virology: traditional surveillance (dark blue)

### RII NIC Activities:

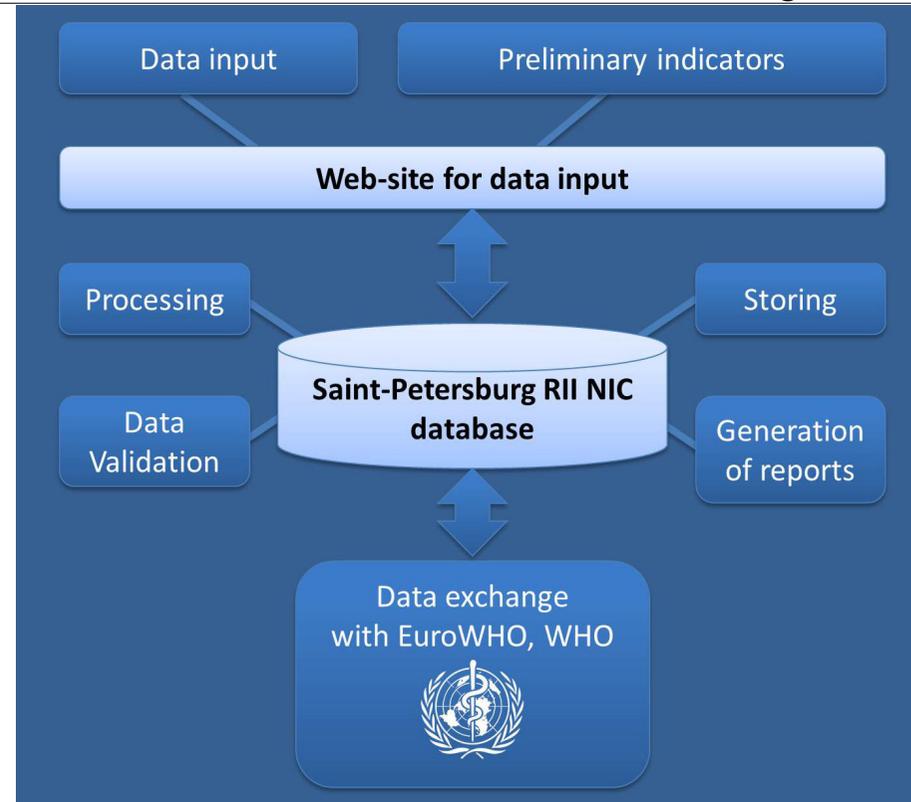
- Registration and weekly analysis of morbidity data
- Determination of epidemic start and spread in Russia
- Counting of morbidity and mortality levels
- Interaction with Regional Base Laboratories (RBLs): isolation, identification and antigenic analysis of influenza viruses
- Analysis of weekly data on rapid IFA and PCR diagnosis of influenza and ARVI

- Determination of susceptibility of isolated strains to antivirals
- Reports to Ministry of Public Health, WHO, WHO CC and RBLs
- Surveillance updates for FluNet
- Presentation of new isolates to WHO CC
- Standardization of reagents and methods used by RBLs
- Training courses for virologists and epidemiologists from RBLs
- Sentinel influenza surveillance (since 2009)

## Russian Influenza Surveillance System Network



## Influenza Surveillance Data Processing



Influenza Surveillance System in Russia is based on compulsory registration of every illness case in polyclinics, hospitals, etc, and submission of these data to NIC.

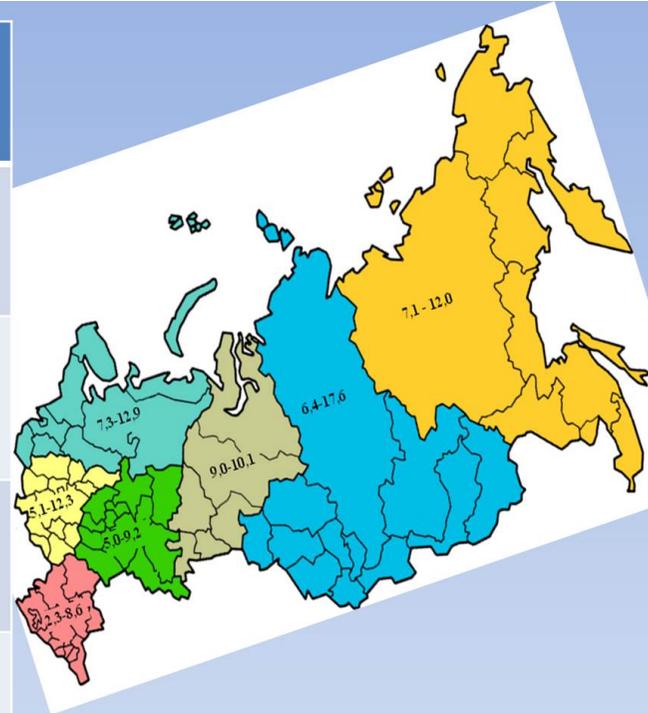
Biological substances taken from patients (nasopharyngeal swabs, blood samples and etc.) are collected and analyzed in Virological Labs. The most interesting viruses are submitted to Research Institute of Influenza.

Data submitted into the database include:

- Total n. of registered influenza and ARI cases per various age groups: 0–2, 3–6, 7–14 years and 15 years and older
- Hospitalizations due to influenza and ARI,
- Influenza and ARI mortalities and their complications
- Virus isolations, virus samples, results of virus antigen detection by IFA and PCR
- Population immunity data (2 times per year)
- SARI, ILI and ARI cases, individual patients anamnesis data, results of influenza and other ARI viruses antigen detection by PCR from 9 cities—Sentinel Surveillance bases

## TRADITIONAL EPIDEMIOLOGICAL AND LABORATORY SURVEILLANCE

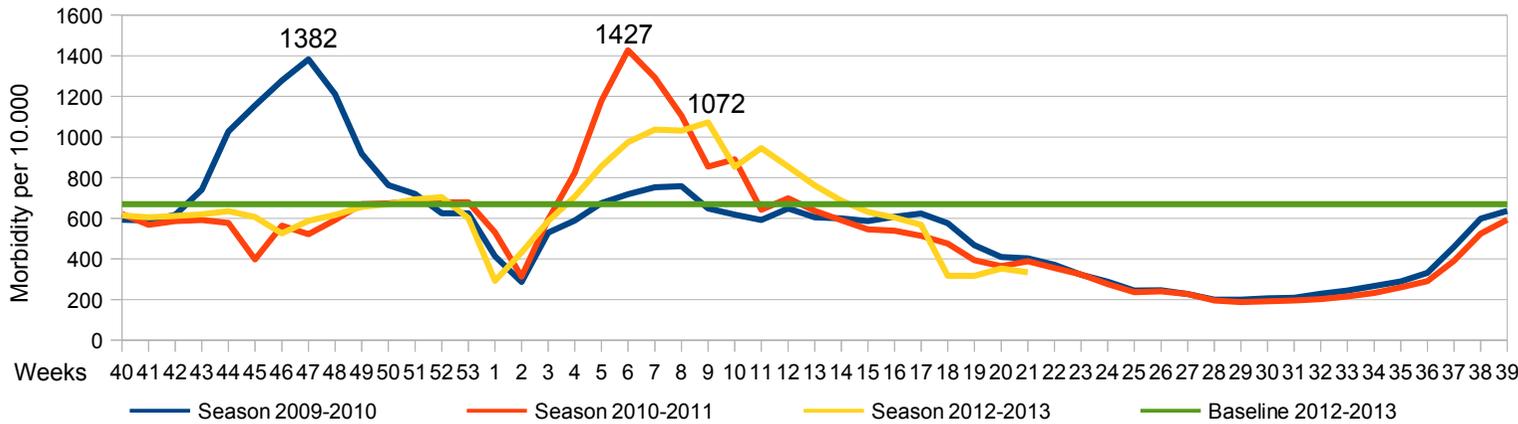
Name of Federal District	Cities under review	Morbidity (%)
Siberian	Chita, Barnaul, Krasnoyarsk, Irkutsk, Ulan-Ude, Novosibirsk, Kemerovo, Omsk, Norilsk	6.4-17.6
North-West	Vologda, Syktyvkar, Petrozavodsk, Arkhangelsk, Pskov, Murmansk, St. Petersburg, Kaliningrad	7.3-12.9
Central	Belgorod, Smolensk, Voronezh, Kursk, Tula, Orel, Ryazan, Moscow, Bryansk, Tver	5.1-12.3
Far East	Magadan, Yuzhno-Sakhalinsk, Khabarovsk, Yakutsk, Petropavlovsk	7.1-12.0
Urals	Chelyabinsk, Yekaterinburg	9.0-10.1
Volga Region	Saratov, Ulyanovsk, Kirov, Nizhny Novgorod, Kazan, Ufa, Izhevsk, Samara, Perm	5.0-9.2
South	Astrakhan, Volgograd, Rostov-na-Donu, Krasnodar	2.3-8.6



**Morbidity rates  
in Federal Districts  
During A(H1N1)pdm09  
Epidemic**

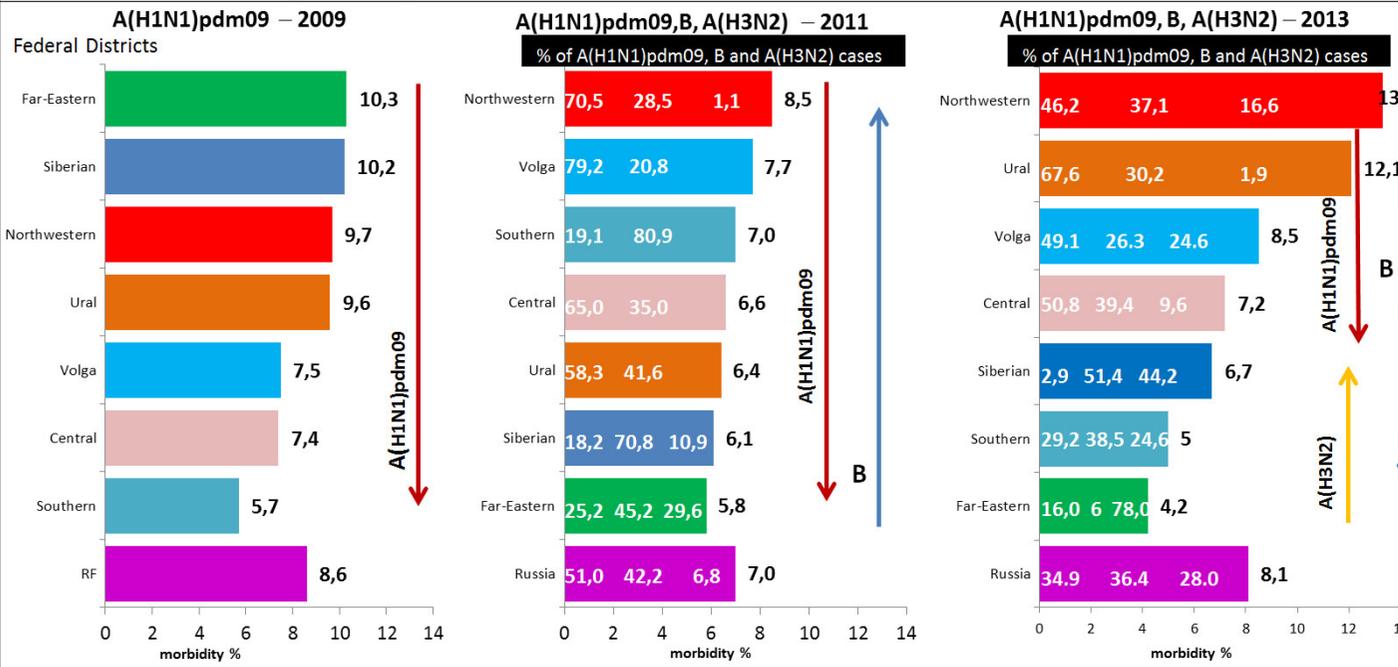
The 2009–2010 season appeared to be an exception characterized by unusually early pandemic morbidity which was registered in early October 2009. The first case of the pandemic virus isolation was registered in May 2009 by WHO NIC in Moscow and later by WHO NIC in St. Petersburg. During spring and summer months A(H1N1)pdm09 was detected by rRT-PCR sporadically in ILI cases mostly in passengers arriving from affected countries. A sharp increase in the number of diagnosed influenza A(H1N1)pdm09 cases accompanied by growth of epidemic morbidity was observed in October 2009.

## Comparison of influenza and ARI morbidity during influenza epidemic seasons involving A(H1N1)pdm09 influenza strain in 59 cities of Russia



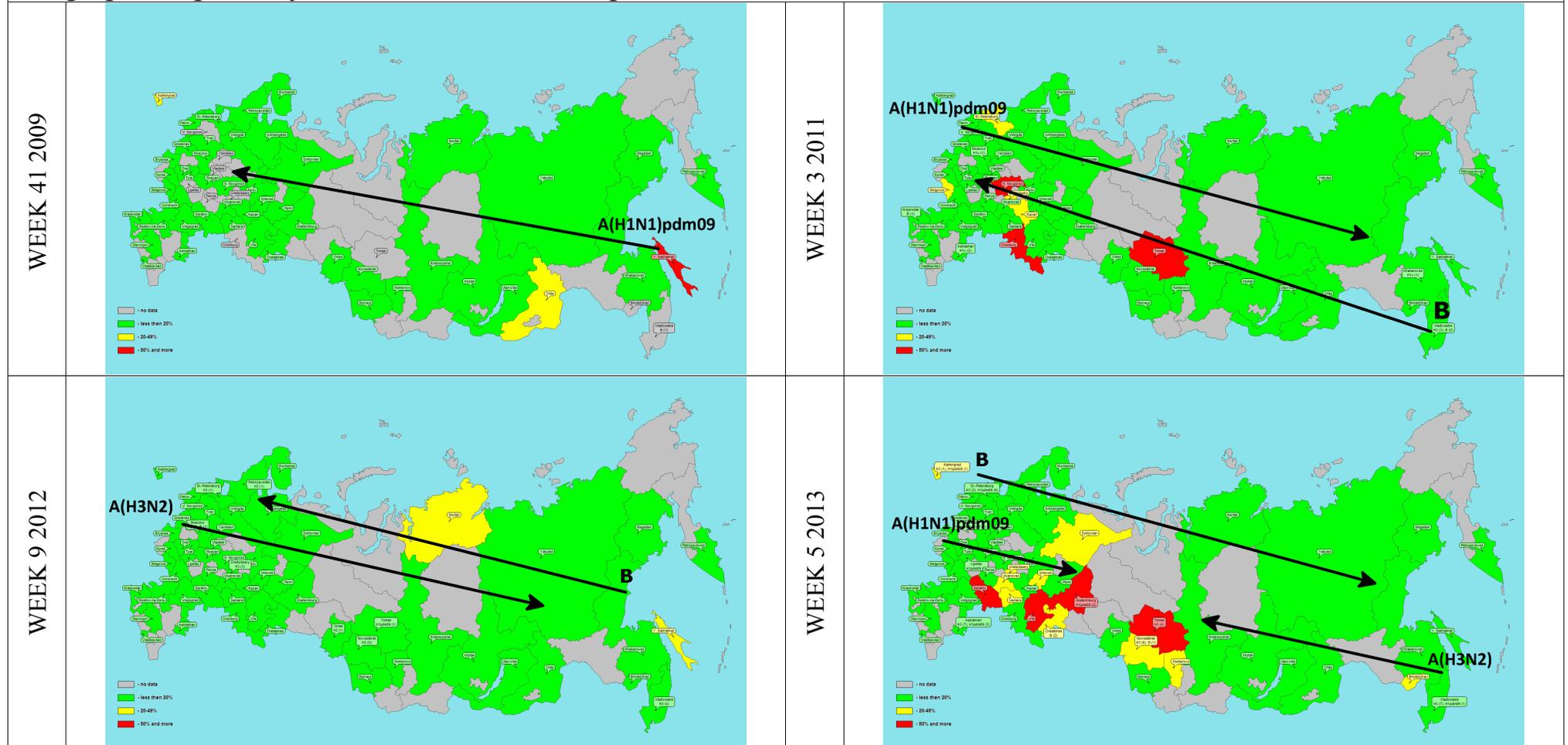
<The first wave of A(H1N1)pdm09 pandemic began unusually early in week 39, 2009. Morbidity rose for 8 weeks in 2009, for 7 weeks in 2011 and 2013, reaching peak values in weeks 47, 8 and 9, respectively. Highest morbidity was observed in 2011 (1,43%), lowest in 2013 (1,07%). The three epidemics lasted 17, 14 and 16 weeks, respectively.

## Influenza geographical pathways, etiology and morbidity, seasons 2009, 2011 and 2013



<The intensity of epidemics in Federal districts depended on the disease etiology and the pathways they(epidemics) spread by. It was higher in the districts of origin where influenza A(H1N1)pdm09 prevailed. Along the eastern pathway the highest morbidity was recorded in the Far Eastern and Siberian FDs. Along the western pathway the highest morbidity was recorded during mixed epidemics of 2011 in Northwestern and Volga FDs, 2013 in Northwestern and Ural FDs.

# Geographical pathways of influenza strains, epidemic seasons 2009–2013



2009 influenza pandemic in Russia spread from the Far East westerly. During 2010–2011 epidemic season, influenza A(H1N1)pdm09 spread from west easterly, while influenza B spread from the Far East in westerly direction. During 2011–2012 epidemic season, influenza A(H3N2) spread from west to east, while influenza B spread vice versa. In 2012–2013 season influenza A(H1N1)pdm09 and B spread from Europe easterly, while A(H3N2) — from the Far East westerly.

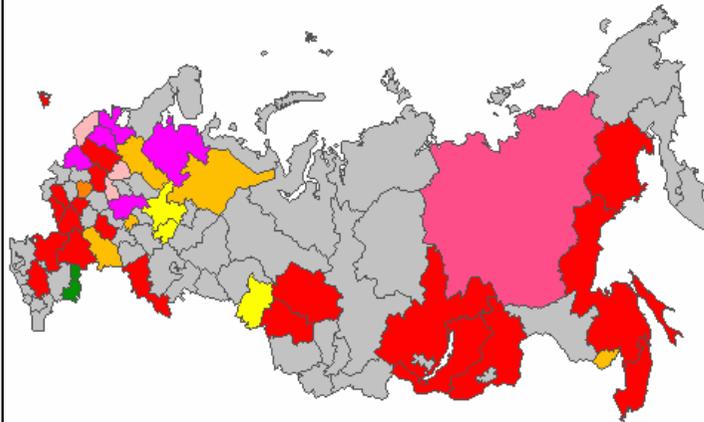
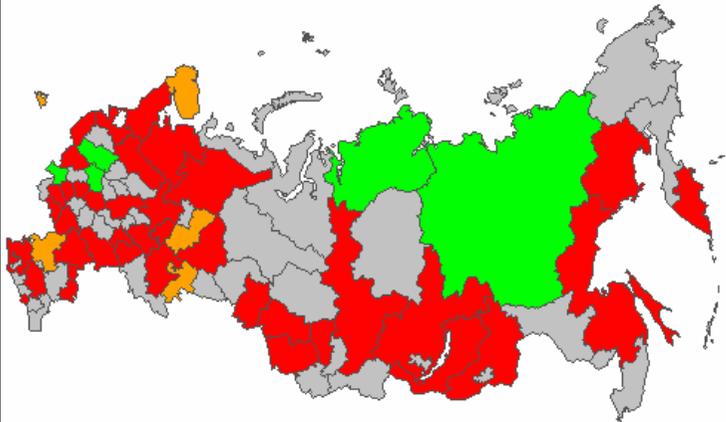
**Cartography of Influenza and ARVI Morbidity and Influenza Laboratory Diagnosis  
(IFA, PCR, virus isolation) During Weeks of Peak Morbidity in Russia, Seasons 2009–2013**

**INFLUENZA ACTIVITY IN RUSSIA**

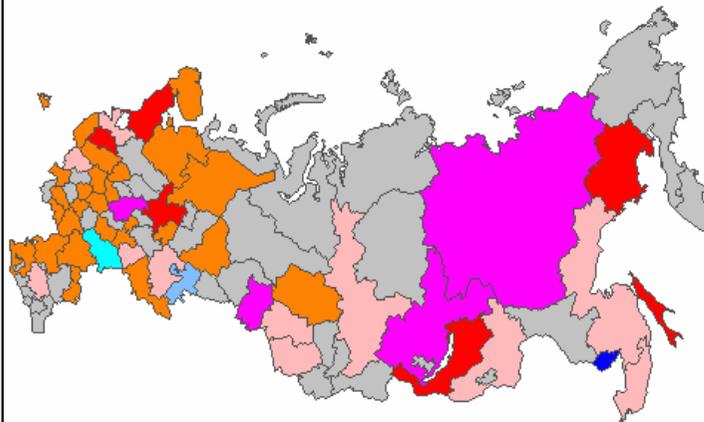
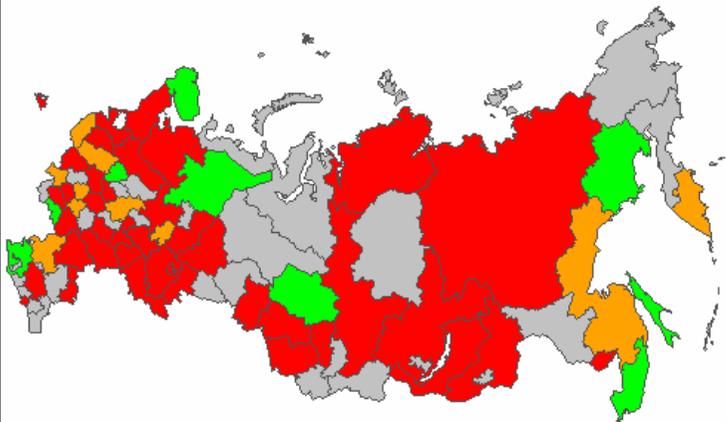
Exceeding of morbidity epidemic thresholds

Cumulative number of diagnosed influenza cases

WEEK 47 2009



WEEK 6 2011



Grey	No data
Green	Less 20%
Orange	20–49%
Red	50% and more

Grey	No data	Orange	H1pdm09+B	Cyan	B
Dark Grey	No detection	Pink	H1pdm09+H3	Blue	H3
Red	H1pdm09	Light Pink	H1pdm09+H3+B	Light Blue	H3+B

The 2010–2011 epidemic season was mainly caused by the pandemic virus (second pandemic wave) and influenza virus type B. A(H3N2) influenza virus activity didn't increase again until the 2011–2012 season, when the epidemic was of low intensity. This was partly due to population immunity status. Studies established that 66–68% of adults in different regions of Russia had protective levels of immunity to seasonal influenza A(H1N1), A(H3N2) and B viruses in October 2009, but only 10.1% were positive for influenza A(H1N1)pdm09 virus. During the next year as a result of the natural spread of influenza A(H1N1)pdm09 virus and vaccination of the population, immunity increased up to 36.2% in October 2010, but didn't achieve the level typical for immunity against seasonal influenza viruses. This contributed to the development of the second pandemic wave. As a result, further increase of the population immunity to the pandemic virus (54.3% of population acquired protective titers of antibody by April 2011) was registered.

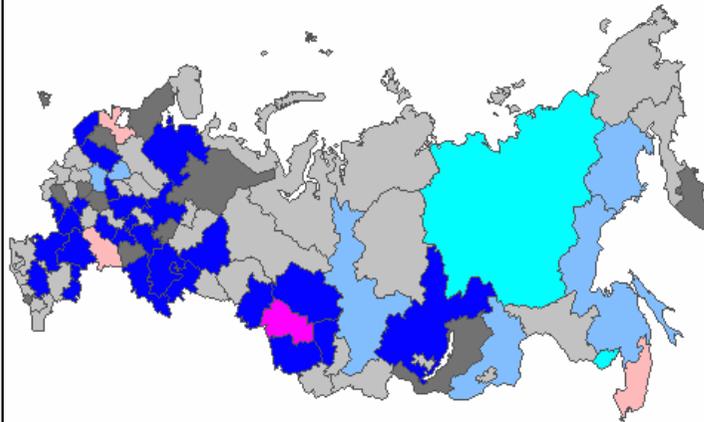
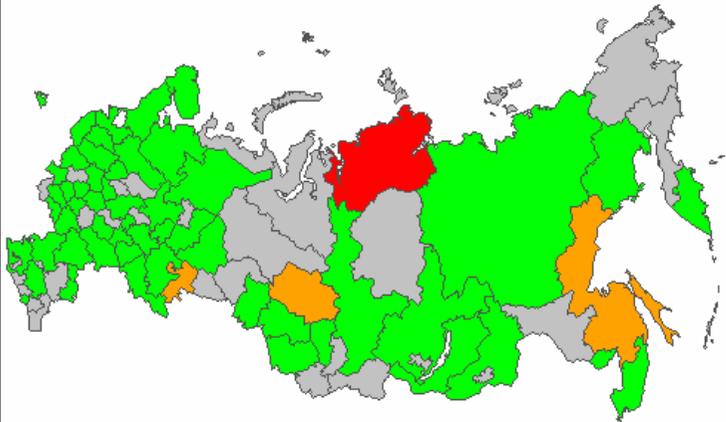
**Cartography of Influenza and ARVI Morbidity and Influenza Laboratory Diagnosis  
(IFA, PCR, virus isolation) During Weeks of Peak Morbidity in Russia, Seasons 2009–2013**

**INFLUENZA ACTIVITY IN RUSSIA**

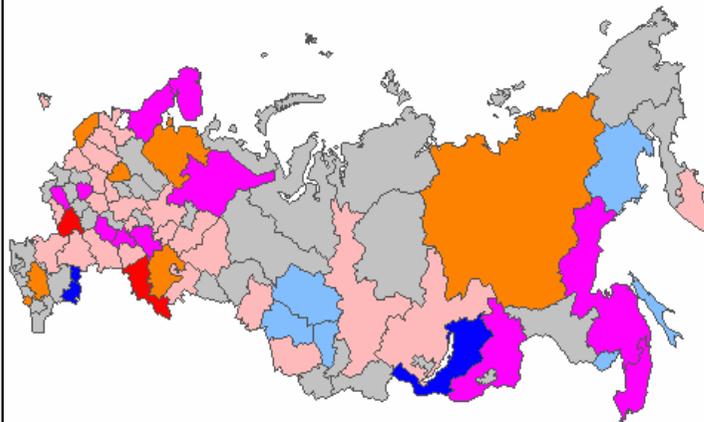
Exceeding of morbidity epidemic thresholds

Cumulative number of diagnosed influenza cases

WEEK 10 2012



WEEK 9 2013



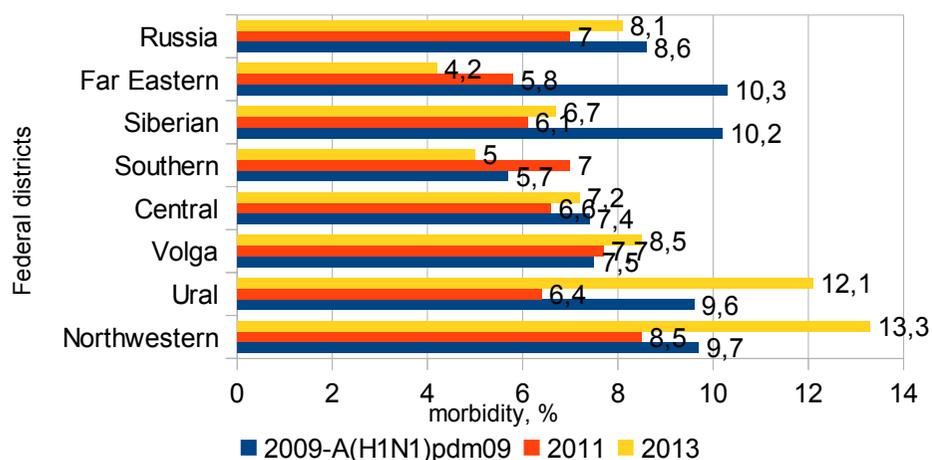
	No data
	Less 20%
	20–49%
	50% and more

	No data		H1pdm09+B		B
	No detection		H1pdm09+H3		H3
	H1pdm09		H1pdm09+H3+B		H3+B

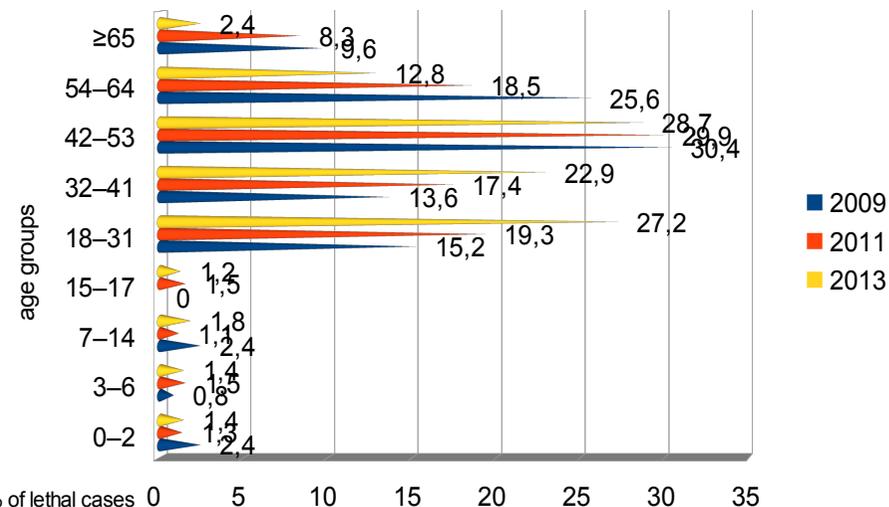
A decrease of immunity to influenza A(H3N2) virus which didn't circulate during the two previous seasons was found in October 2011 (geometric mean titers decreased from 43 to 35.3 and the percent of people with protective titers of antibody decreased from 68% to 58%). This decrease in immunity to H3N2 promoted reappearance of influenza A(H3N2) viruses throughout the country. Low epidemic activity of influenza virus A(H1N1)pdm09 in the 2011–2012 season was registered.

During 2012–2013 epidemic season influenza activity in Russia was higher than in the previous season. All three seasonal viruses, mainly influenza A(H1N1)pdm09 virus were the etiological agents of the past pandemic in the country although some peculiarities of virus circulation revealed by virus isolation, PCR and IFA testing was observed in different Federal Districts. Thus, influenza A(H1N1)pdm09 was spread more widely in Northwestern, Central, Volga and Ural FDs where epidemic was characterized with higher intensity and duration, whereas influenza A(H3N2) was registered more often in Far East and Siberia.

Influenza morbidity per Federal District, seasons 2009, 2011 and 2013

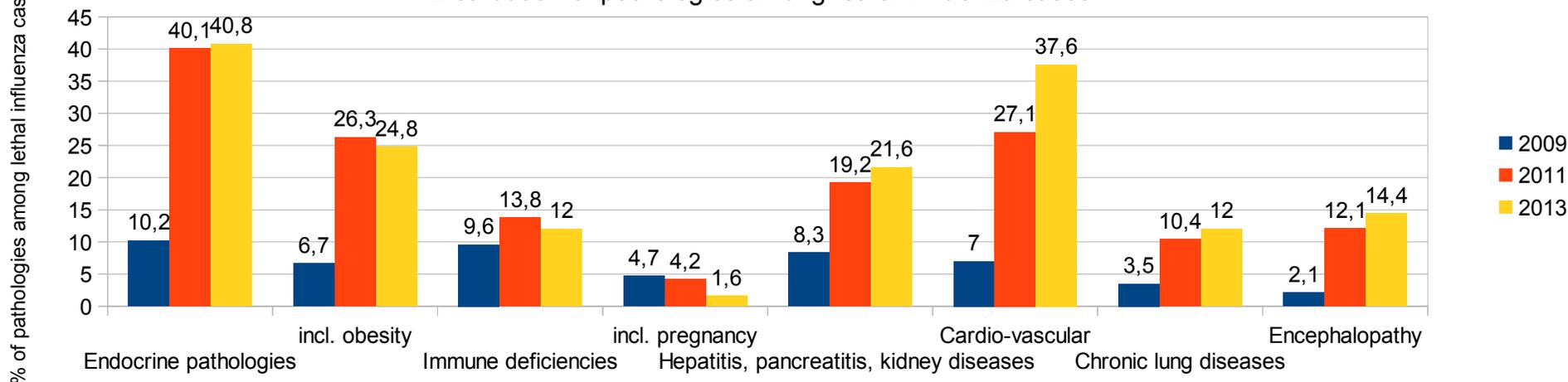


Age distribution of influenza mortality, seasons 2009, 2011 and 2013



Intensity, incidence rate and age distribution varied during 2009, 2011 and 2013 influenza epidemic seasons.

Distribution of pathologies among lethal influenza cases



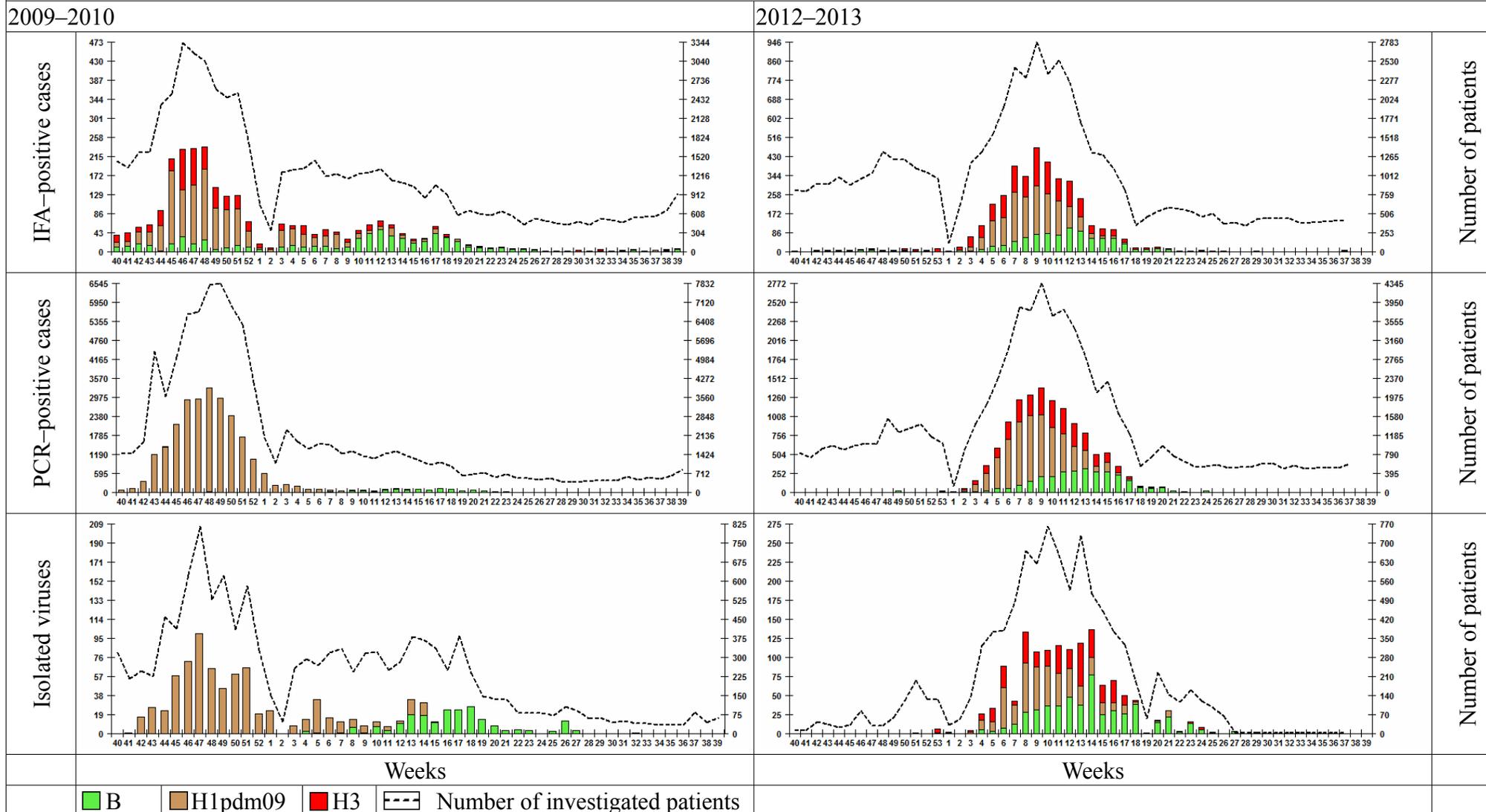
Chronic pathologies were the primary risk factors of pandemic influenza A(H1N1)pdm09 related deaths. In 2009 endocrine pathologies were observed in 10,2% of influenza related deaths, including obesity (6,7%), immune deficiencies — 9,6%, including pregnancy (4,7%). Other pathologies such as CVDs (7%) were less frequent. In 2011 and 2013 the rate of observed moderate pathologies rose significantly (up to 6,9 times higher in 2013) and the overall distribution changed: CVDs took 2<sup>nd</sup> place from immune deficiencies. This is associated with a shift of age distribution to children and seniors.

## Main Epidemic Parameters

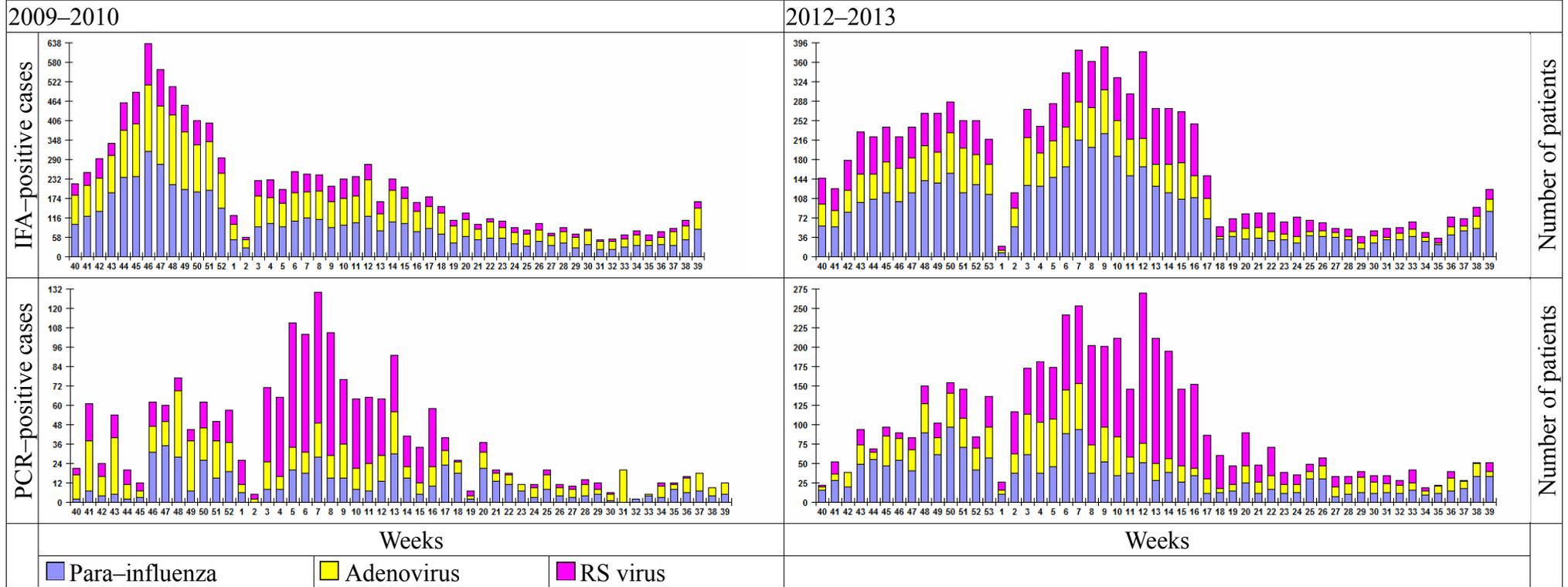
What is compared		Epidemic seasons			
		2009-2010	2010-11	2012-13	
<b>Duration of an epidemic in weeks</b>		<b>39-2009 – 03-2010 (17)</b>	<b>01-2011 – 14-2011 (14)</b>	<b>02-2013 – 17-2013 (16)</b>	
<b>Peak of Influenza and ARVI morbidity from overall population (%)</b>		<b>1,38 (week 47)</b>	<b>1,43 (week 8)</b>	<b>1,07 (week 9)</b>	<p>The intensity of 2013 influenza epidemic with influenza A(H1N1)pdm09 circulating strain approached that of 2011 influenza epidemic. Compared with 2009 influenza epidemic, the following parameters decreased:</p> <ul style="list-style-type: none"> <li>—The involvement of all age groups in the epidemic (down to 86.4%–64.4%);</li> <li>—Influenza mortality in all age groups (15 times), especially among people aged 15 to 64 (12 times)</li> <li>—Influenza morbidity among people aged 15–64 and school children aged 7–14 (1.3 times)</li> <li>—Duration of the epidemic among adult population (6.3 weeks)</li> </ul> <p>The following parameters increased:</p> <ul style="list-style-type: none"> <li>—Duration of the epidemic among children, especially pre-school children (+2 weeks)</li> </ul>
<b>% of cities involved into the epidemic by age group</b>	<b>overall population</b>	<b>98,3</b>	<b>96,6</b>	<b>88,1</b>	
	<b>0-2</b>	<b>89,8</b>	<b>74,6</b>	<b>64,4</b>	
	<b>3-6</b>	<b>91,5</b>	<b>91,5</b>	<b>86,4</b>	
	<b>7-14</b>	<b>100</b>	<b>93,2</b>	<b>84,7</b>	
	<b>15 and older</b>	<b>98,3</b>	<b>94,9</b>	<b>72,9</b>	
<b>Average duration of an epidemic period in weeks</b>	<b>overall population</b>	<b>6,8</b>	<b>5,4</b>	<b>7,0</b>	
	<b>0-2</b>	<b>4,4</b>	<b>5</b>	<b>6,2</b>	
	<b>3-6</b>	<b>5,0</b>	<b>4,8</b>	<b>7,0</b>	
	<b>7-14</b>	<b>6,7</b>	<b>5</b>	<b>6,9</b>	
	<b>15 and older</b>	<b>6,7</b>	<b>4,8</b>	<b>6,3</b>	
<b>Average influenza and ARI morbidity during epidemic (%)</b>	<b>overall population</b>	<b>8,5</b>	<b>7,0</b>	<b>8,1</b>	
	<b>0-2</b>	<b>32,6</b>	<b>32,4</b>	<b>41,2</b>	
	<b>3-6</b>	<b>36,0</b>	<b>33,2</b>	<b>46,7</b>	
	<b>7-14</b>	<b>29,0</b>	<b>20,2</b>	<b>22,8</b>	
	<b>15-64</b>	<b>5,0</b>	<b>3,8</b>	<b>3,9</b>	

	<b>65 and older</b>	<b>0,9</b>	<b>1,1</b>	<b>1,6</b>	<p>—Influenza morbidity in pre-school children (1.4 times) and seniors (1.8 times)</p> <p>—The proportion of people aged &gt;65 and children aged 0–2 in the age structure of influenza mortality</p> <p>—The proportion of people with endocrine (40.8%) and cardiovascular (up to 37.6%) pathologies in the age structure of influenza mortality</p>
<b>Number of hospitalized patients diagnosed with influenza</b>		<b>21319</b>	<b>15742</b>	<b>8704</b>	
<b>Number of hospitalized patients diagnosed with influenza and ARI</b>		<b>150924</b>	<b>122082</b>	<b>131734</b>	
<b>% of Influenza in all hospitalized cases</b>		<b>14,1</b>	<b>12,9</b>	<b>6,6</b>	
<b>Mortalities</b>	<b>overall population</b>	<b>622</b>	<b>264</b>	<b>125</b>	
<b>Mortalities by age (%)</b>	<b>0-2</b>	<b>1,4</b>	<b>2,3</b>	<b>2,4</b>	
	<b>3-6</b>	<b>1,4</b>	<b>1,5</b>	<b>0,8</b>	
	<b>7-14</b>	<b>1,8</b>	<b>1,1</b>	<b>2,4</b>	
	<b>15-64</b>	<b>93,0</b>	<b>86,8</b>	<b>84,8</b>	
	<b>65 and older</b>	<b>2,4</b>	<b>8,3</b>	<b>9,6</b>	
<b>Influenza mortality to influenza and ARI morbidity (%)</b>	<b>overall population</b>	<b>0,03</b>	<b>0,003</b>	<b>0,002</b>	
	<b>0-2</b>	<b>0,002</b>	<b>0,0004</b>	<b>0,0002</b>	
	<b>3-6</b>	<b>0,001</b>	<b>0,0002</b>	<b>0,0001</b>	
	<b>7-14</b>	<b>0,002</b>	<b>0,0002</b>	<b>0,0003</b>	
	<b>15-64</b>	<b>0,06</b>	<b>0,008</b>	<b>0,005</b>	
	<b>65 and older</b>	<b>0,05</b>	<b>0,013</b>	<b>0,006</b>	
<b>Geographical spread of influenza in Russia</b>		<b>A(H1N1)09 – from east</b>	<b>A(H1N1)09 – from west, B – from east</b>	<b>A(H1N1)09 and B – from west, A(H3N2) – from east</b>	

# Monitoring of influenza according to results of virus isolation, IFA and PCR diagnosis in RBLs of two WHO NICs in Russia, SEASONS 2009–2013



Monitoring of para-influenza, adeno- and RS- virus circulation according to results of IFA and PCR in Russia, SEASONS 2009–2013

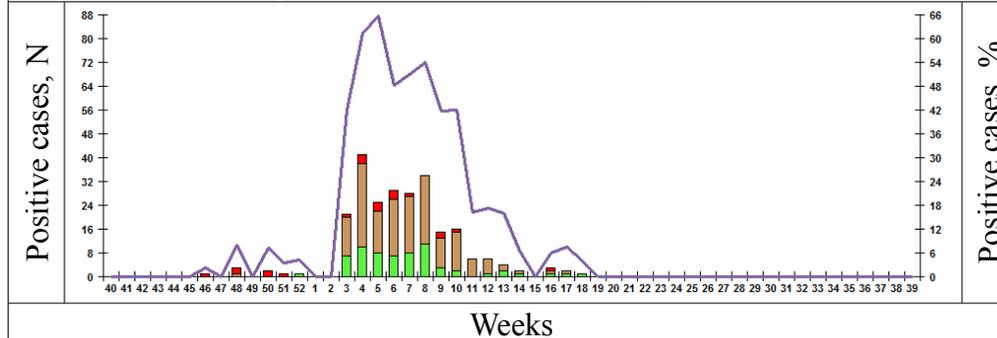


Para-influenza, Adenovirus, RS virus were a major cause of ARI cases.

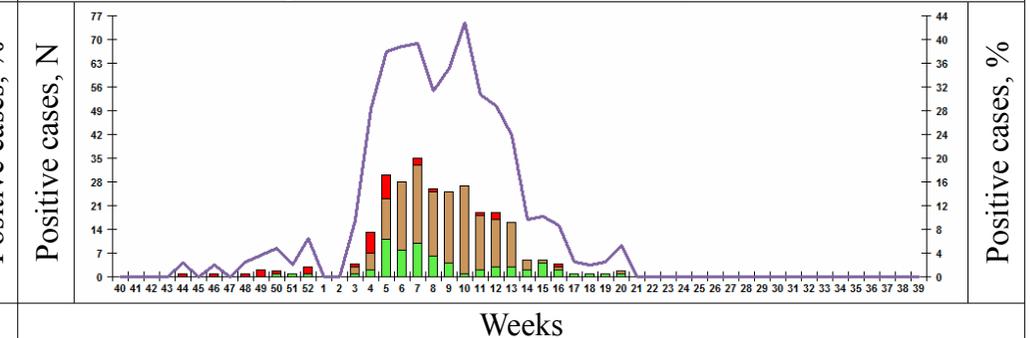
## Sentinel surveillance system in Russia

New influenza surveillance system was developed in Russia in 2009 and was introduced in 2010. There are 18 hospitals and 14 ambulances of 9 pilot sites of 6 Federal Districts in different climatic regions of Russia that are participating in this project. SARI and ILI or/and ARI case definitions were used (WHO European Guidance for Influenza Surveillance in Human, 2009). Epidemiological data of all age groups of patients and results of influenza PCR–diagnosis were collected weekly using on-line input data system developed at the RII WHO NIC in St. Petersburg (SPb).

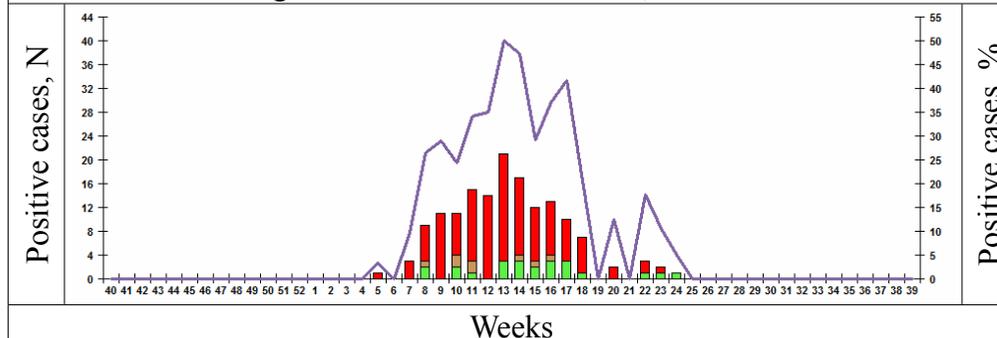
Results of monitoring of SARI in 9 sentinel cities, 2010–2011



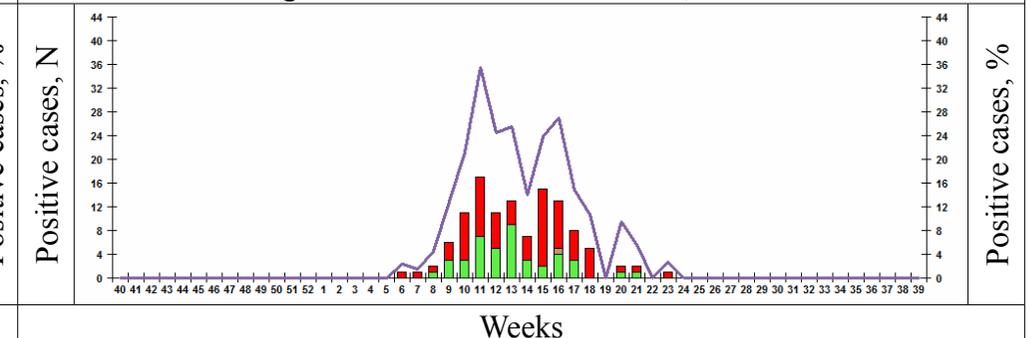
Results of monitoring of ILI/ARI in 7 sentinel cities, 2010–2011



Results of monitoring of SARI in 9 sentinel cities, 2011–2012

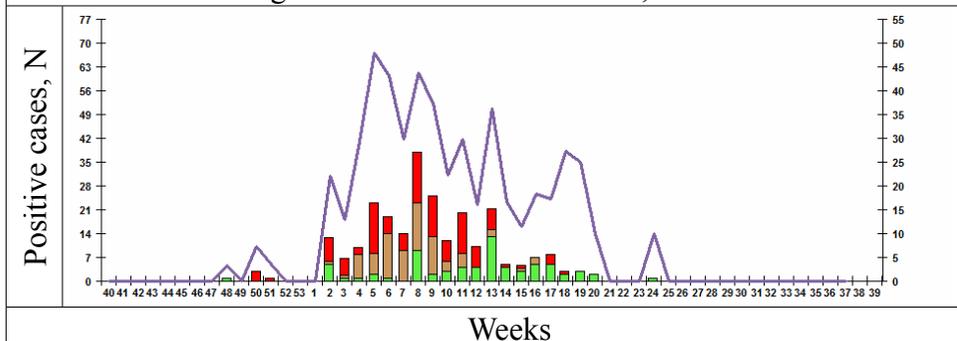


Results of monitoring of ILI/ARI in 7 sentinel cities, 2011–2012



B
  H1pdm09
  H3
  % of positive cases

Results of monitoring of SARI in 9 sentinel cities, 2012–2013



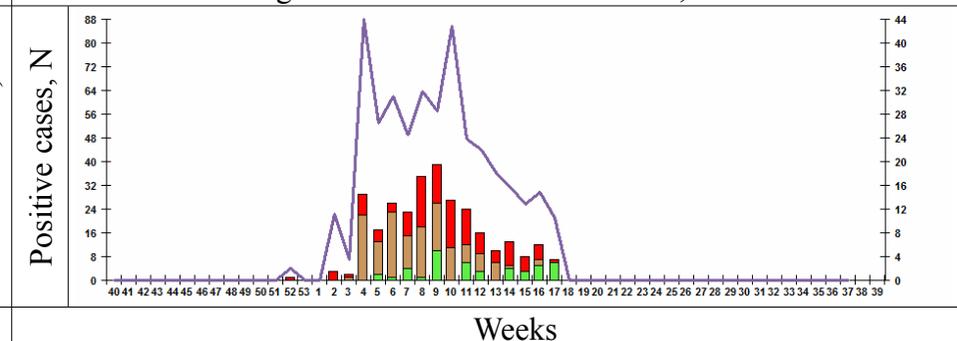
Positive cases, N

Positive cases, %

Weeks

■ B ■ H1pdm09 ■ H3 — % of positive cases

Results of monitoring of ILI/ARI in 7 sentinel cities, 2012–2013



Positive cases, N

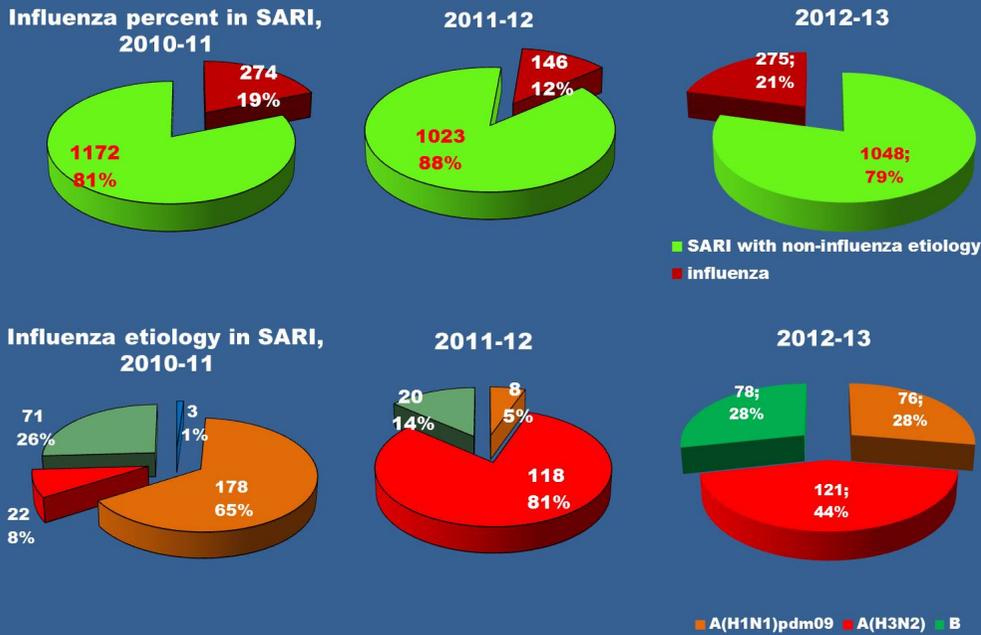
Positive cases, %

Weeks

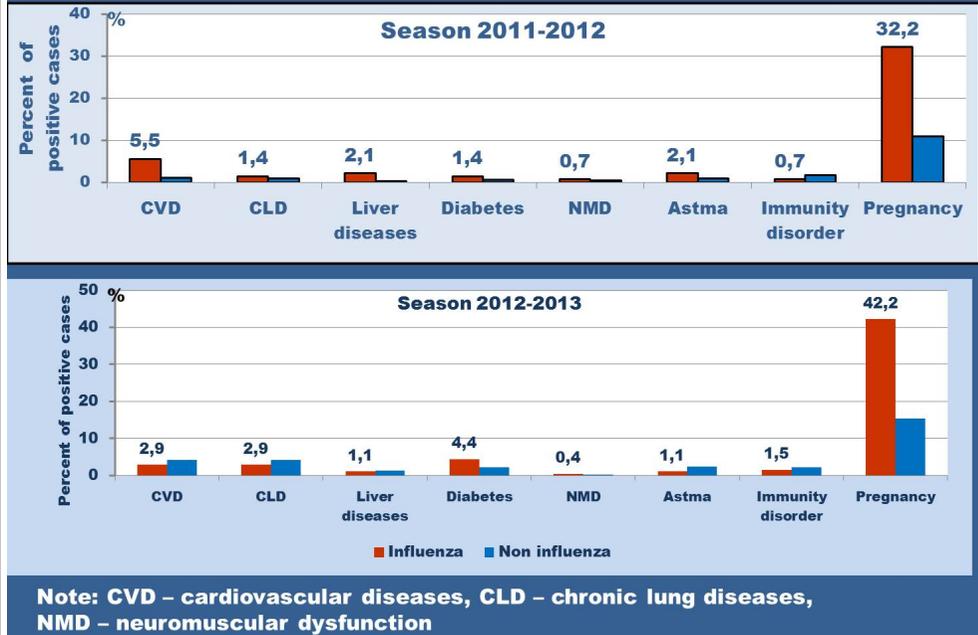
Standardized data collection instruments and case definitions for SARI, ILI and ARI consistent with global standards and standardized protocols were used. Clinical samples with accompanying standard forms were sent from RII to participating RBLs (at FGUZ Centres for Hygiene and Epidemiology) for laboratory RT–PCR diagnosis and virus isolation. Obtained results were reported by RBLs to WHO NIC at the Research Institute of Influenza on a weekly basis via on-line internet system on base of individual and cumulative SS–RBLs weekly data. Those reports included individual data for all investigated SARI cases (age, gender, data of start of disease, data of clinical samples collection, data of underlying somatic diseases such as ischemic heart diseases, chronic lung diseases, liver diseases, diabetes, nervous-muscular dysfunction, asthma, immunity disorder and pregnancy, status of vaccination and antiviral treatment, pneumonia symptoms, result of PCR–test for influenza and from 2012–2013 other respiratory viruses including PI, Ad, RS, rino–, metapnevmo–, corona- and boca– viruses).

Conclusion: The obtained data supported the conclusion of SARI and ILI/ARI SS surveillance (in limited number of sites) results to reflect structure and dynamics of epidemically important influenza viruses spread in Russia. In general, SS data from 9 RBLs correlated well with results of routine laboratory surveillance obtained from 49 RBLs collaborating with WHO NIC at the RII.

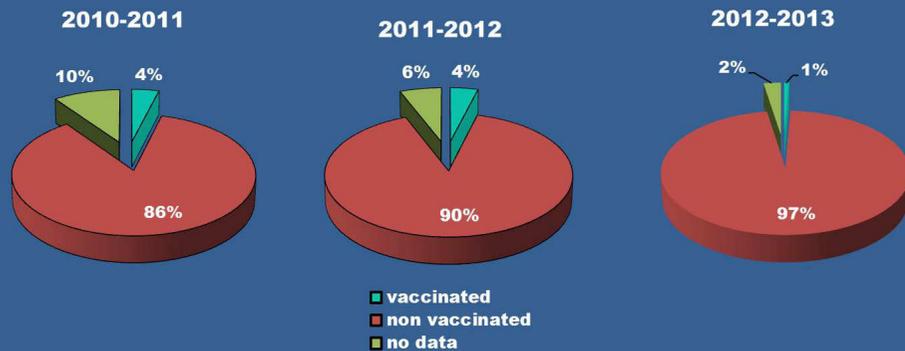
**SARI WITHIN SENTINEL SURVEILLANCE IN RUSSIA, SEASONS 2010-2011, 2011-2012, 2012-2013**



**COMPARATIVE DATA ON STRUCTURE OF UNDERLYING CONDITIONS IN INFLUENZA AND NON-INFLUENZA SARI CASES, SEASONS 2011-12, 2012-13**



**PROPORTION OF VACCINATED PERSONS AMONG SARI CASES WITH INFLUENZA ETIOLOGY, SEASONS 2010-2013**



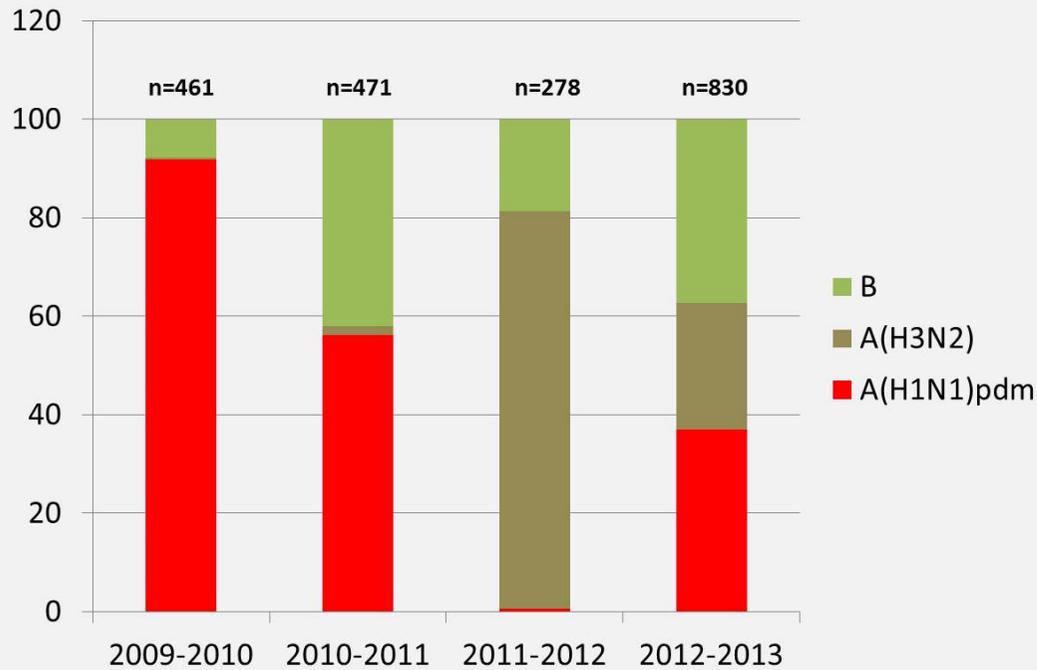
—Influenza constituted 12% to 21% of SARI cases during the last three epidemic seasons (2010–2013).

—Very few patients with influenza–related SARI cases, including patients of high–risk groups had been immunized with influenza vaccine.

—Pregnancy was the leading risk factor for influenza–related SARI. Accompanying Cardio–vascular diseases, chronic lung diseases and diabetes were also observed more frequently in influenza–related SARI cases.

## Investigating the antigenic and genetic proprieties of influenza viruses

### Structure of influenza viruses isolated during 2009–2013

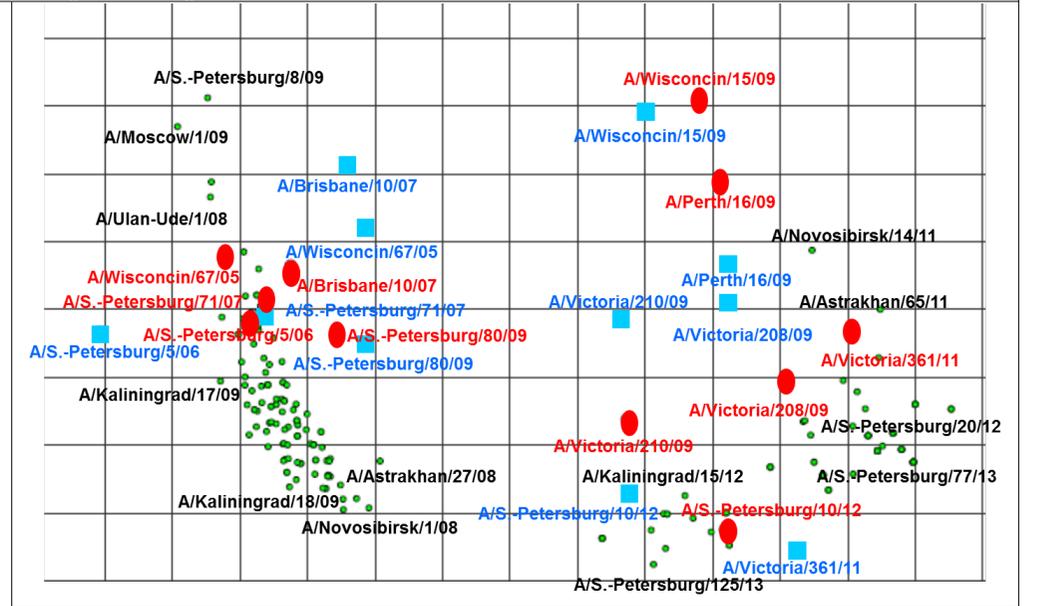
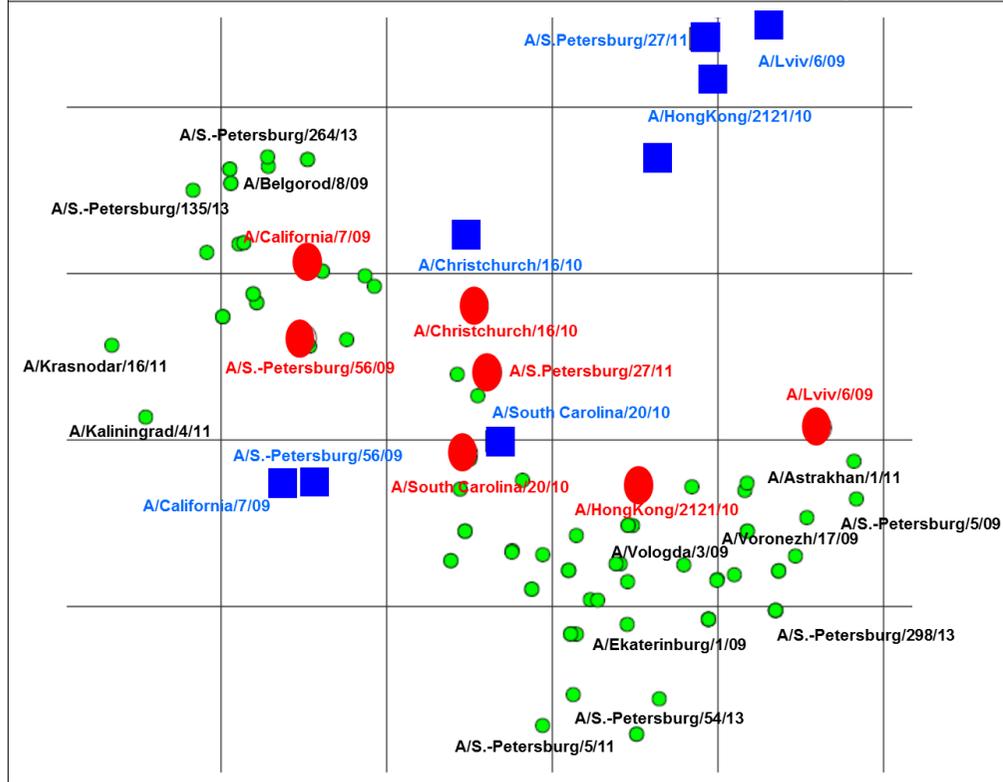


In the last four epidemic seasons (2009–2013) more than 2 000 influenza strains were isolated in different regions of Russia, identified and studied in the HAI test. A growth of morbidity in 2009–2010 and in 2010–2011 was caused by emergence and spread of the new A(H1N1)pdm09 pandemic virus. The contribution of pandemic influenza in those two seasons has been 92% and 56% respectively. In the epidemic season 2011–2012 influenza strains A(H3N2) prevailed in the virus population.

Season 2012–2013 was characterized by practically equal-part isolation of influenza strains: A(H1N1)pdm09 (37%), A(H3N2) (25,7%) and B (37,3%). Influenza viruses B were isolated in all mentioned epidemic periods though their activity was essential at the end of epidemic seasons. Data of antigenic analysis were plotted on the antigenic maps, which represent a computed graphic mapping of the HAI data. The antigenic cartography was carried out using the open software

free of charge that can be found on the following web-site: <http://antigenic-cartography.org>.

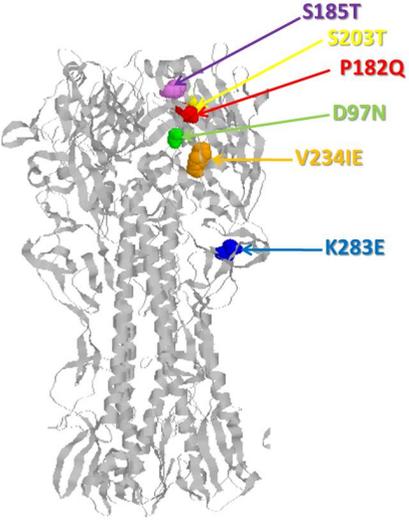
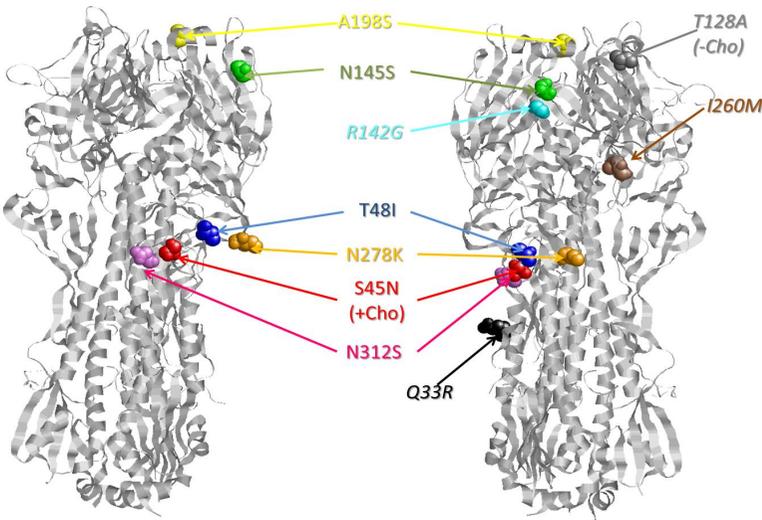
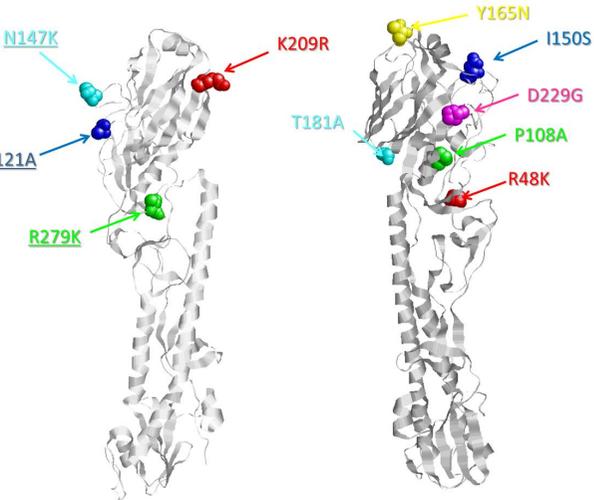
Graphic symbols on antigenic maps are: squares represent antisera, circles — antigens, big circles or ovals — reference antigens which were used to produce antisera. Antigens of one season are marked with the same color. Antigens which fall into one square have the same HAI titers with the reference antiserum. If they fall in the neighboring squares the difference in the HAI titer is  $\frac{1}{2}$ .



^Influenza viruses A(H1N1)pdm09 did not undergo any significant drift and are represented on the map as a homogenous group. The isolates of different seasons are still similar to the reference strain A/California/07/09 in their antigenic properties.

^The main part of influenza strains A(H3N2), isolated in 2011–2013 was significantly different from the strains of 2008–2009 epidemic season and were similar to the A/Perth/16/09 and A/Victoria/208/09 reference strains. Further analysis has shown that Russian isolates were closer in their antigenic properties to the modern epidemic strain A/St.Petersburg/10/12 or similar strains which belong to the antigenic sub-group A/Victoria/361/11.



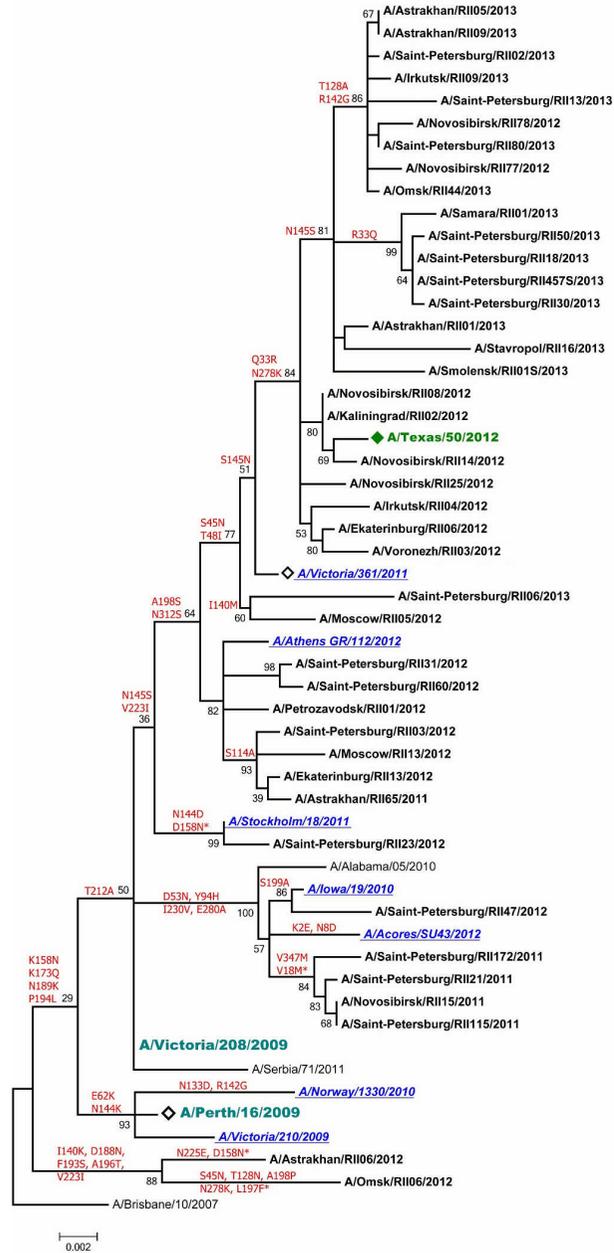
HA A(H1N1)pdm09	HA A(H3N2) group 3C (1–left, 2–right)	HA B Victoria(left), B Yamagata(right)
		
<p>Most of the 2013 isolates possess substitutions common for genetic group 6. Some viruses possess amino acid substitution in site 182.</p>	<p>In all studied 2013 isolates HAs are related to 3C genetic group</p>	<p>2013 B Victoria viruses belong to B/Brisbane/60/2008 genetic clade. 2013 B Yamagata viruses belong to 2 genetic group, as does B/Massachusetts/02/2012 reference strain.</p>

## Molecular genetic peculiarities of influenza A and B viruses circulating in Russia during 2009–2013

Continuous monitoring of variability of circulating influenza strains allows assessing influenza A and B viral populations' heterogeneity, studying strains phylogeny and their relationship with vaccine strains as well as revealing mutations coding for drug resistance. All these have a great significance when choosing vaccine strains for specific influenza prophylaxis and antivirals for its treatment.

Influenza viruses A of two subtypes (H1N1pdm09, H3N2) and B of Victoria and Yamagata lineages have circulated during 2009–2013 in the territory of Russia. The 2009 epidemic was caused by only one virus type A/H1N1pdm09 which strains were characterized by genetic homogeneity. Influenza strains A/H1N1pdm09 isolated in 2010–2011 belonged to different genetic groups. The first group of strains was A/Saint-Petersburg/27-like with characteristic substitutions D97N, S185T in the HA antigenic site Sb. The second genetic group contained 4 amino acid substitutions D97N, S143G (in the antigenic site Ca2), S185T, A197T (Sb). The third group belonged to phylogenetic group of strains of Southern hemisphere A/Christchurch/16-like with N125D substitution (Russian representative strain A/Astrakhan/RII35/2011 which also had two strain specific substitutions T82P and D222A (in HA antigenic site Cà)). The next group of strains was characterized by 4 substitution in HA: D97N, R20K(Ca), I216V, V249L and was similar to A/Astrakhan/01/2011 strain. The fifth A/Toulon/1173-like phylogenetic group with A134T and S183P included strains from Chita and Saint Petersburg.





<HA phylogenetic tree of influenza A/H3N2 viruses circulating on the territory of Russia from 2009 to 2013. The tree was built using maximum likelihood method (ML), evolution model TN93+G, boot strap analysis 1000 replications. Vaccine strains are marked with green diamond ◆, vaccine strain of the previous season are marked with black diamond ◇. Reference strains are highlighted in blue, italic and underlined.

Thus, it can be assumed that viruses with T128N substitution in HA should be more resistant to neutralization of lung collectins. The emergence in these viruses of a new previously unknown potential glycosylation site at position 45 is difficult to assess. It should also be noted that strains with T128A substitution also had substitution R142G in the HA antigenic site A. Substitutions in HA antigenic site A (N121D, S124N, I140M) were common for these strains. All influenza A strains were predicted to be susceptible to neuraminidase inhibitors and resistant to adamantane antivirals. None of them carried H275Y substitution in NA, and all had S31N substitution in M2. Some strains had substitution of an aspartic acid residue to asparagine or glycine residue at position 151 of NA. This mutation is likely to be functionally significant, as it is located at the gene region encoding the catalytic site of NA.

Influenza B strains circulating in Russia in 2010–2011 belonged to Victoria lineage and were similar to the vaccine strain B/Brisbane/60/2008. All analyzed strains related to clade 1B and had L58P in HA as the reference strain of this group B/Hong Kong/514/2009. Strains were genetically homogenous but some substitutions were found in HA antigenic sites: T199I (loop 190) and I117V (loop 120).

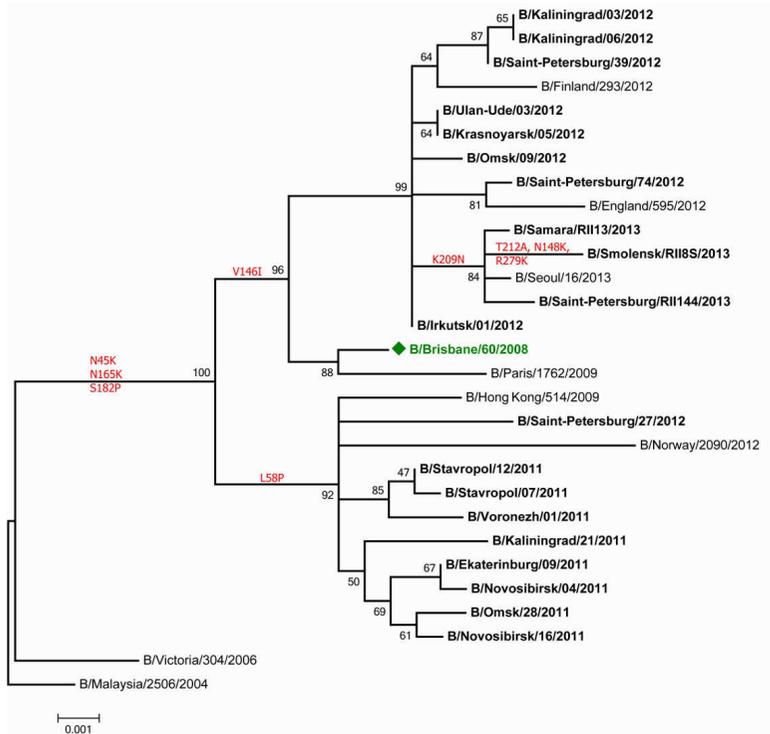
Analysis of influenza B strains of 2011–2012 showed that viruses of two Victoria and Yamagata lineages circulated in Russia during this epidemic season. All Victoria lineage strains were B/Brisbane/60/08-like. Some strains showed drift in the region of loop 190 (HA receptor binding site) as well as during the previous epidemic seasons, N197K and T199A substitutions, for example. Only 3 strains from Saint Petersburg contained substitution at position 58 of HA characteristic for the clade 1B strains.

NA phylogenetic analysis of influenza B strains of Victoria lineage circulating in 2011–2012 showed B/Saint-Petersburg/44/2012 strain was similar by its HA gene to genetic group 1A (B/Brisbane/60/08-like) but by its NA gene to genetic group 4 (B/Malaysia/2506/2004-like) with characteristic substitutions in NA S41P, P42S, K404E, D463N. Thus this strain can be considered as intra-clade reassortant. This strain had also 6 additional substitutions in NA S34L, I262M, V271T, E272Q, E320K, M375K. All the rest analyzed strains of Victoria lineage were B/Brisbane/60/08-like by their HA and NA. Analysis of Yamagata lineage strains isolated in the period from 2011 to 2012 showed that they belong to clade 3. The three strains from Novosibirsk had amino acid substitutions in the 120 and 190 loops, N116K and N202S, respectively, and two substitutions K298E, E312K. Also strains B/Saint-Petersburg/42/2012 and B/Saint-Petersburg/24/2012 had an amino acid substitution at position 181 (in antigenic site D) threonine residue on lysine residue. Influenza B Yamagata strains according to NA as well as HA gene analysis belonged to clade 3.

In 2012–2013 all strains of B/Victoria lineage fell into clade 1A and had common substitution K209T in HA1 unlike B/Victoria strains isolated in 2012 that fell into clades 1A and 1B and had N197K and T199A substitutions in receptor-binding site. No intra-clade reassortant HA-1A/NA-4 was identified in this season. B/Yamagata lineage strains of clade 2 (B/Brisbane/03/2007-like) bore amino acid changes R48K (in antigenic site BC), I150S (in BA), Y165N (in BB2), T181A (in BD). Only two strains belonged to clade 3 (B/Wisconsin/01/2010-like).

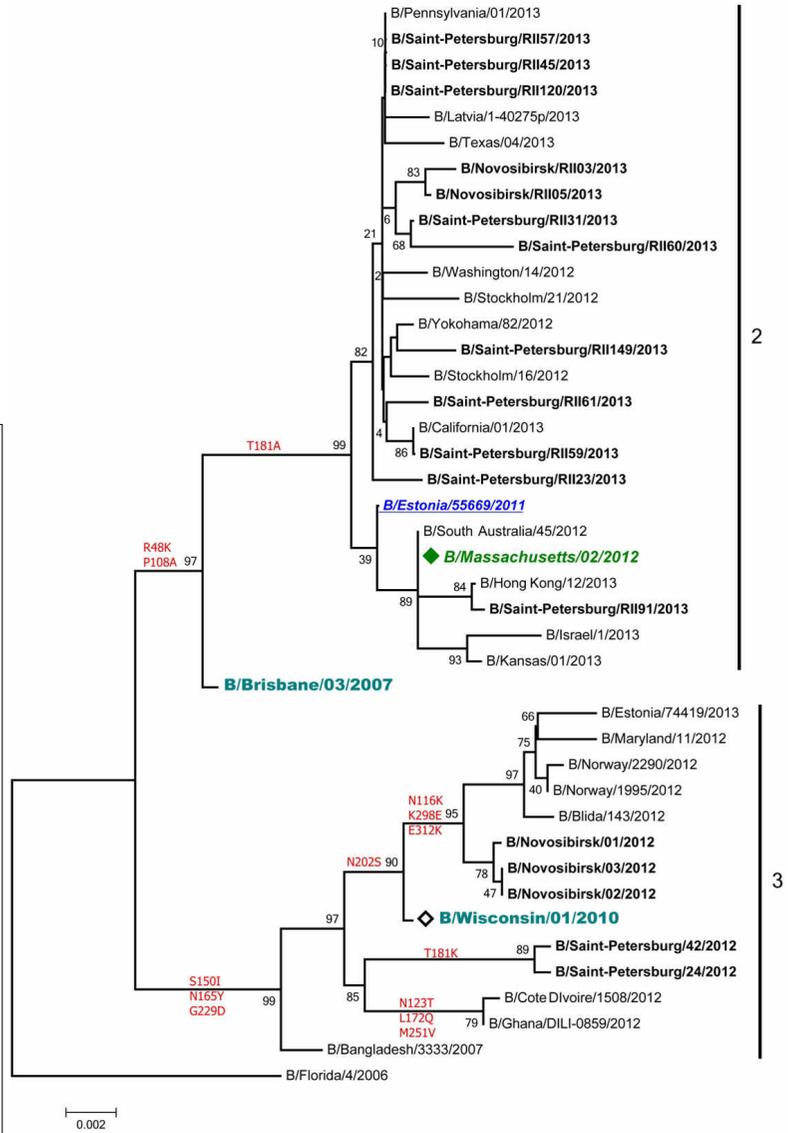
No changes conferring resistance to oseltamivir or zanamivir were found in influenza B strains isolated till 2013.

Thus, we studied the genetic diversity of influenza virus A and B strains that have circulated in the territory of Russia from 2009 to 2013. Phylogenetic affiliation of circulating strains to vaccine strains was analyzed, the structure of the major antigens of the influenza viruses was examined, and drug resistance of these strains were revealed.



<HA phylogenetic tree of influenza B viruses of Victoria lineage circulating on the territory of Russia from 2009 to 2013. The tree was built using maximum likelihood method (ML), evolution model TN93+G, boot strap analysis 1000 replications. Vaccine strains are marked with green diamond ◊.

> HA phylogenetic tree of influenza B viruses of Yamagata lineage circulating on the territory of Russia from 2009 to 2013. The tree was built using maximum likelihood method (ML), evolution model TN93+G, boot strap analysis 1000 replications. Vaccine strains are marked with green diamond ◊, vaccine strains of the previous season are marked with black diamond ◊. Reference strains are highlighted in blue, italic and underlined.



## Monitoring of susceptibility to antiviral drugs

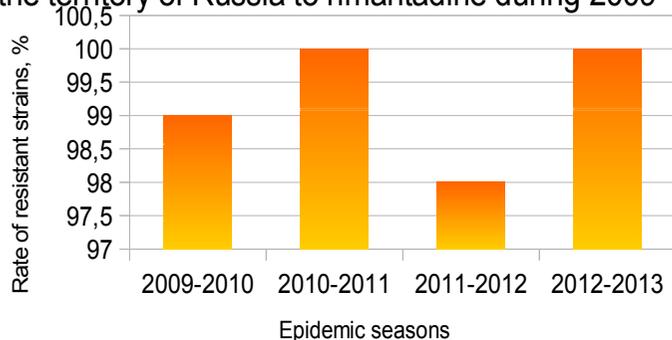
Chemoprophylaxis and chemotherapy are used along with vaccination for prevention and treatment of influenza. Currently for these purposes wide set of pathogenetic and immunomodulating drugs along with the remedies of specific anti-influenza chemotherapy is available. The last group of drugs is represented with chemical compounds of two groups that differ in their mechanism of activity and targets in the viral life cycle. The compounds of the first group — rimantadine and amantadine — block influenza virus protein M2. The drugs of the second group are directed to inhibit viral neuraminidase that is an enzyme necessary for normal budding of progeny viral particles and manifestation of infectious properties of the virus. this group contains such drugs as zanamivir (Relenza), oseltamivir (Tamiflu), peramivir (Rapiacta) and laninamivir (Inavir), the last two not being registered in Russia so far.

Both groups of compounds have their disadvantages. Regarding adamantane derivatives it should be said that they are relatively toxic, have narrow spectrum of anti-viral activity (they are active against influenza A but not influenza B), and fast selection of resistant mutants. For neuraminidase inhibitors slightly lower efficacy and high price are typical, which makes these drugs less affordable for wide use. In addition, similar to rimantadine, sharp increase of the rate of resistant strains in viral population was shown for oseltamivir. For these reasons the monitoring for susceptibility of circulating viral strains to antivirals is an important part of the global system of surveillance for influenza in the world.

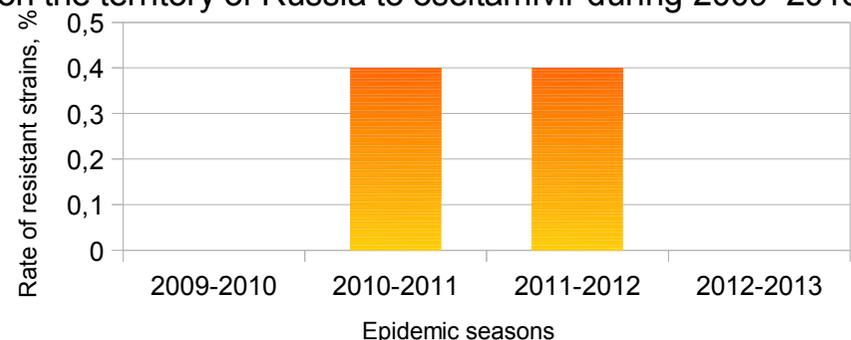
Starting from 2005, in the Laboratory of Molecular Anti-Viral Chemotherapy in the framework of the system of global influenza surveillance the testing of susceptibility of viral isolates for main antivirals (rimantadine, zanamivir and oseltamivir) is carrying out. The study of rimantadine resistance is done by virus yield reduction assay, of resistance to neuraminidase inhibitors by WHO- and CDC-adopted fluorescent test MUNANA. The laboratory systematically passes the test for adequacy and reliability of the methods used by determining the susceptibility of influenza reference strains sent by WHO, to antivirals.

Based on the results of this study it was estimated that during the period 2009–2013 no change has been detected in the rate of oseltamivir-resistant strains of influenza among all isolated viruses, the fact that is in accordance with the results of other laboratories around the globe. Similar to other regions, no zanamivir-resistant strains were identified. In addition, 100% resistance of circulating influenza strains to rimantadine has been confirmed.

Dynamics of susceptibility of influenza A virus isolates on the territory of Russia to rimantadine during 2009–2013



Dynamics of susceptibility of influenza A virus isolates on the territory of Russia to oseltamivir during 2009–2013



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## Selected papers, published by RII researchers, 2009–2013

2009

- **Development of a live-attenuated influenza B DelNS1 intranasal vaccine candidate**  
N. Wressnigg, D. Voss, T. Wolff, J. Romanova, T. Ruthsatz, I. Mayerhofer, M. Reiter, S. Nakowitsch, J. Humer, A. Morokutti, T. Muster, A. Egorov, C. Kittel  
Vaccine. – 2009. – Vol.27, № 21. – P.2851-2857
- **Influenza B mutant viruses with truncated NS1 proteins grow efficiently in Vero cells and are immunogenic in mice**  
N. Wressnigg, A.-P. Shurygina, T. Wolff, M. Redlberger-Fritz, T. Popow-Kraupp, T. Muster, A. Egorov, C. Kittel  
J. Gen. Virology. –2009. Vol. 90, pt. 2. – P. 366-374

2010

- **Antiviral properties, Metabolism, and Pharmacokinetics of a Novel Azolo-1,2,4-Triazine-Derived Inhibitor of Influenza A and B virus replication**  
Karpenko I., Deev S., Kiselev O., Charushin V., Rusinov V., Ulomsky E., Deeva E., Yanvarev D., Ivanov A., Smirnova O., Kochetkov S., Chupakhin O., Kukhanova M.  
Antimicrobial Agents and Chemotherapy - 2010. –V. 54. # 5 – P. 2017-2022

2011

- **Comparison of influenza outbreaks in the Republic of Kazakhstan and Russia induced by 2009 yearly new variant of A(H1N1) influenza virus**  
Karpova L.S., Popovtseva N.M., Stolyarova T.P., Stolyarov K.A., Mamadaliyev S.M., Khairullin B.M., Sandybayev N.T., Kydyrbayev Zh.K., Orynbayev M.B., Ospanov K.S., Baiserkin B.S., Boibosinov E.U.  
Virologica Sinica. – 2011. – Vol.26, № 5. – P. 306-314.
- **Antimycotic-antibiotic amphotericin B promotes influenza virus replication in cell culture**  
Roethl E., Gassner M., Krenn B.M., Romanovskaya-Romanko E.A., Seper H., Romanova J., Nakowitsch S., Sturlan S., Wolschek M., Sirotkin A., Kiselev O., Muster T., Egorov A.  
Journal of Virology. – 2011. – Vol. 85, № 21. – P. 11139-11145.
- **Single HA2 mutation increases the infectivity and immunogenicity of a live attenuated H5N1 intranasal influenza vaccine candidate lacking NS1**  
Krenn B.M., Egorov A., Romanovskaya-Romanko E., Wolschek M., Nakowitsch S., Ruthsatz T., Kiefmann B., Morokutti A., Humer J., Geiler J., Cinatl J., Wressnigg N., Sturlan S., Ferko B., Batishev O.V., Indenbom A.V., Zhu R., Kastner M., Hinterdorfer P., Kiselev O., Muster T., Romanova J.  
PLoS One. – 2011. – Vol. 6, № 4, e 18577. DOI: 10.1371/journal.pone.0018577

2012

- **Multisegment one-step RT-PCR fluorescent labeling of influenza A virus genome for use in diagnostic microarray application**  
Vasin A.V., Sandybaev N.T., Plotnikova M.A., Klotchenko S.A., Chervyakova O.V. Stochkov V.M., Taylakova E.T., Elpaeva E.A., Komissarov A.B., Egorov V.V., Koshemetov J.K., Kiselev O.I., Mamadaliyev S.M.

Journal of Physics: Conference Series. – 2011. – Vol. 291, № 1, 012006. DOI: 10.1088/1742-6596/291/1/012006

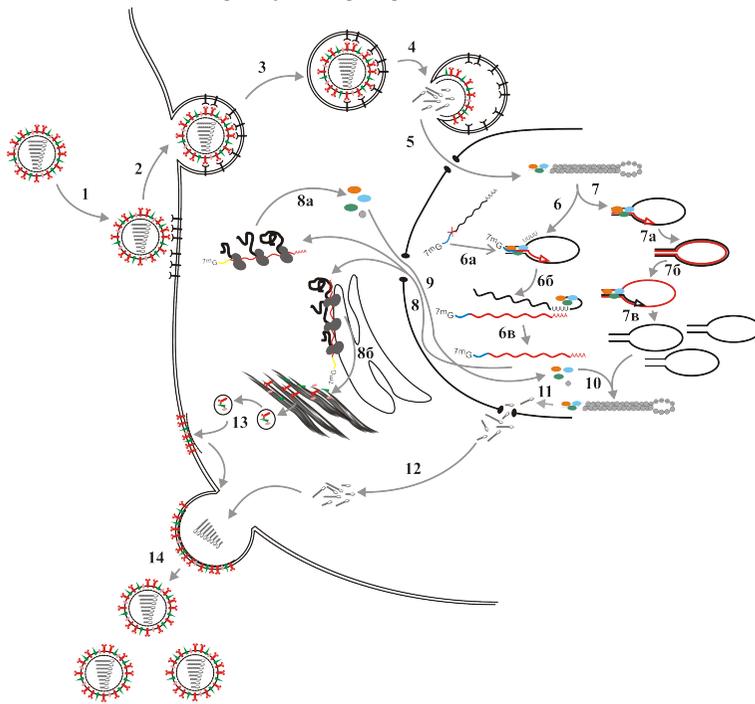
- **Characterization of Cold-adapted Influenza Strain A/HongKong/1/68/162/35 as a Potential Donor of Attenuation and High Reproduction**  
Tsybalova L.M., Gorev N.E., Potapchuk M.V., Repko I. A., Korotkov A.V., Sergeeva M.V., Komissarov A.B., Pisareva M.M., Kuznetsov V.V., Grudinin M.P., Kiselev O.I.  
Voprosy virusologii. – 2012. – V. 57. – №6. – P. 13-17.
- **Genetic Diversity and Molecular Evolution of the Influenza A Viruses in Russia during 2006-2012**  
Grudinin M. P., Komissarov A.B., Pisareva M.M., Stukova M.A., Buzitskaya J.V., Payankova A.A., Elpaeva E.A., Zadonskaya A.V., Ivanov Y.V., Kiselev O. I.  
Voprosy virusologii. –2012. – V. 57. – №6. – P. 37-42.

## 2013

- **A nanovaccines produced in plants by tobacco mosaic virus-based vectors Immunogenicity and protective efficacy of candidate universal influenza**  
Petukhova N.V., Gasanova T.V., Stepanova L.A., Rusova O.A., Potapchuk M.V., Korotkov A.V., Skurat E.V., Tsybalova L.M., Kiselev O.I., Ivanov P.A., Atabekov J.G.  
Current Pharmaceutical Design. – 2013. doi:10.2174/13816128113199990337(epub)
- **A molecular assembly system for presentation of antigens on the surface of HBc virus-like particles**  
Blokhina E.A., Kuprianov V.V., Stepanova L.A., Tsybalova L.M., Kiselev O.I., Ravin N.V., Skryabin K.G.  
Virology. – 2013. – V. 435. – N.2 – P.293-300
- **Transmission studies resume for avian flu**  
Fouchier R.A.M., Garcia-Sastre A., Kiselev O.I. et al  
Science. – 2013. Vol.339/6119. – P.520-521.
- **Protective properties of inactivated virosomal influenza vaccine**  
Erofeeva M.K., Nickonorov I.J., Maksakova V.L., Stukova M.A., Konshina O.S., Okhapkina E.A., Voicehovskaya E.M., Korovkin S.A., Melnikhov S.J., Kiselev O.I.  
7th Vaccine & ISV Congress 2013, Barcelona, Spain, October 27–29, 2013
- **High specific activity of the vaccine preparation comprising recombinant protein with 4 copies of the influenza virus M2e**  
Tsybalova L., Stepanova L., Kupriyanov V., Potapchuk M., Korotkov A., Ravin N.  
7th Vaccine & ISV Congress 2013, Barcelona, Spain, October 27–29, 2013
- **Main factor of the low antigen content of inactivated H5N1 influenza vaccines – decreased stability of the H5 hemagglutinin protein**  
Sergeeva M.V., Krokhin A.A., Tsybalova L.M., Romanova J.R.  
Options for the control of influenza VIII, Cape Town, South Africa, September 5–10, 2013

## The Basic Research on Influenza and Influenza Virus

*The life cycle of influenza A virus*



tools to analyze influenza virus morphogenesis.

Since a small size of genome influenza viruses use different molecular mechanisms, enhancing its coding capacity, and involve cellular factors to accomplish different steps of the life cycle.

The main focus of the basic research, made in the Department of Molecular Virology of Research Institute of Influenza, is the study of new “accessory” proteins of influenza virus and multiple interactions between the virus and cellular components in order to understand the mechanisms of influenza-associated complications and find new anti-influenza viral and host drug targets. To reveal new details of the biology of influenza virus the laboratory is integrating tools of molecular and systems biology, virology, biophysics, electron microscopy and computational biology.

Our research activities include the study of virus-host interactions using high-throughput techniques, such as microarray, next-generation sequencing and mass-spectrometry. We study the secretome of influenza virus infected cells, gene expression (mRNA and miRNA profiling) of cells, infected with different influenza virus strains, protein-protein interactions between viral and cellular factors, secondary structure of viral RNAs, the molecular mechanisms of neurologic complications of influenza. We also apply electron and atomic force microscopy



## Selected Publications:

### Molecular mechanisms enhancing the proteome of influenza A viruses: an overview of recently discovered proteins

Vasin A.V., Temkina O.A., Egorov V.V., Klotchenko S.A., Plotnikova M.A., Kiselev O.I.  
 Virus Research. 2014

### Oligonucleotide microarray for subtyping of influenza A viruses

Klotchenko SA, Vasin AV, Sandybaev NT, Plotnikova MA, Chervyakova OV, Smirnova EA, Kushnareva EV, Strochkov VM, Taylakova ET, Egorov VV, Koshemetov JK, Kiselev OI, Sansyzybay AR.  
 J Phys: Conf Ser. 2012; 345: 012041.

### Mass Spectrometry and Biochemical Analysis of RNA Polymerase II –targeting by Protein Phosphatase-1

Jerebtsova M, Klotchenko SA, Artamonova TO, Ammosova T, Washington K, Egorov VV, Shaldzhyan AA, Sergeeva MV, Zatulovskiy EA, Temkina OA, Petukhov MG, Vasin AV, Khodorkovskii MA, Orlov YN, Nekhai S.  
 Mol Cell Biochem. 2011; 347(1-2): 79-87.

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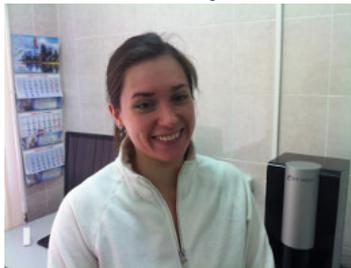
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# Development of a Novel *In Vitro* Diagnostics Solutions [products] for Detection of Infectious Diseases, Based on The Cathodic Electrochemiluminiscence

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Diagnostics play a crucial role in the system of National healthcare, since the appropriate and timely diagnosis is the key to the effective and successful treatment and/or prevention of all types of diseases, especially infectious diseases. The globalization processes, localization of the population density and increase of migration activity lead to the expansion of the range of infectious diseases and the increase in the rate of genetic variation of the corresponding etiologic agents. Despite significant advances in sanitation and medicine, infectious diseases still annually claim in excess of 15 million lives.

The molecular methods for infectious agent detection, initially emerged in the mid-1970s, continues to evolve, since the «ideal» IVD technology is far from the development. The goals of new technologies in diagnostics are to achieve the highest sensitivity and specificity possible to accurately identify the infection status of patient in the shortest time possible. Ease of use, low cost and increased information from a single test (e.g. multiplexing) are also critical areas frequently targeted for improvement. In in vitro diagnostics (IVD) there are, in general, two opposite trends. The first one is towards the extensive automation and consolidation of testing in central laboratories. Such facilities provide multiplex quantitative results with excellent sensitivity, but they require the use of different types of complex and expensive equipment, special laboratory facilities and the use of highly trained personnel. The second trend is towards the decentralization of the diagnostics, so called, point-of-care diagnostics (POCD). POCD can be easily and quickly performed at doctor’s office or even at home. No doubt, this trend is the future of diagnostics, but nowadays the existing POCD technologies cannot provide satisfactory results, despite some latest achievements in this field. The niche between these two approaches is almost empty.

The goal of this project is to develop a series of a novel IVD medical systems, including reagents, instruments and accessories, based on the phenomenon of the cathodic electrochemiluminiscence (CECL).

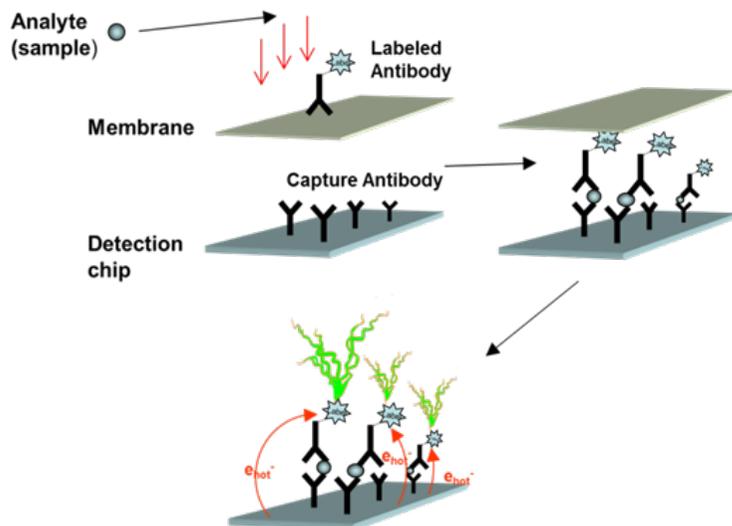
CECL IVD systems will provide high efficiency quantitative rapid POC immunologic diagnostics of socially significant infectious diseases (influenza and other respiratory infections, viral hepatitis, AIDs, tuberculosis).

CECL IVD systems family will include:

- stationary (for small clinics and medical facilities),
- portable (for use in public institutions, such as Immigration and Customs Service, Rescue Service, the Interior Ministry and others)
- handheld (for individuals) solutions.

Electrochemiluminescence (ECL) is a long-known phenomenon wherein luminescent light is achieved from luminophoric molecules in non-aqueous or partially aqueous electrolyte solutions at inert metal electrodes, like gold and platinum. Cathodic ECL (CECL) is a platform detection technology which suits well to all areas of immunodiagnostics in classical immunoassay format. The CECL technology was originally developed in Finland, and is now owned by the Finnish company Labmaster Ltd.

## LM-CECL Immunoassay



CECL chip – is an integrated electrode chip made of silicon or on the surface of glass or polymer substrates. The principle of CECL immunoassay is the same as in the classical immunoassay with fluorescently labeled antibodies (see below). The analyte molecules are incubated with labeled antibodies and then with capture antibodies, immobilized on the surface of silicon electrode chip. Several different antibodies can be immobilized on a single chip. After the washing procedure we obtain «sandwich» made of the immobilized capture antibodies – analyte molecules – labeled antibodies. The specific binding is detected by electron induced chemiluminescence.

The advantages of CECL detection against common fluorescence detection:

- Sensitivity, accuracy - comparable to lab tests ( low pg/ml, variaton, CV% 4 – 7)
- Dynamic range: 5 orders of magnitude
- Whole blood capability
- Extremely easy to use test procedure
- Fast test time - less than 6 minutes
- Low price reader due to mass produced electrical components
- Cheap test cartridge due to cheap materials and well developed

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- Cloning and expression of immunomodulator genes in bacterial and yeast cells;
- Studying of molecular mechanisms of action of antivirals and their rational design;
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