

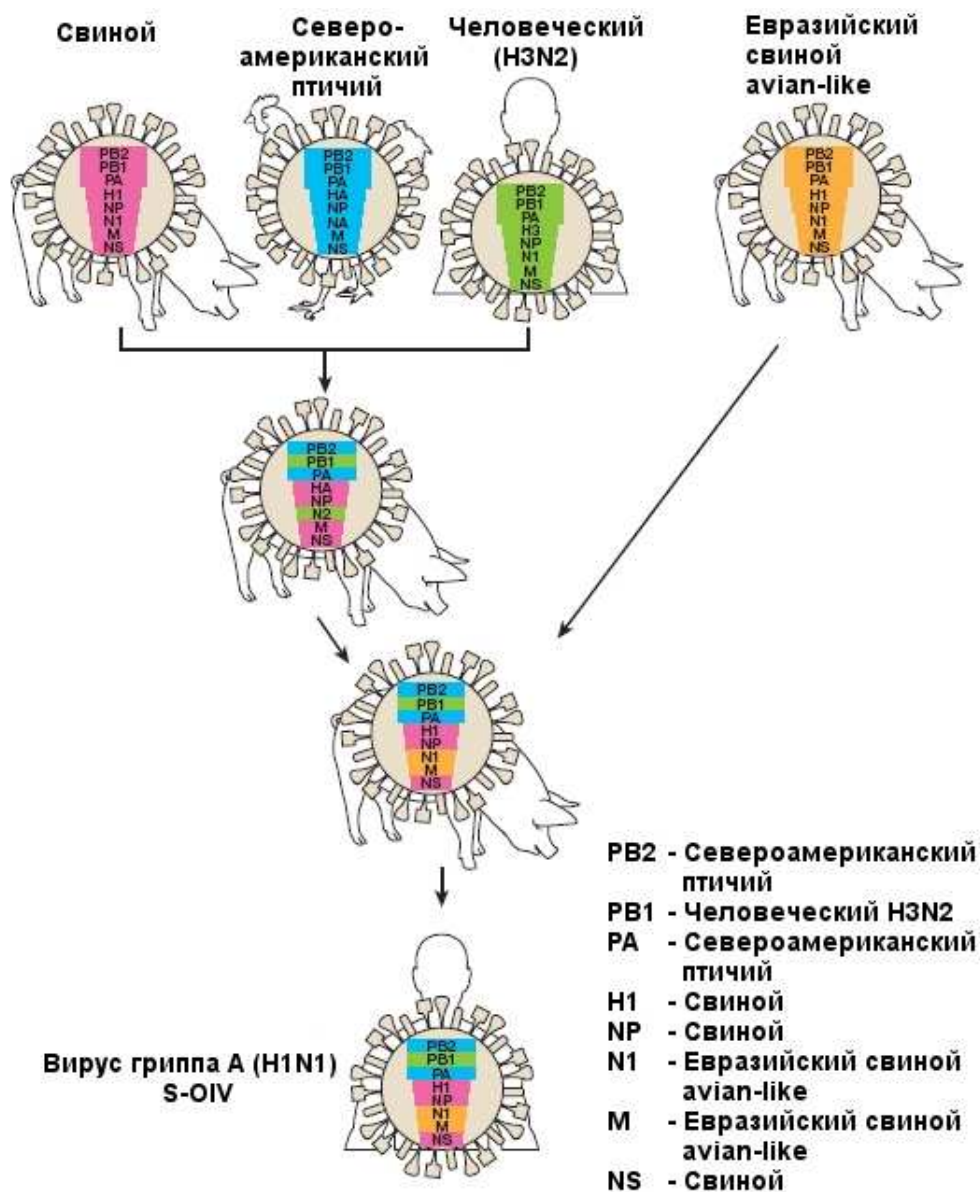


# ***PREPAREDNESS TO INFLUENZA PANDEMIC IN RUSSIA***

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# Derivation of S-OIV



(Из Neumann et al., 2009)

# ***Pathogenicity determinants in influenza A(H1N1)v viruses***

- **PB2**

**E627K**      *active replication at 33°C*      **NO**

**D701N**      *PB2 importation into nucleus*      **NO**

- **PB1-F2**

**N66S**      *Apoptosis induction*      **NO**

- **HA**

*multiple basic aminoacids in proteolysis site*      **NO**

- **NS1**

*Non known function*      **NO**, but mutation

*D92G was identified in two New York strains*

**PDZ-домен**      **NO**

***Pandemic is a result of high transmission of influenza A(H1N1)v virus but not of its high pathogenicity:***

- ***Clinically most of the cases are mild***
- ***About 10% of patients needs in hospitaliation***
- ***Only 0.3% of patients needs in intensive therapy***

## ***WHO RECOMMENDED TESTS FOR CONFIRMATION OF AH1N1)v INFECTION***

- ***r RT-PCR assay (subtype specific test)***
- ***Virus isolation (MDCK cells, chicken embryos) and identification in HI***
- ***Serology (fourfold increase of antibody titers in HI test or MN test)***

## ***RT-PCR kits applied for the detection of new influenza A(H1N1)v cases in Russia***

<b><i>Designation of kit</i></b>	<b><i>Producer</i></b>	<b><i>Occupant</i></b>
<b><i>CDC rRT-PCR kit for Detection and Characterization of swine influenza (version 2009)</i></b>	<b><i>Centre for Disease Control and Prevention (CDC), Atlanta, USA</i></b>	<b><i>Research Institute of Influenza, Ivanovsky Institute of Virology</i></b>
<b><i>AmpliSens A/H1-swine FL-kit</i></b>	<b><i>Central Institute of Epidemiology, Moscow, Russia</i></b>	<b><i>Base Virological Laboratories at the Centres of H&amp;Epi</i></b>
<b><i>In- house rRT-PCR kit for detection of RNA of influenza A(H1N1)v cases</i></b>	<b><i>Research Institute of Influenza. Primers and probes were synthesized at the “Syntol” (Moscow) in accordance with CDC recommendation</i></b>	<b><i>Research Institute of Influenza.</i></b>



# ***Antigens and antisera for the detection of new influenza A(H1N1)v cases in Russia***

<b><i>Designation of kit</i></b>	<b><i>Producer</i></b>	<b><i>Occupant</i></b>
<b><i>Serology (fourfold increase of antibody titers in patients sera in HI test)</i></b>	<b><i>Research Institute of Influenza, St-Petersburg, Russia</i></b>	<b><i>Base Virological Laboratories of WHO NIC at the Centres of H&amp;Epi</i></b>
<b><i>Pandemic influenza A(H1N1)v viruses identification</i></b>	<b><i>Research Institute of Influenza, St-Petersburg, Russia</i></b>	<b><i>Base Virological Laboratories of WHO NIC at the Centres of H&amp;Epi</i></b>
<b><i>Investigaton of population immunity among non vaccinated volunteers</i></b>	<b><i>Research Institute of Influenza, St-Petersburg, Russia</i></b>	<b><i>Base Virological Laboratories of WHO NIC at the Centres of H&amp;Epi</i></b>

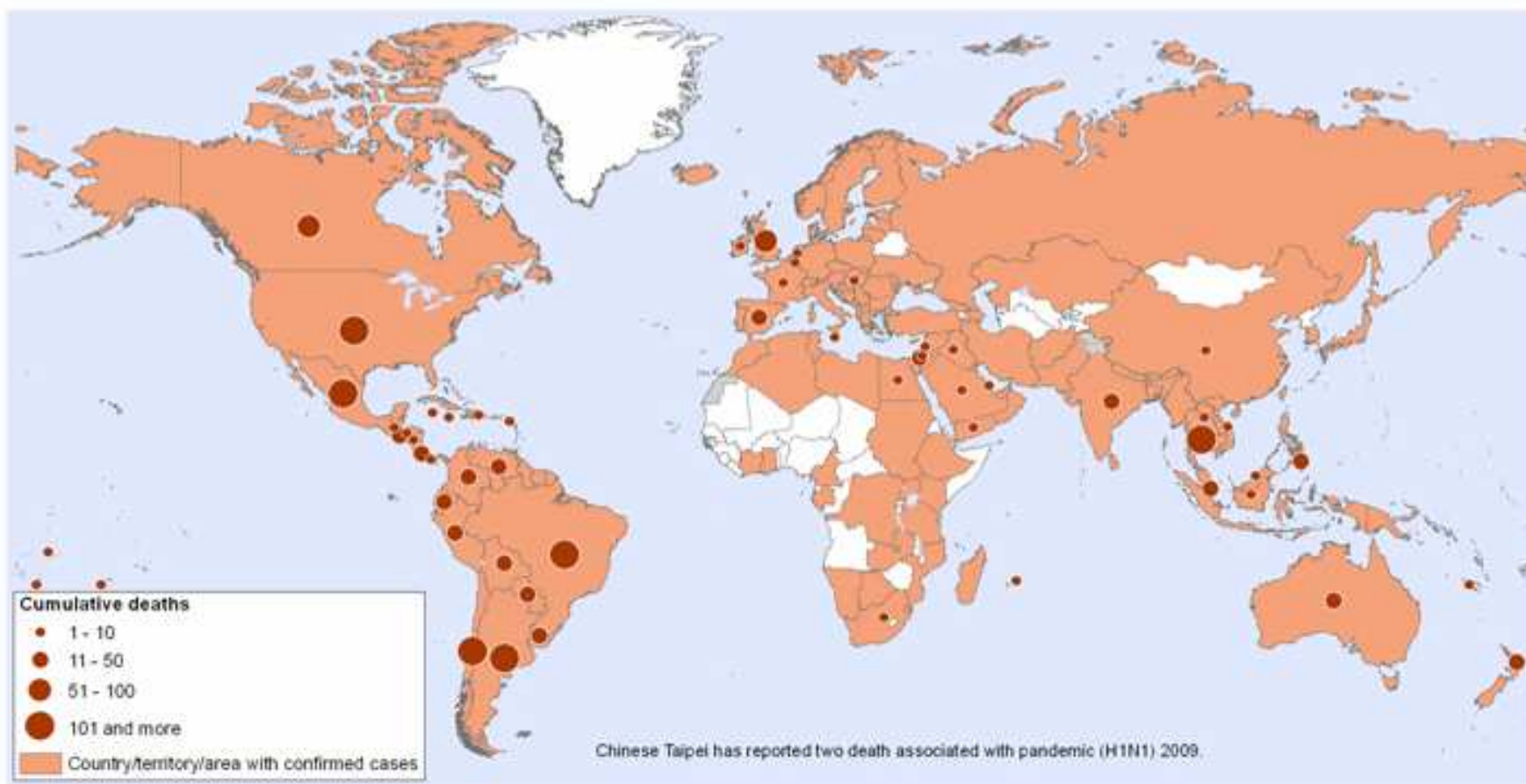


World Health  
Organization

Timeline (22 July 2009 onwards)  
Pandemic (H1N1) 2009 laboratory confirmed cases  
And number of deaths as reported to WHO

Status as of: 23 August 2009

 Previous



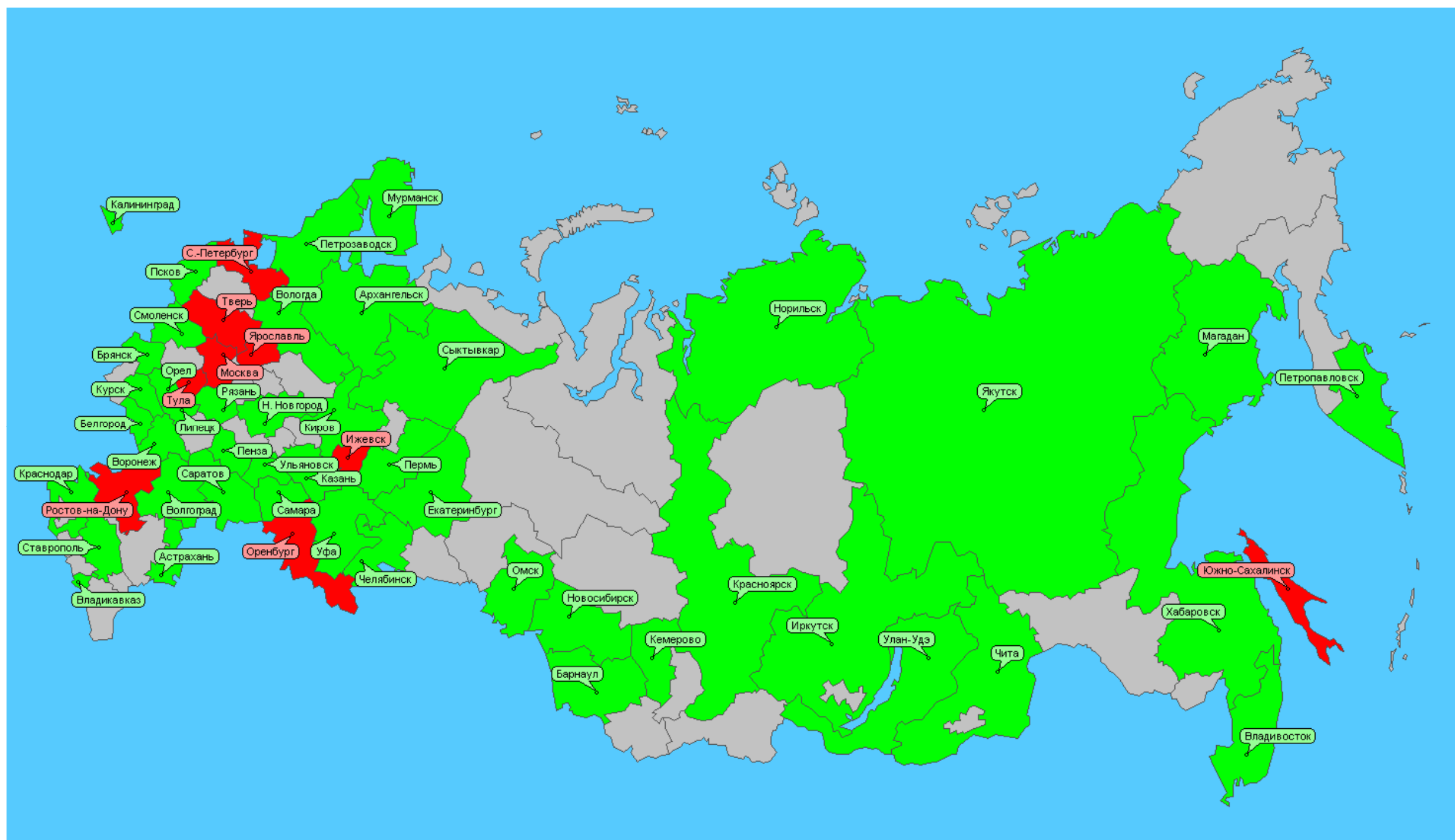
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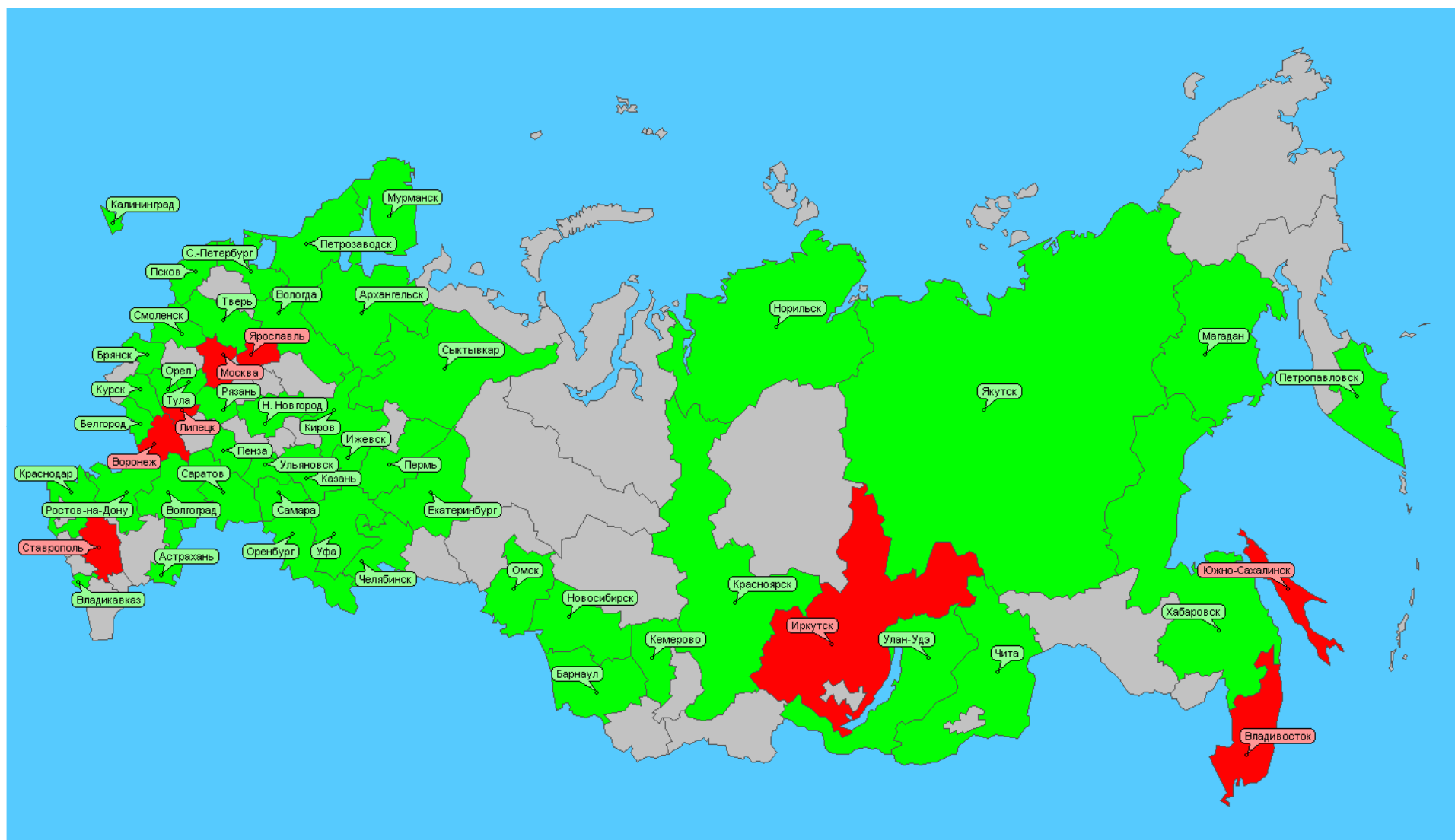
## ***The pandemic (H1N1) 2009 confirmed case(s) as of 23 August 2009***

<b><i>Region</i></b>	<b><i>Cumulative total as of 23 Aug 2009</i></b>	
	<b><i>Cases*</i></b>	<b><i>Deaths</i></b>
<b><i>WHO Regional Office for (AFRO)</i></b>	<b><i>3843</i></b>	<b><i>11</i></b>
<b><i>WHO Regional Office for the (AMRO)</i></b>	<b><i>110113</i></b>	<b><i>1876</i></b>
<b><i>WHO Regional Office for the (EMRO)</i></b>	<b><i>3128</i></b>	<b><i>10</i></b>
<b><i>WHO Regional Office for (EURO)</i></b>	<b><i>Over 42,557</i></b>	<b><i>At least 85</i></b>
<b><i>WHO Regional Office for (SEARO)</i></b>	<b><i>15771</i></b>	<b><i>139</i></b>
<b><i>WHO Regional Office for the Western Pacific (WPRO)</i></b>	<b><i>34026</i></b>	<b><i>64</i></b>
<b><i>Total</i></b>	<b><i>Over 209438</i></b>	<b><i>At Least 2185</i></b>

## Influenza A(H1N1)v cases in Russia, week 33. 2009



## Influenza A(H1N1)v cases in Russia, week 34. 2009



**Results of pandemic influenza A(H1N1)v diagnosis in Russia  
for period since week 19 till week 34.2009.**

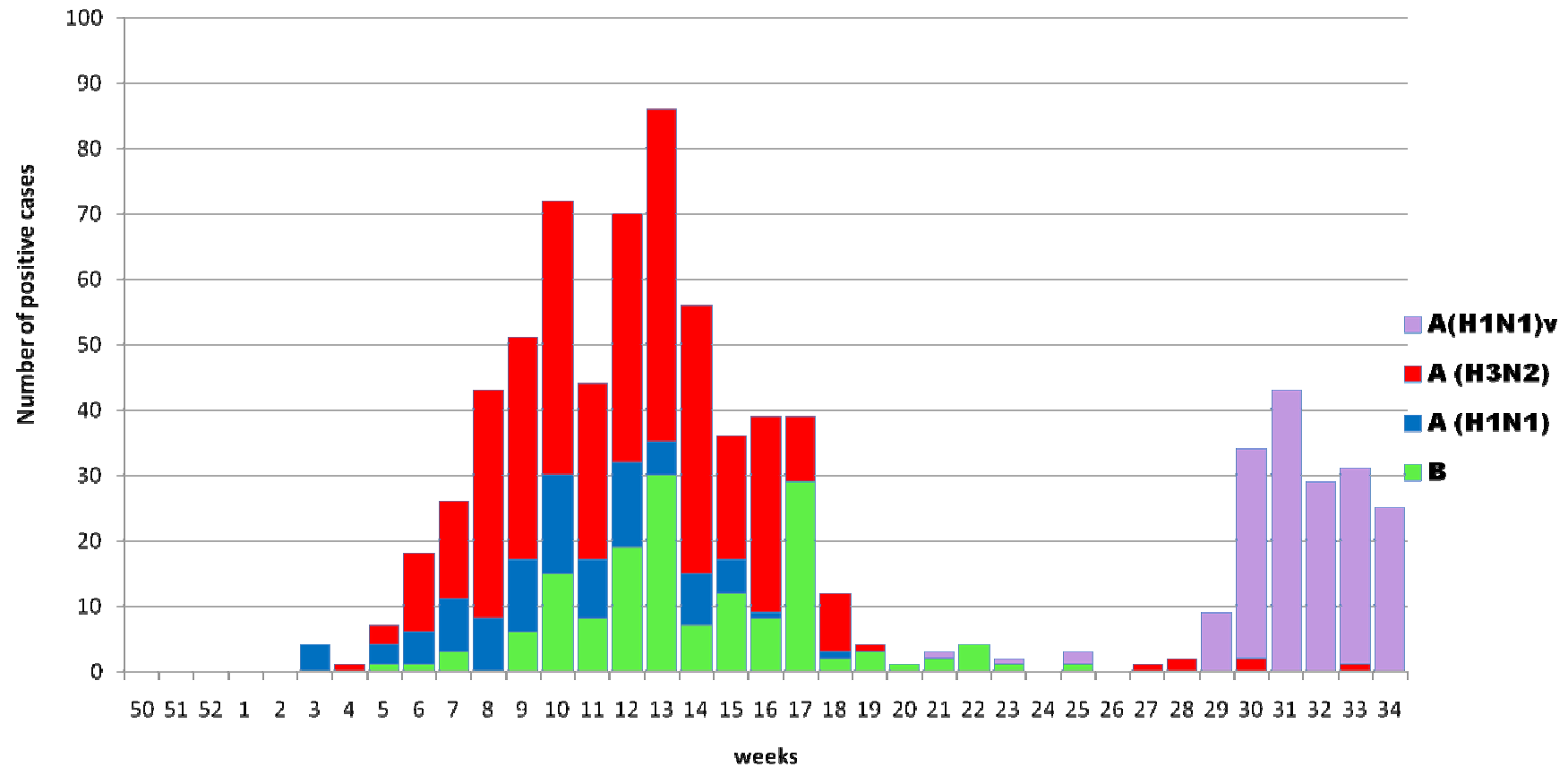


## ***Results of RT-PCR detection of influenza A(H1N1)v cases in Russia***

<b>Week #</b>	<b>City</b>	<b>Number of cases</b>
<b>21</b>	<b>Moscow</b>	<b>1</b>
<b>23</b>	<b>Moscow</b>	<b>1</b>
<b>25</b>	<b>Moscow, St.-Petersburg</b>	<b>2</b>
<b>29</b>	<b>Moscow</b>	<b>9</b>
<b>30</b>	<b>Moscow, Vladivostok, Yekaterinburg, Perm, St.-Petersburg, Voronezh</b>	<b>32</b>
<b>31</b>	<b>Moscow, Perm, St.-Petersburg, Chelyabinsk, Yuzhno-Sakhalinsk, Rostov-na-Donu, Yakutsk, Lipetsk, Penza, Ufa</b>	<b>43</b>
<b>32</b>	<b>Moscow, St.-Petersburg, Chelyabinsk, Lipetsk, Voronezh, Ufa</b>	<b>29</b>
<b>33</b>	<b>Moscow, St.-Petersburg, Yuzhno-Sakhalinsk, Rostov-na-Donu, Orenburg, Izhevsk, Tula, Tver, Yaroslavl</b>	<b>29</b>
<b>34</b>	<b>Irkutsk, Stavropol, Yuzhno-Sakhalinsk, Moscow, Lipetsk, Yaroslavl, Vladivostok, Voronezh</b>	<b>25</b>



## ***Monitoring of influenza viruses circulation in Russia, season 2008—2009***

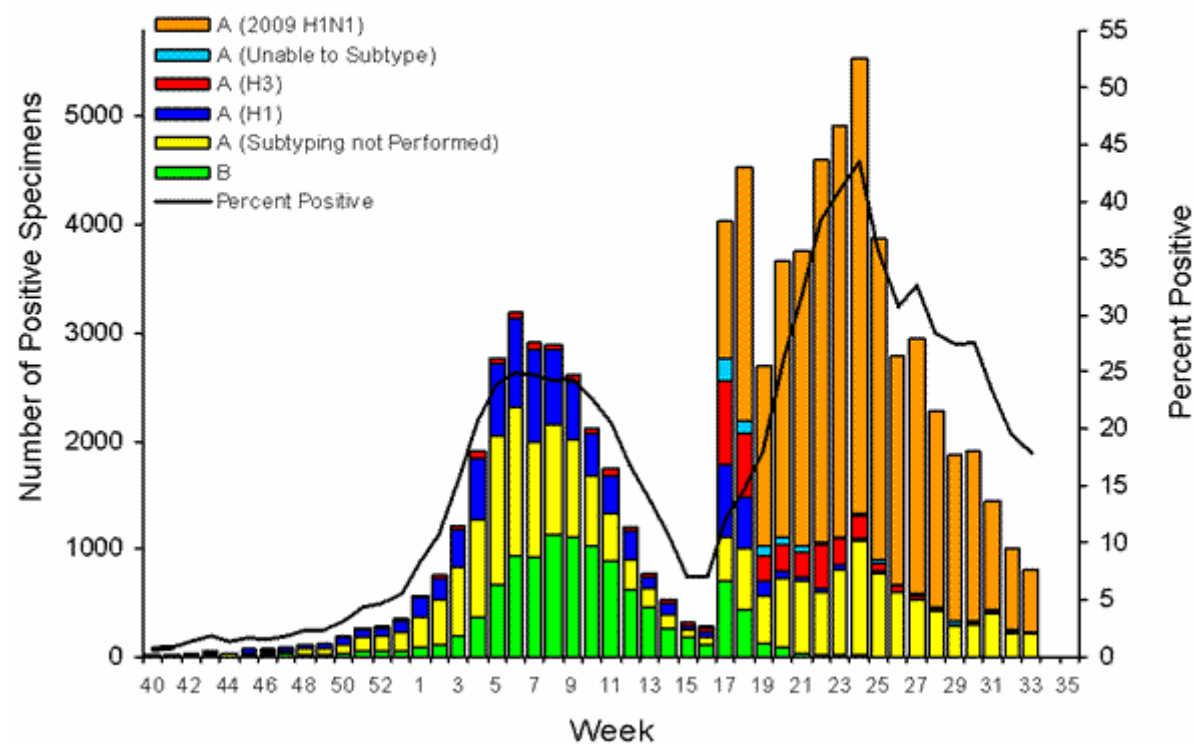


**Note:**

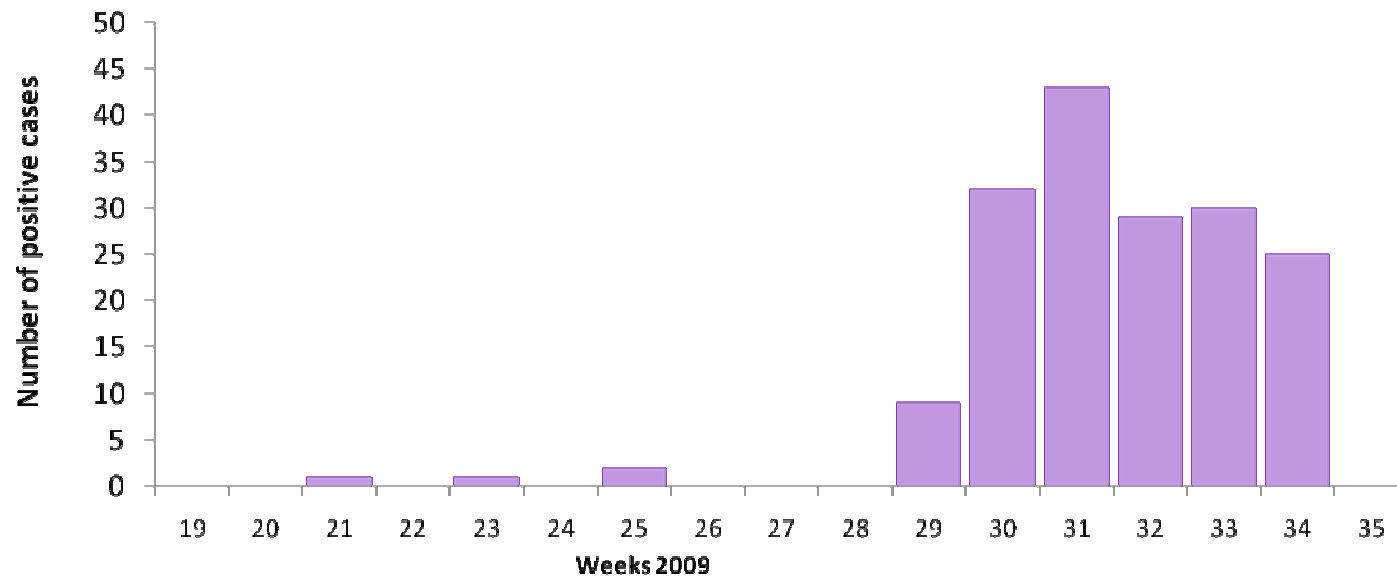
**Season influenza A(H1N1), A(H3N2) and B – data on virus isolation only.**

**Data on influenza A(H1N1)v - aggregated positive cases according to virus isolation + PCR.**

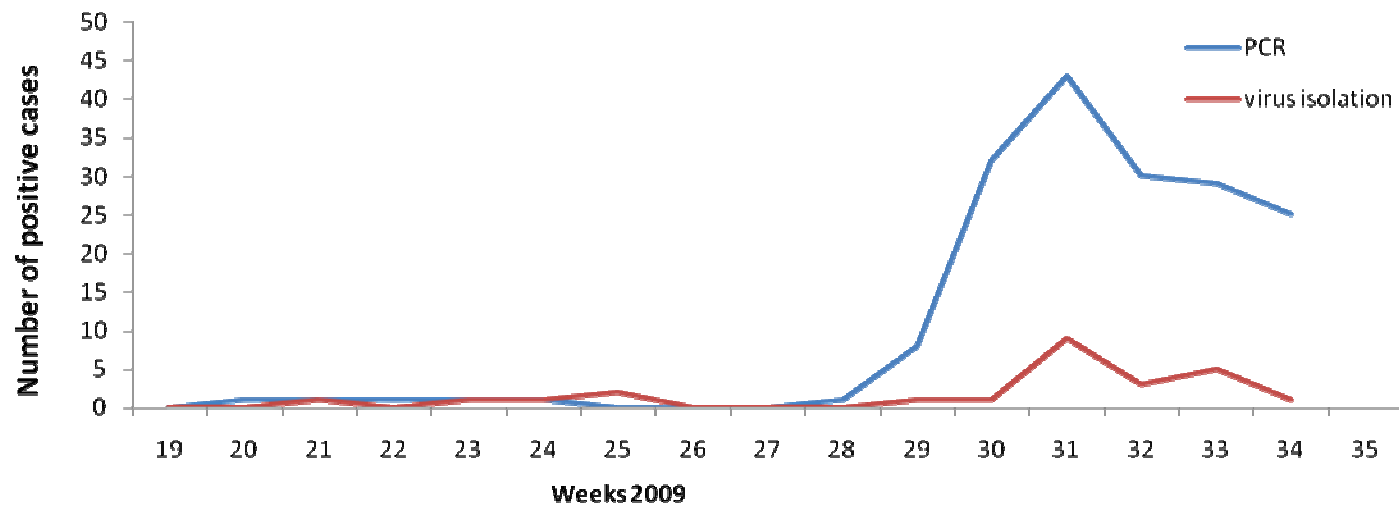
# Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09



## Aggregated data on virus isolation + RT-PCR



## Data on virus isolation and RT-PCR diagnosis (separately)



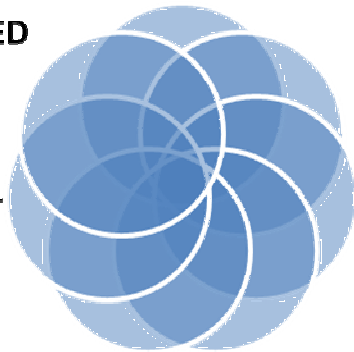
# INFLUENZA VACCINES

## INACTIVATED

NONADJUVANTED

VIROSOMAL  
(BROAD IMMUNE  
RESPONSE)

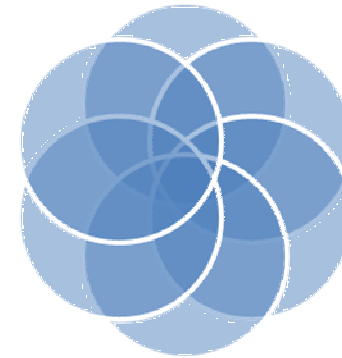
ADJUVANTED (ADVANTAGE  
IN NAÏVE INDIVIDUALS)



SUBUNIT  
(HA + NA)

SPLIT

## LIVE ATTENUATED (CLOSELY MIMIC A NATURAL INFECTION)



CA  
REASSORTANT  
BASED

NS1 DEL  
BASED

# ***Russian Influenza A(H1N1)v vaccines ( State Order about 40 mln doses):***

## ***Inactivated influenza vaccines:***

- ***Subunit with polyoxidonium – “Petrovax”- 6 mln doses monthly***
  - ***“SPb IVS” – 1.5 mln doses monthly***
- ***Subunit with aluminum hydroxide – “Microgen” (Ufa) 3- 4,5 mln doses monthly***

## ***Live attenuated influenza vaccine:***

- ***CA reassortant based - “Microgen” (Irkutsk) - 1,5 mln doses monthly***
- ***NS1 del based (in progress)***



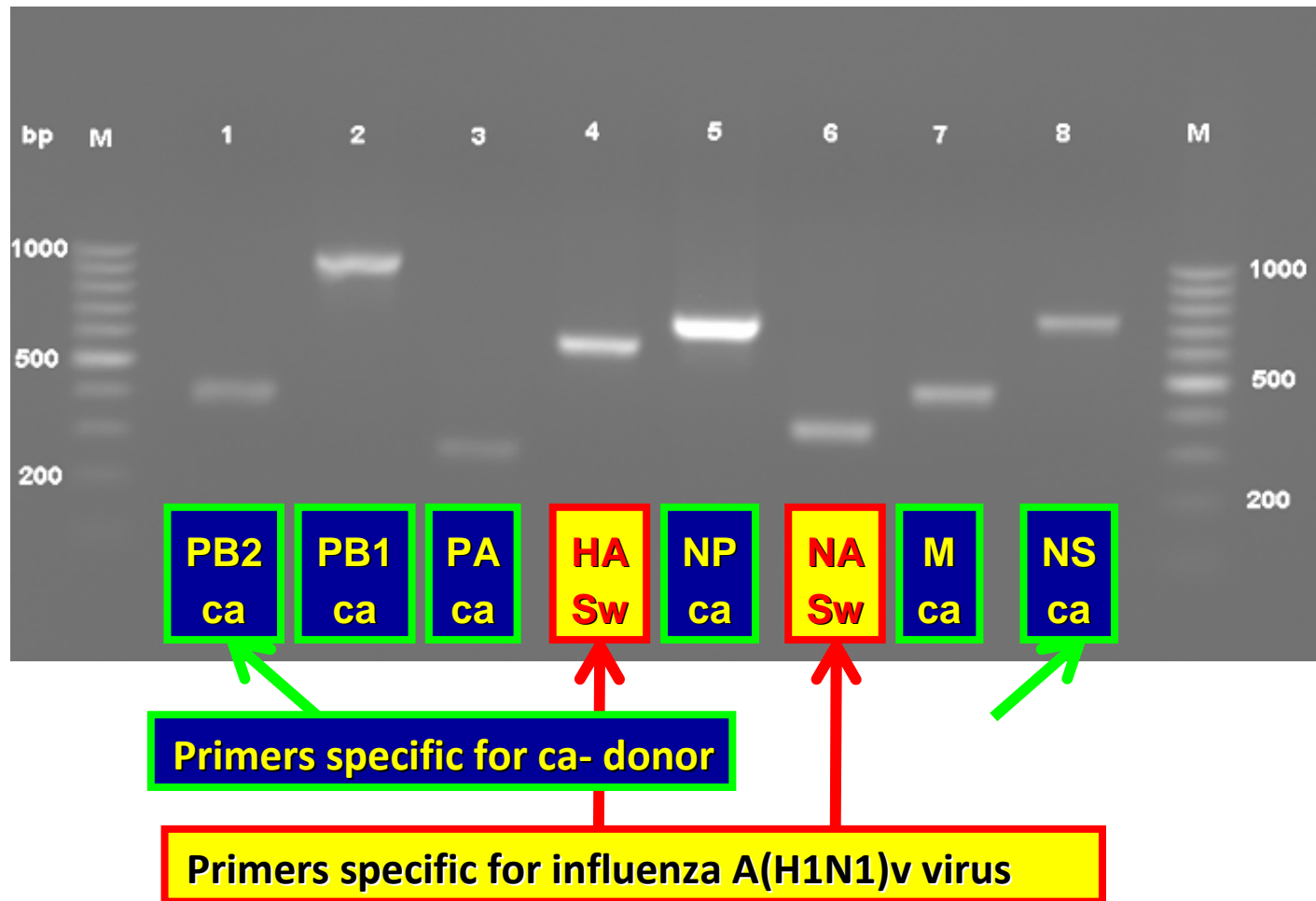
## ***Advance of new influenza A(H1N1)v vaccine strains in Russia (as for August 31.2009)***

<b><i>Vaccine strain</i></b>	<b><i>Designer of the strain</i></b>	<b><i>Technology</i></b>	<b><i>Stage of preparation</i></b>	<b><i>Stage of investigation</i></b>
<b><i>IDCDC - RG15 A/Texas/5/2009 (H1N1)v for IIV</i></b>	<b><i>WHO CC, CDC, Atlanta,USA</i></b>	<b><i>Reverse Genetic</i></b>	<b><i>Ready. Safety for ferrets has been shown</i></b>	<b><i>The strain obtained by RII from CDC on June 10.2009 . Distributed between Institutes for research task</i></b>
<b><i>X - 179A A/California/7/ 2009 (H1N1)v for IIV</i></b>	<b><i>NYMC, New York, USA</i></b>	<b><i>Classical reassort ment</i></b>	<b><i>Ready. Safety for ferrets has been shown</i></b>	<b><i>Experimental lots of influenza (H1N1)v vaccines are under control</i></b>
<b><i>A/California/7/2009 (H1N1)v for LAIV</i></b>	<b><i>RIEM, St- Petersburg, Russia</i></b>	<b><i>Reassortment with ca- donor</i></b>	<b><i>Ready. Safety for ferrets has been shown</i></b>	<b><i>Experimental lots of influenza (H1N1)v vaccines are under control</i></b>

## **Time-table for pandemic influenza A(H1N1)v vaccine preparation and issue in Russia**

Executor	Stages of investigation	Schedule times (Month No. of 2009)									
		5	6	7	8	9	10	11	12		
Institute of Experimental Medicine	Development and control of ca-reassortant for LAIV	★	★	★							
Research Institute of Influenza	Investigation of vaccine strains received from CDC (reproduction level, specificity, lyophilization of the virus)	★	★								
	Distribution of influenza A(H1N1)v vaccine strains between manufacturers of vaccines		★								
	Evaluation of safety and immunogenicity of live and inactivated influenza vaccines in clinical trials					x	x	x			
“Microgen” enterprises (Irkutsk)	Preparation of seed virus for LAIV.			★							
	Preparation and control of experimental lots of LAIV vaccines				★	★					
	Production and distribution of vaccines								x	→	
“Microgen” enterprises (Ufa) & SPb RIVS	Preparation of seed virus for IIV			★							
	Preparation and control of experimental lots of inactivated influenza vaccines				★	★					
	Production and distribution of vaccines								x	→	
GISC	Analysis of updated technical documentation	★	★	★							
	Control of seed virus				★						
	Control and standardization of LAIV and IIV					x	x	x			

# ***Genome structure of vaccine strain: 6:2***



# ***PHENOTYPIC PROPERTIES OF ca - VACCINE STRAIN***

***★ Mices and guinea pigs-  
acute toxicity***

***★ safety and immuno-  
genicity in ferrets***



**ViroClinics**

Dr. Molenwaterplein 50  
3015 GE ROTTERDAM  
The Netherlands  
[www.viroclinics.com](http://www.viroclinics.com)



**IEM**



- ✳ **The GPO (Bangkok, Thailand) was one of manufacturers in developing countries chosen by the WHO for a program to expand global pandemic vaccine production beyond a few wealthy countries that possess such capacity. Russian pandemic LAIV is a part of this program.**





# SEED MATERIAL PREPARATION AND PRECLINICAL INVESTIGATION IN THAILAND



***Most of influenza A(H1N1)v viruses appeared to be sensitive to oseltamivir and zanamivir but appearance of oseltamivir resistant strains (NA: H275Y) was firstly reported :***

- ***A/Denmark/528/2009 (09.06.2009)***
- ***A/Hong Kong/2369/2009 (11.06.2009)***
- ***A/Hunan/SWL3/2009 (13.06.2009)***
- ***Yamaguchi/22/2009***
- ***A/Osaka/180/2009***
  
- ***A total 12 oseltamivir resistant strains were reported from different countries (Japan-4, USA – 2, Hong Kong – 2 and 1 in Denmark, Canada, Singapore and China each) to the end of August.2009, among them:***
  - ***8 cases –postexposure prophylaxis***
  - ***1 case –treatment***
  - ***2 cases – tratment of immunocompromised patients***
  - ***1 case – without treatment history***

***All investigated strains were resistant to rimantadine (contain mutation S31N in M2 gene responsible for resistance to this drug)***

**Подавление репродукции вируса A/California/07/09 (H1N1)swl противовирусными препаратами  
(in vitro)**

Препарат	Доза	Клеточная культура	Вirus-ингибирующее действие ( $\Delta \lg ID_{50}$ )	Оценка эффективности
			По РГА	
<b>Тамифлю (озельтамивира карбоксилат)</b>	<b>0,04 мкг/мл</b>	MDCK	<b>2</b>	высокая
<b>Ремантадин</b>	<b>15-20 мкг/мл</b>	MDCK	<b>0</b>	эффект отсутствует
<b>Ингавирин*</b>	<b>15-20 мкг/мл</b>	MDCK	<b>0</b>	эффект отсутствует
<b>Рибавирин</b>	<b>15-20 мкг/мл</b>	MDCK	<b>1,0</b>	слабая
<b>Арбидол</b>	<b>15 мкг/мл</b>	MDCK	<b>3,5</b>	средняя
<b>Кагоцел</b>	<b>10 мг/мл</b>	MDCK	<b>2,0</b>	средняя
<b>Циклоферон</b>	<b>200 мкг/мл</b>	MDCK	<b>2,5</b>	средняя
<b>Альфа-интерферон</b>	<b>100 МЕ/мл</b>	Vero	<b>3,0</b>	средняя
<b>Гамма-интерферон (Ингарон)</b>	<b>100 МЕ/мл</b>	Vero	<b>5,0</b>	высокая
<b>Арбидол+кагоцел</b>	<b>15 мкг/мл+ 10 мг/мл</b>	MDCK	<b>4,5</b>	высокая
<b>Альфа-интерферон + рибавирин</b>	<b>10 000 МЕ +100 мкг/мл</b>	Vero	<b>5,0</b>	высокая
<b>Арбидол + ингавирин</b>	<b>15 мкг/мл +300 мкг/мл</b>	MDCK	<b>3,5</b>	средняя
<b>Альфа+гамма интерферон</b>	<b>100 МЕ (в любой комбинации)</b>	Vero или A549	<b>5,5</b>	высокая
<b>Ремантадин + но-шпа</b>	<b>15-20 мкг/мл</b>	MDCK	<b>3,0</b>	средняя