



# La Sorveglianza Virologica dell'Influenza

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Department of Infectious, Parasitic and  
Immune-Mediated Diseases***

*Roma, 15 Maggio 2015*

# Virological Influenza Surveillance System



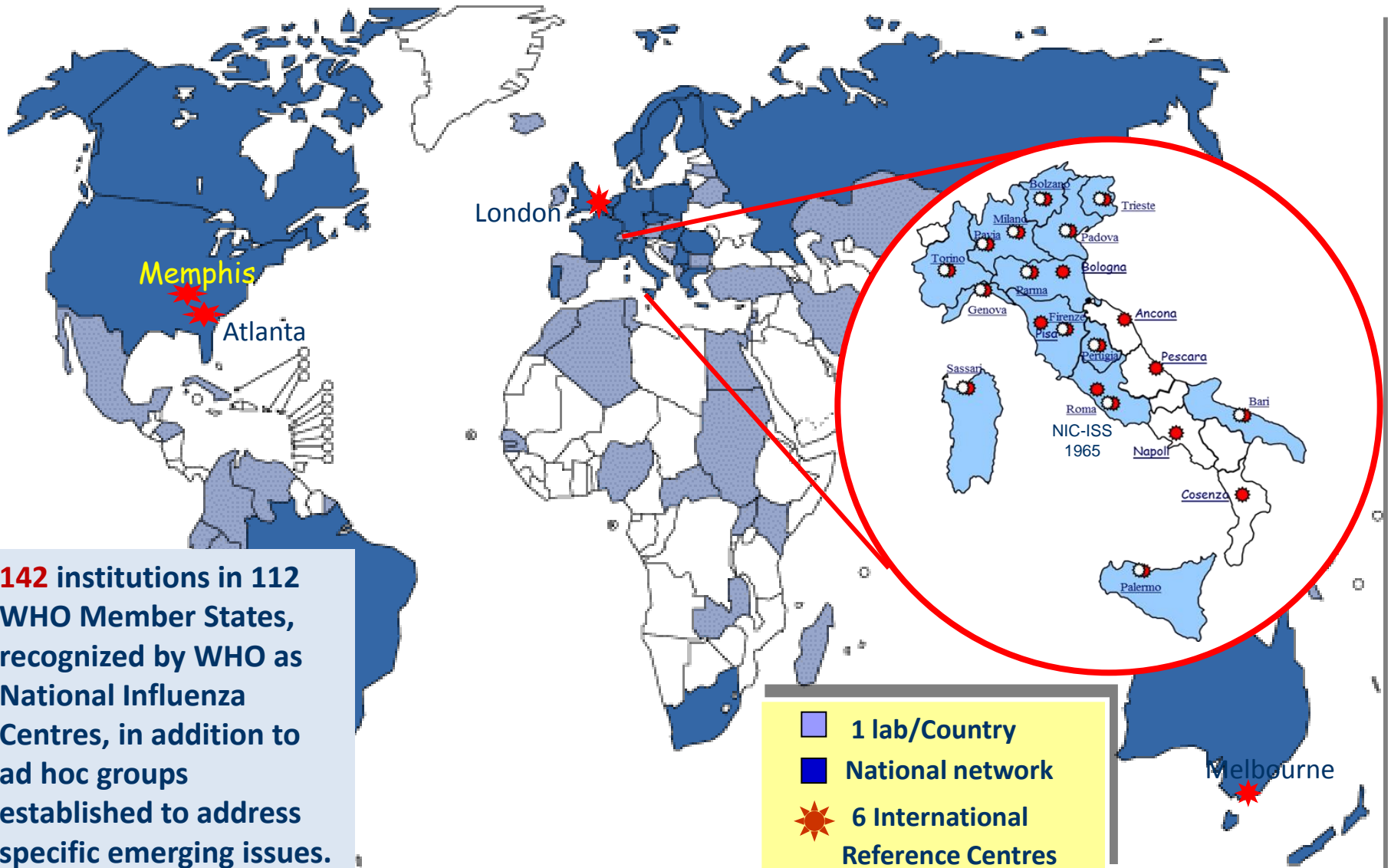
Laboratories for detection of both seasonal and novel emerging human influenza viruses



Laboratories for detection of novel emerging human influenza viruses

1. Università degli Studi di Genova (F. Ansaldi)
2. Università degli Studi di Milano (E. Pariani)
3. IRCCS, Policlinico "San Matteo" Pavia (F. Baldanti)
4. Università degli Studi di Trieste (P. D'Agaro)
5. AO "Amedeo di Savoia" Torino (V. Ghisetti)
6. Università degli Studi di Padova (G. Palù)
7. Università degli Studi di Palermo (F. Vitale)
8. AS Alto Adige Bolzano (E. Pagani)
9. Università degli Studi di Parma (P. Affanni)
10. Università degli Studi di Firenze (A. Azzi)
11. Università degli Studi di Perugia (B. Camilloni)
12. Università Cattolica "S. Cuore" Roma (M. Sanguinetti)
13. UOC Policlinico di Bari (M. Chironna)
14. Università degli Studi di Sassari (C. Serra)
15. IRCCS "Lazzaro Spallanzani" Roma (M. Capobianchi)
16. AO Sant'Orsola Malpighi Bologna (M. P. Landini)
17. Università degli Studi di Pisa (L. Ceccherini-Nelli)
18. AO "Ospedali Riuniti" Ancona (P. Bagnarelli)
19. PO "Spirito Santo" Pescara (P. Fazii)
20. AO Ospedali dei Colli Napoli (R. Smeraglia)
21. UOC AO "Annunziata" Cosenza (C. Giraldi)

# WHO Global Influenza Surveillance and Response System – Surveillance Laboratory Network



# European Influenza Surveillance Network (EISN)



## European Reference Laboratory Network for Human Influenza (ERLI-Net)

- 1 Austria: Vienna
- 2 Belgium: Brussels
- 3 Bulgaria: Sofia
- 4 Croatia: Zagreb
- 5 Cyprus: Nicosia
- 6 Czech Republic: Prague
- 7 Denmark: Copenhagen
- 8 Estonia: Tallinn
- 9 Finland: Helsinki
- 10 France: Paris, Lyon
- 11 Germany: Berlin
- 12 Greece: Athens, Thessaloniki
- 13 Hungary: Budapest
- 14 Iceland: Reykjavik
- 15 Ireland: Dublin
- 16 Italy: Rome
- 17 Latvia: Riga
- 18 Lithuania: Vilnius
- 19 Luxembourg: Luxembourg
- 20 Malta: Msida
- 21 The Netherlands: Rotterdam, Bilthoven
- 22 Norway: Oslo
- 23 Poland: Warsaw
- 24 Portugal: Lisbon
- 25 Romania: Bucharest
- 26 Slovakia: Bratislava
- 27 Slovenia: Ljubljana
- 28 Spain: Madrid, Barcelone, Valladolid
- 29 Sweden: Stockholm
- 30 UK: London, Belfast, Glasgow, Cardiff



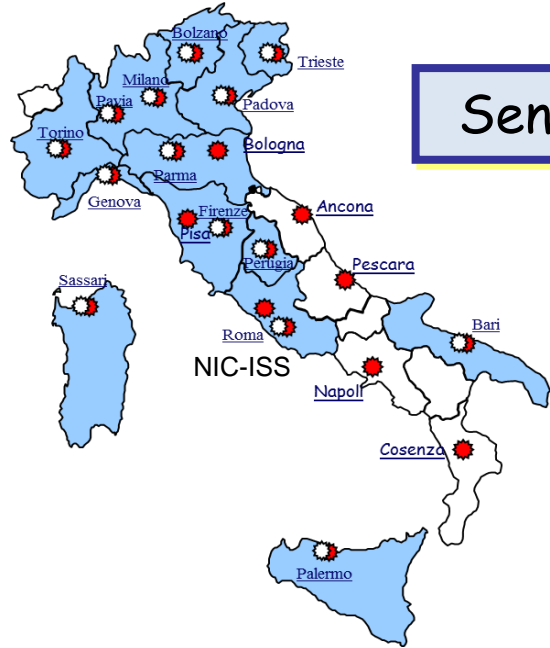
# Objectives of sentinel surveillance

## ILI/ARI and SARI



- Provide **data** to inform international, national and local health systems for influenza prevention and control, including vaccination campaigns;
- Provide **influenza virus isolates** for monitoring genetic mutations or re-assortments that could reduce the match of circulating viruses with the vaccine strain, the intrinsic severity of the virus or antiviral susceptibility;
- Provide a mechanism to establish baseline thresholds and reliable trend data for both mild and severe disease associated with influenza;
- Provide a platform for surveillance data that includes additional common respiratory pathogens that may be of additional interest; and
- Provide data that can contribute to the estimation of the burden of severe respiratory disease associated with influenza and other respiratory pathogens.

# NIC Activities



Sentinel General Practitioners / Hospitalised cases

Oropharyngeal Swabs

Regional Laboratories

Positive Samples

- ❖ Characterization of seasonal strains
- ❖ Annual vaccine updating

❖ Collection Point for Influenza Isolates  
❖ Further Ag/Molecular Analysis

**NIC - ISS**

Information and Selected samples

WHO Reference Center  
London, UK

Virological Information

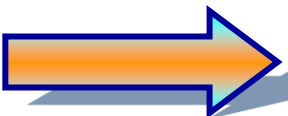
MoH  
WHO  
ECDC



# NIC Activities

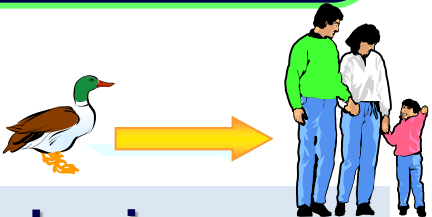


**INTER-PANDEMIC PERIOD**



**PANDEMIC PREPAREDNESS**

**Isolation/characterization of seasonal epidemic strains**



**Global alert mechanism for the emergence of a pandemic**



**Annual vaccine updating**

**Recognition of unusual events "early warning system"**



# WHO: External Quality Assessment (EQA)

- ❖ 1° QCMD EU (EISS, July 2006)
- ❖ 2° QCMD EU (ECDC, Apr 2007)

Pandemic preparedness

H5N1

CLADES  
1/ 2.1 / 2.2

H3,H1,B

- ❖ 1° EQA-WHO (Feb, 2007)
- ❖ 2° EQA-WHO (Sept, 2007)
- ❖ 3° EQA-WHO (Feb, 2008)
- ❖ 4° EQA-WHO (July, 2008)
- ❖ 5° EQA-WHO (Feb, 2009)
- ❖ 6° EQA-WHO (June, 2009)
- ❖ 7° EQA-WHO (Jan, 2010) + H1N1pdm09
- ❖ 8° EQA-WHO (June, 2010)
- ❖ 9° EQA-WHO (Jan, 2011)
- ❖ 10° EQA-WHO (June, 2011)
- ❖ 11° EQA-WHO (Apr, 2012)
- ❖ 12° EQA-WHO (Apr, 2013)
- ❖ 13° EQA-WHO (May, 2014)
- ❖ 14° EQA-WHO (May, 2015)
- ❖ 15° EQA-WHO (June 2015)

H5N1	1
	2.1
CLADES	2.2
	2.3
	2.3.2
	2.3.4
	2.3.2.1

update

H5N1

H5,H7,H9

H9N2

H7N9

?????

?????



**2014-2015 Flu Season**

**A/H3N2**

**A/H1N1**

**B**

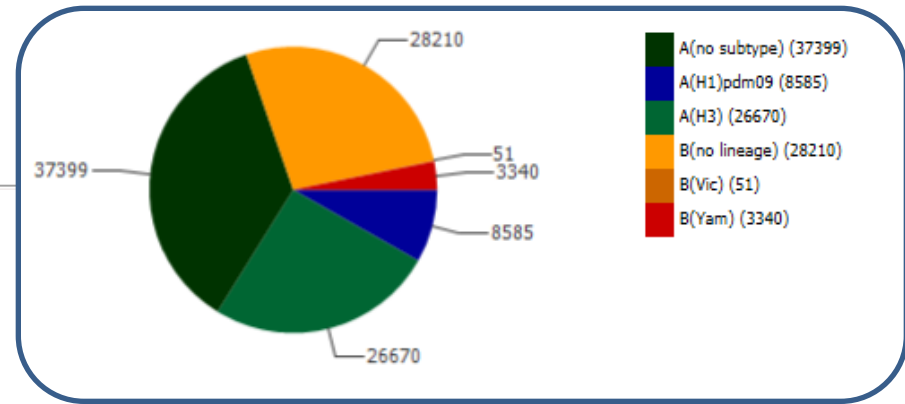
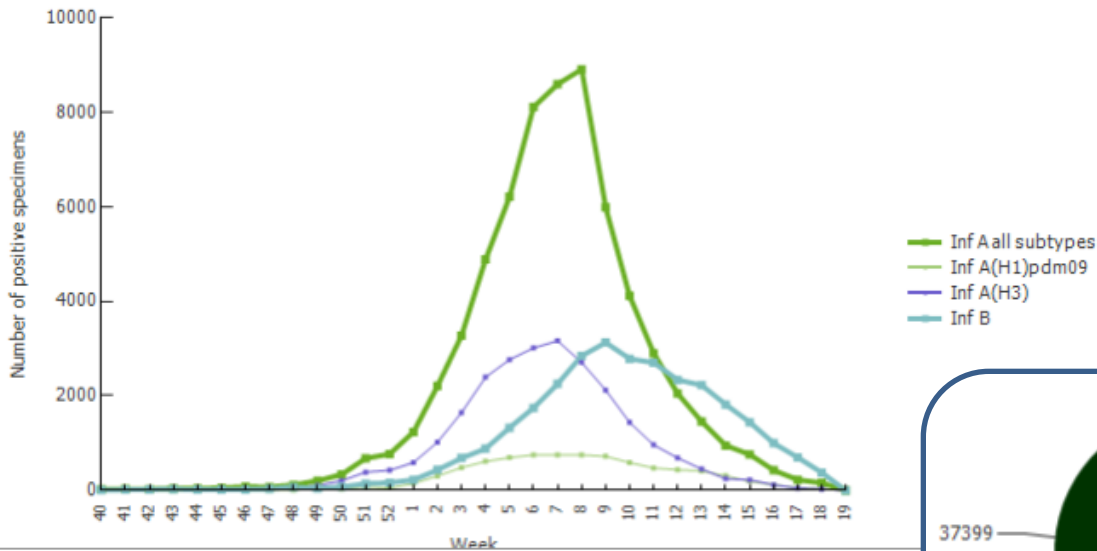
**Zoonotic Flu viruses**

# Influenza virological overview - Europe -



Influenza Virological Overview for EU/EEA, Season 2014/15

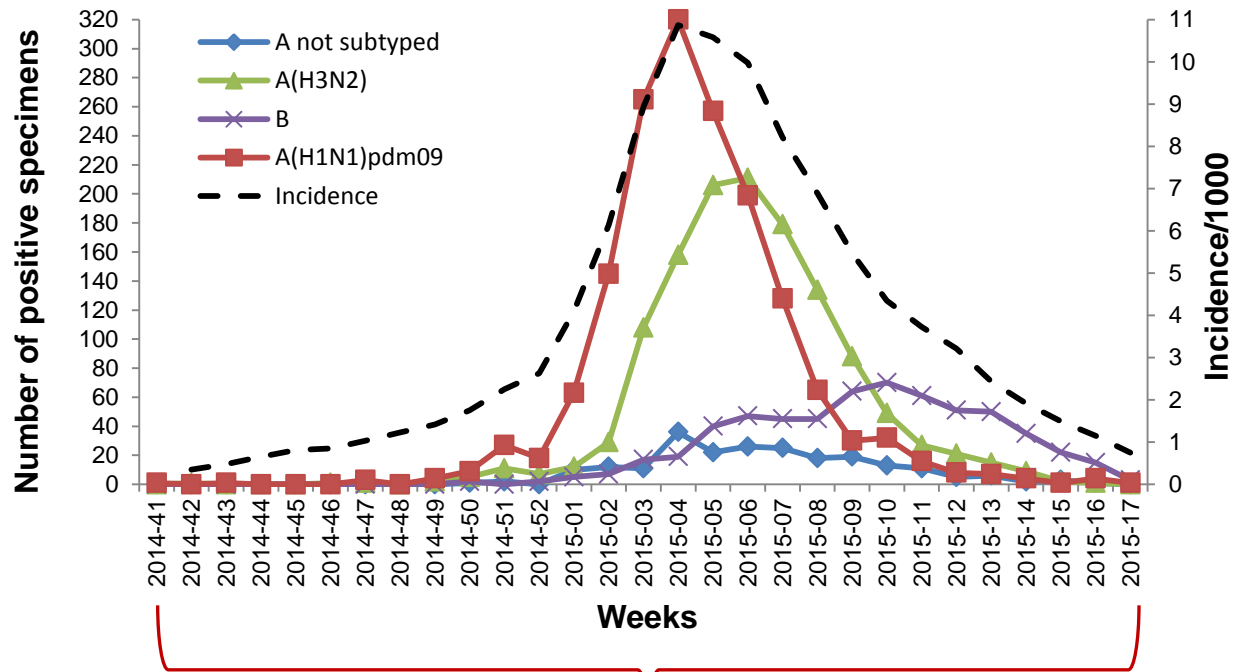
Number of positive sentinel and non-sentinel specimens for influenza A and B viruses



# Influenza virological overview - Italy -



Number of positive sentinel and non-sentinel specimens for influenza A and B viruses



7 months of surveillance activities

# Influenza virological overview

## - Italy -



### Season 2014/2015

N° of specimens: 10.470  
Positive samples: 3.708 (35%)

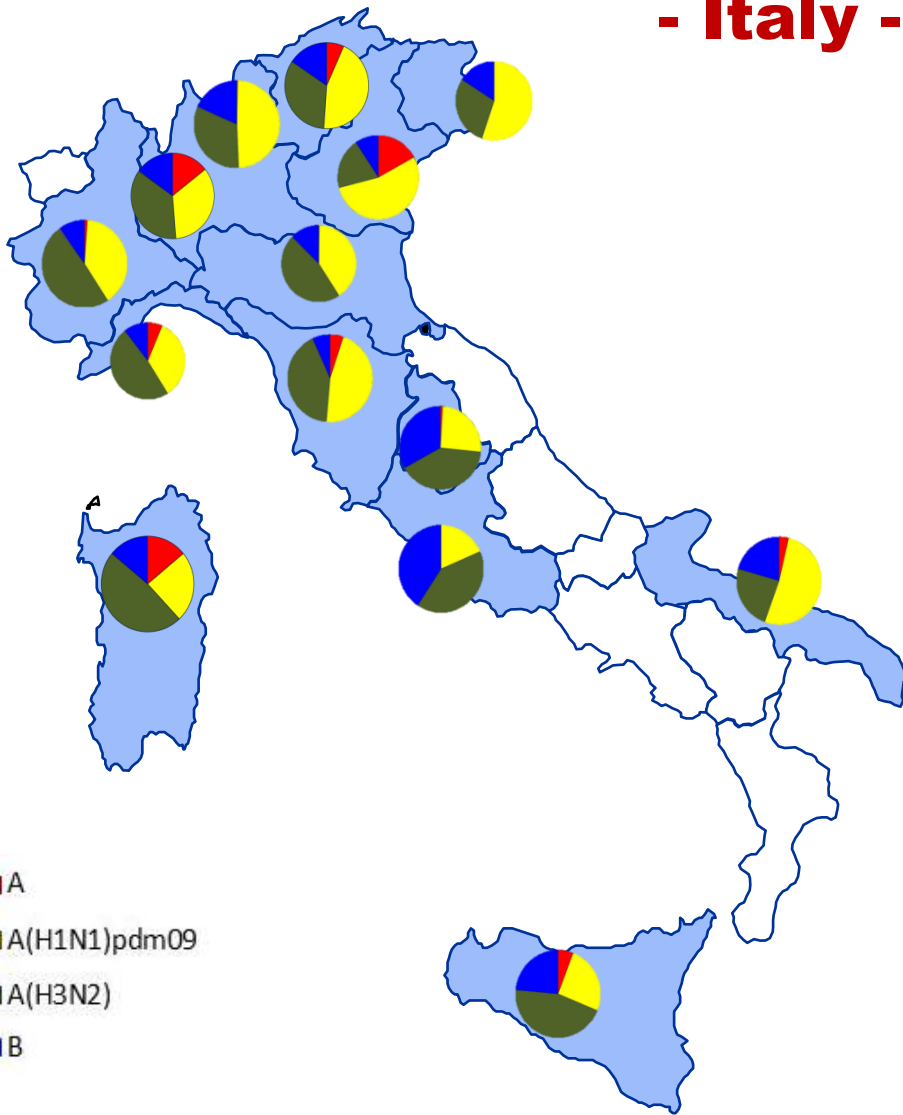
Type A: 3.108 (84%)

H3N2: 1.277 (41%)

H1N1: 1.608 (52%)

Not subtyped: 223 (7%)

Type B: 600 (16%)



Regions with InfluenzaNet laboratories

Problems With  
**A/H3N2** Virus  
Characterisation

# Influenza virological overview

## - Italy -

Phylogenetic comparison  
of **A/H3N2** HA genes

Vaccine virus 2015/16

Vaccine virus 2014/15

Reference viruses

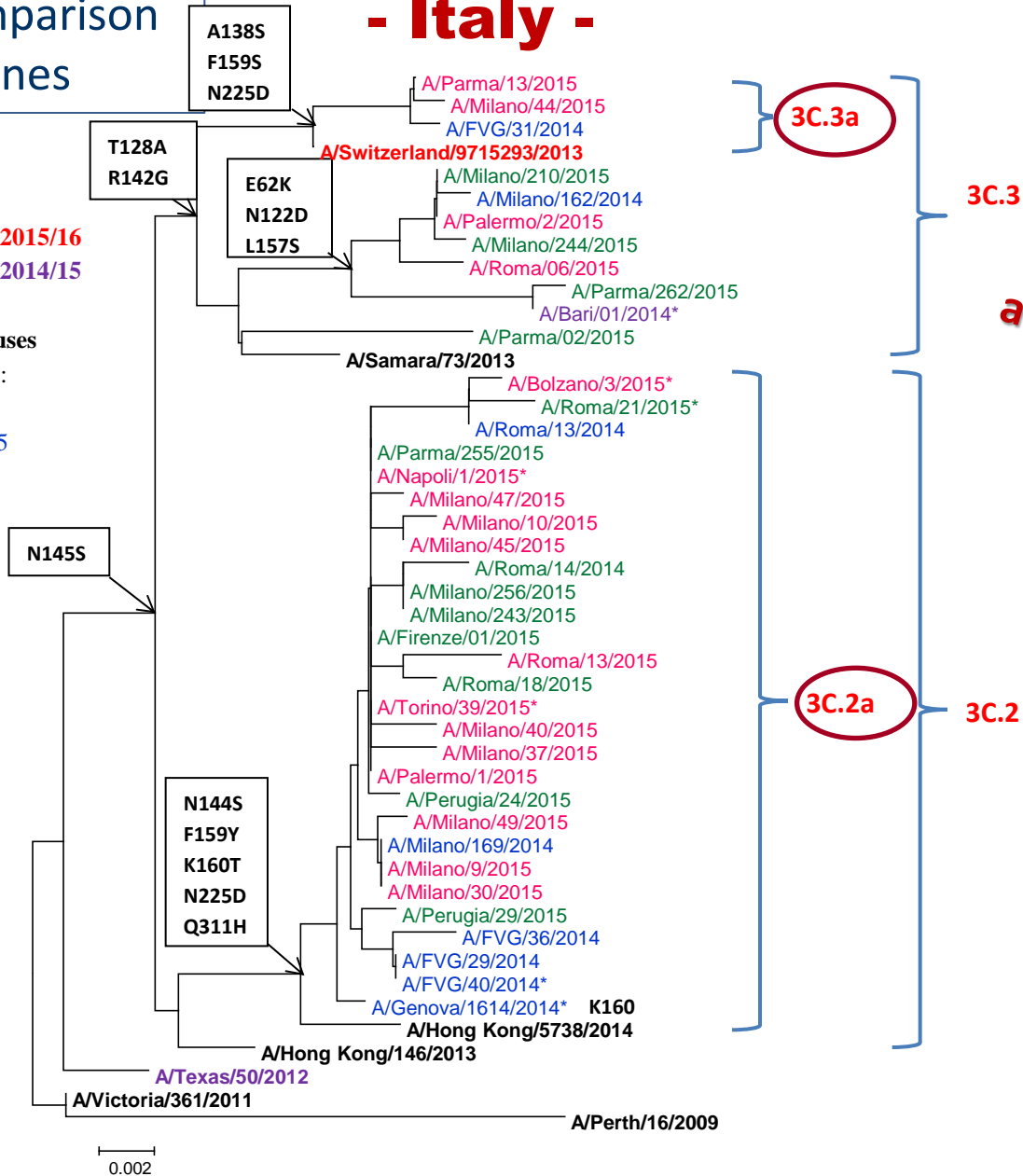
Collection date:

October 2014

December 2015

January 2015

February 2015



antigenic drift



# Loss of Red Blood Cell Binding by Many Recent H3N2 Viruses

Virus		Haemagglutination titre		
		Chicken	Turkey	Guinea Pig
X31 (A/Aichi/2/68)		2048	4096	1024
A/Toulouse/878/2001		4	512	256
A/Trieste/2/2003		<	16	128
A/Finland/486/2004		<	512	1024
A/Hong Kong/4443/2005		<	<	32
A/Esfahan/6117/2010		<	<	64
A/Hong Kong/3615/2010		<	<	64

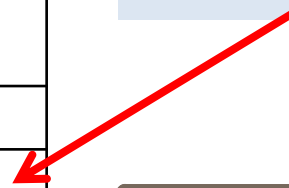
addition of  
20 nM Oseltamivir



## 2013-2014 viruses

A/Iceland/08202/2014	3C.3	<	<	16
A/Switzerland/9715293/2013	3C.3a	<	8	32
A/Hong Kong/6315/2014	3C.3a	<	<	16
A/Hong Kong/6013/2014	3C.2a	<	<	<
A/Hong Kong/7278/2014	3C.2a	<	<	<

All the WHO CCs reported difficulties with 3C.2a viruses failing to agglutinate red blood cells of any species.

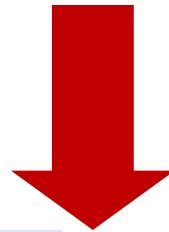




# Human seasonal **A/H3N2** viruses



Lack of red blood cell agglutination



Risk of viruses causing CPE failing to be correctly identified as an influenza virus

Impact on other viral properties?

Alternative assays:  
Sialidase assay (MUNANA, NA Star)  
ELISA (NP or M)  
Infectivity neutralization assay

# Influenza virological overview

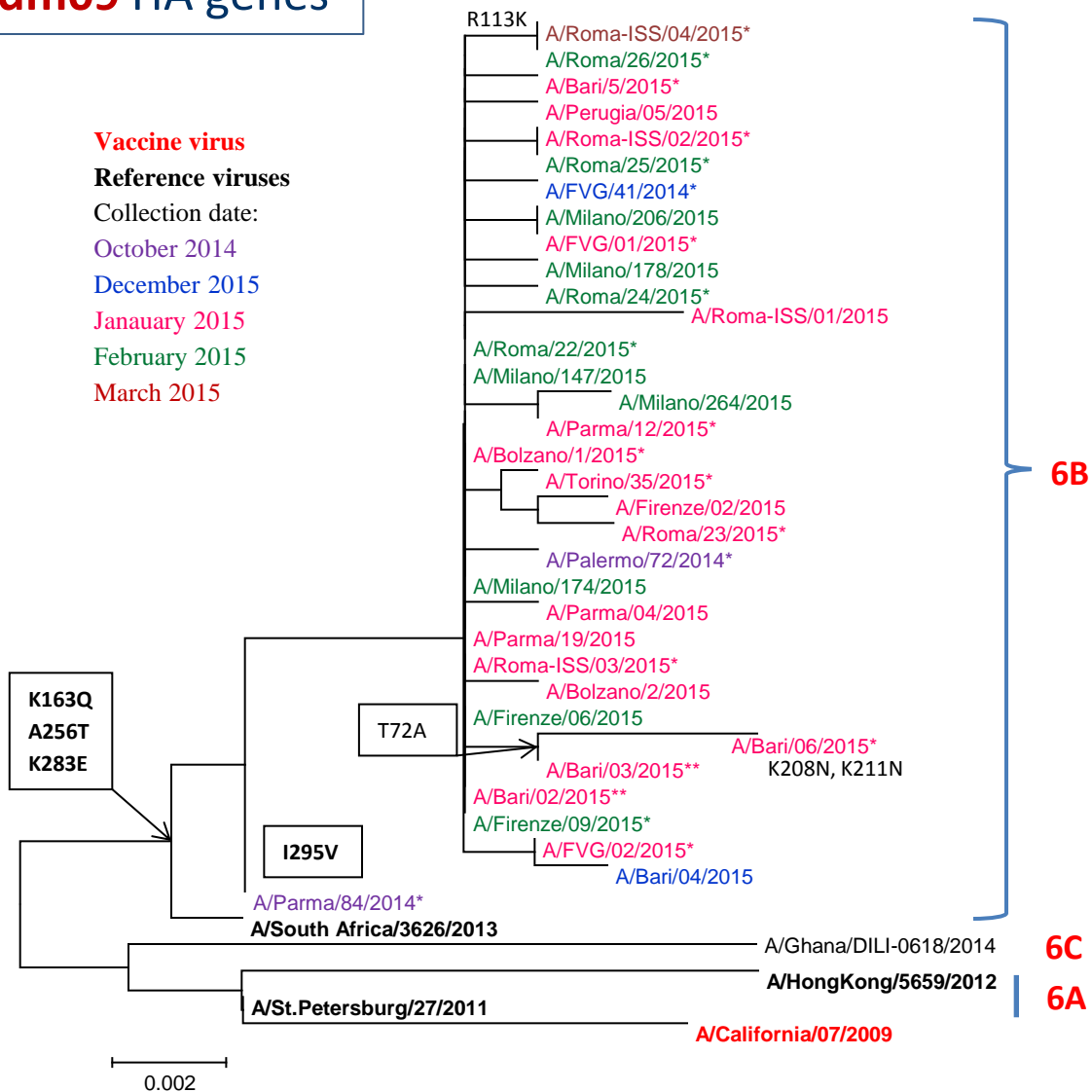
## - Italy -

A/H1N1 Viruses

# Influenza virological overview

## - Italy -

Phylogenetic comparison  
of **A/H1N1pdm09** HA genes



# Transmission of Hemagglutinin D222G Mutant Strain of Pandemic (H1N1) 2009 Virus

Simona Puzelli, Marzia Facchini, Domenico Spagnolo, Maria A. De Marco, Laura Calzoletti, Alessandro Zanetti, Roberto Furnagalli, Maria L. Tanzi, Antonio Cassone, Giovanni Rezza, Isabella Donatelli, and the Surveillance Group for Pandemic A (H1N1) 2009 Influenza Virus in Italy<sup>1</sup>

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 5, May 2010

JOURNAL OF VIROLOGY, Nov. 2010, p. 12069–12074  
0022-538X/10/\$12.00 doi:10.1128/JVI.01639-10  
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## NOTES

### Altered Receptor Specificity and Cell Tropism of D222G Hemagglutinin Mutants Isolated from Fatal Cases of Pandemic A(H1N1) 2009 Influenza Virus<sup>†‡</sup>

Yan Liu,<sup>1§</sup> Robert A. Childs,<sup>1§</sup> Tatyana Matrosovich,<sup>2§</sup> Stephen Wharton,<sup>3</sup> Angelina S. Palma,<sup>4</sup> Wengang Chai,<sup>1</sup> Rodney Daniels,<sup>2</sup> Victoria Gregory,<sup>3</sup> Jennifer Uhlendorff,<sup>2</sup> Makoto Kiso,<sup>5</sup> Hans-Dieter Klenk,<sup>2</sup> Alan Hay,<sup>3</sup> Ten Feizi,<sup>1\*</sup> and Mikhail Matrosovich<sup>2\*</sup>

Short communication

HA222 polymorphism in Influenza A(H1N1) 2009 isolates from Intensive Care Units and ambulatory patients during three influenza seasons

F. Corcioli<sup>a</sup>, R. Arvia<sup>a</sup>, F. Pierucci<sup>a</sup>, V. Clausi<sup>a</sup>, M. Bonizzoli<sup>b</sup>, A. Peris<sup>b</sup>, A. Azzi<sup>a,\*</sup>

<sup>a</sup> Department of Experimental and Clinical Medicine, University of Florence, Viale Morgagni 48, 50134 Florence, Italy

<sup>b</sup> Anesthesia and Intensive Care Unit of Emergency Department, Careggi Teaching Hospital, Largo Brambilla 3, 50134 Florence, Italy

## RAPID COMMUNICATIONS

### Observed association between the HA1 mutation D222G in the 2009 pandemic influenza A(H1N1) virus and severe clinical outcome, Norway 2009–2010

A Kilander<sup>a</sup>, R Rylkivini<sup>a</sup>, S G Dudman<sup>a</sup>, O Hungnes (olav.hungnes@fhi.no)<sup>a</sup>

<sup>1</sup> Department of Virology, Norwegian Institute of Public Health, Oslo, Norway

Citation style for this article:

Citation style for this article: Kilander A, Rylkivini R, Dudman SG, Hungnes O. Observed association between the HA1 mutation D222G in the 2009 pandemic influenza A(H1N1) virus and severe clinical outcome, Norway 2009–2010. *Euro Surveill.* 2010;15(5):pii=19498. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19498>

This article has been published on 4 March 2010

DOI:10.1111/ir.12146  
[www.influenzajournal.com](http://www.influenzajournal.com)

Original Article

### A(H1N1)pdm09 hemagglutinin D222G and D222N variants are frequently harbored by patients requiring extracorporeal membrane oxygenation and advanced respiratory assistance for severe A(H1N1)pdm09 infection

Tina Ruggiero,<sup>a</sup> Francesco De Rosa,<sup>b\*</sup> Francesco Cerutti,<sup>a</sup> Nicole Pagani,<sup>b</sup> Tiziano Allice,<sup>a</sup> Maria L. Stella,<sup>b</sup> Maria G. Milia,<sup>a</sup> Andrea Calcagno,<sup>b</sup> Elisa Burdino,<sup>a</sup> Gabriella Gregori,<sup>a</sup> Rosario Urbino,<sup>c</sup> Giovanni Di Perri,<sup>b</sup> Marco V. Ranieri,<sup>c</sup> Valeria Ghisetti<sup>a\*</sup>

## DISPATCHES

### Severity of Influenza A(H1N1) Illness and Emergence of D225G Variant, 2013–14 Influenza Season, Florida, USA

Nicole M. Iovine, J. Glenn Morris, Jr., Kristianna Fredenburg, Kenneth Rand, Hassan Alnuaimat, Gloria Lipori, Joseph Brew, John A. Lednicky

Despite a regional decline in influenza A(H1N1)pdm09 virus infections during 2013–14, cases at a Florida hospital were more severe than those during 2009–10. Examined strains had a hemagglutinin polymorphism associated with enhanced binding to lower respiratory tract receptors. Genetic changes in this virus must be monitored to predict the effect of future pandemic viruses.

During the same period in 2013–14, a 12,496 (Figure 1) (1.67%) of 746,560 illnesses met definition ( $p < 0.0001$  by  $\chi^2$  test) (Figure 1).

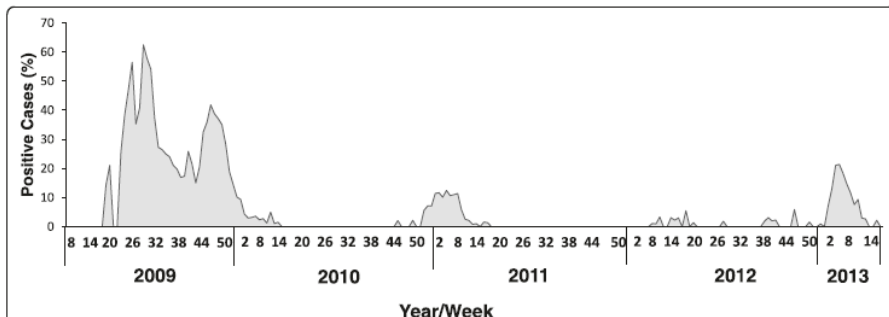
During September 1, 2013–March 21, 2014, 20 rapid test results for influenza-positive inpatient outpatients at a major tertiary referral center for the Florida region. Rapid point-of-care and respiratory panel tests were performed: 808 (>97%) of 826 samples were influenza A virus, and of 181 samples typed, 163 (90%) were H1N1 virus. During this 387 patients with laboratory-confirmed influenza admitted to the hospital; 15 died, yielding an influenza

RESEARCH ARTICLE

Open Access

## Return of pandemic H1N1 influenza virus

Hilda Sherbany<sup>1</sup>, John McCauley<sup>2</sup>, Tal Meningher<sup>1,3</sup>, Musa Hindiyeh<sup>3</sup>, Rita Dichtiar<sup>4</sup>, Michal Perry Markovich<sup>4</sup>, Ella Mendelson<sup>1,5</sup> and Michal Mandelboim<sup>1\*</sup>



**Figure 1** Distribution of H1N1 pandemic virus infection in hospitalized patients. The percentage of patients hospitalized (on a weekly basis, X axis) due to influenza-like syndrome and infected with the pandemic 2009 influenza virus.

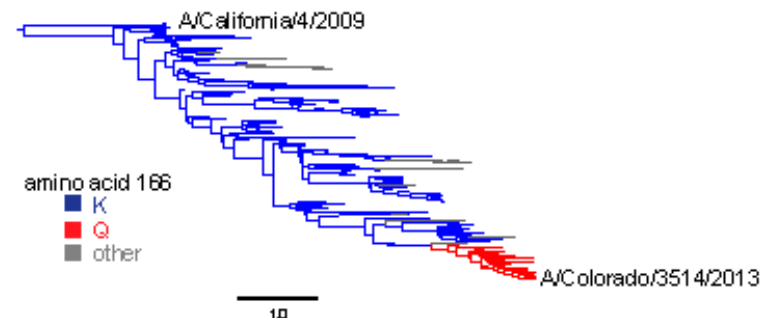
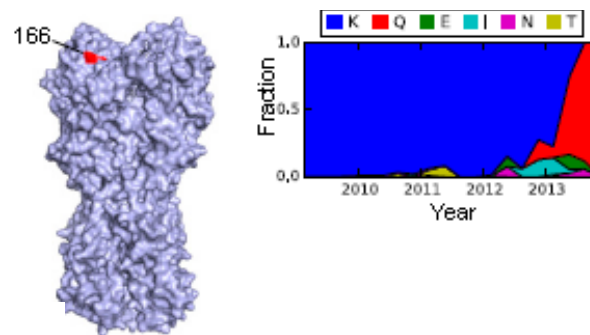
## Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013–2014 influenza season

Susanne L. Linderman<sup>a,b,1</sup>, Benjamin S. Chambers<sup>a,c,1</sup>, Seth J. Zost<sup>a,c,1</sup>, Kaela Parkhouse<sup>a</sup>, Yang Li<sup>a,c</sup>, Christin Herrmann<sup>a,c</sup>, Ali H. Ellebedy<sup>d,e</sup>, Donald M. Carter<sup>f</sup>, Sarah F. Andrews<sup>g</sup>, Nai-Ying Zheng<sup>g</sup>, Min Huang<sup>g</sup>, Yunping Huang<sup>g</sup>, Donna Strauss<sup>h</sup>, Beth H. Shatz<sup>i</sup>, Richard L. Hodinka<sup>h,i</sup>, Gustavo Reyes-Terán<sup>k</sup>, Ted M. Ross<sup>l</sup>, Patrick C. Wilson<sup>g</sup>, Rafi Ahmed<sup>d,e</sup>, Jesse D. Bloom<sup>l</sup>, and Scott E. Hensley<sup>a,b,c,2</sup>

15798 15803 | PNAS | November 4, 2014 | vol. 111 | no. 44

- Human sera that had K166 HA-specificity based on HAI assays failed to efficiently neutralize K166Q-possessing viruses in *in vitro* neutralization assay
- pH1N1 viruses with K166Q mutation are antigenically indistinguishable from the A/California/7/2009 pH1N1 vaccine strain

## K166Q HA mutation (at the interface of the Sa/Ca antigenic sites)

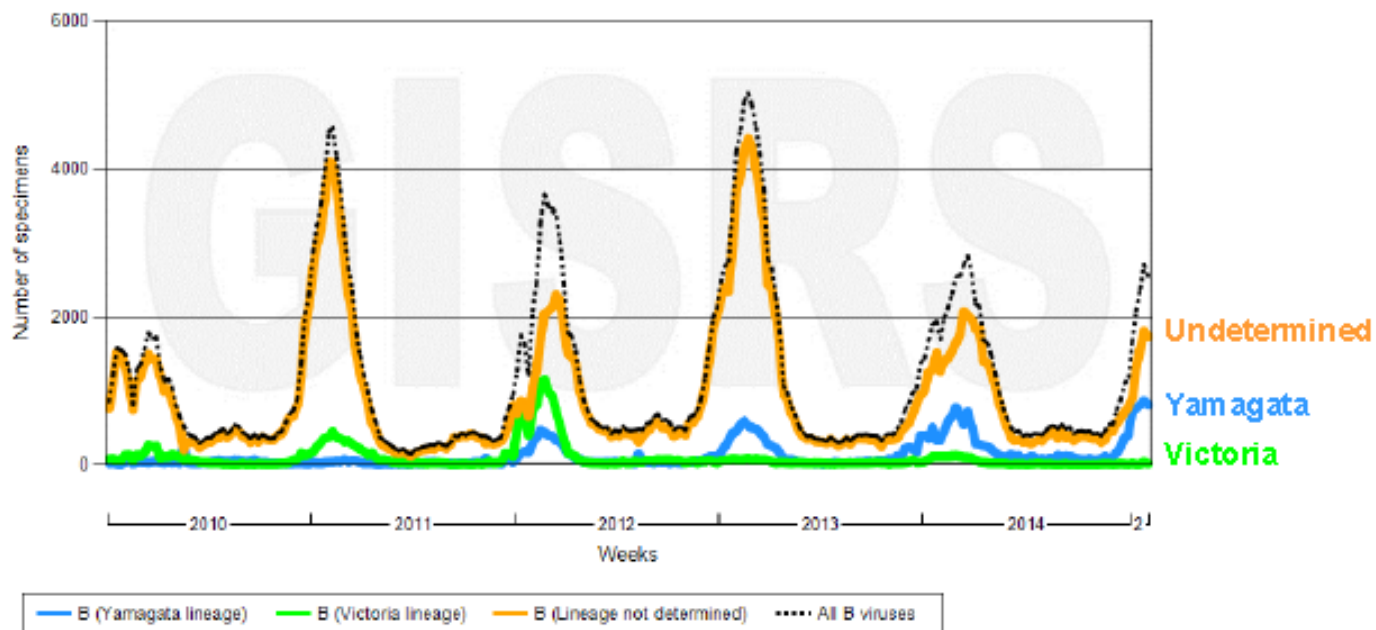


# Influenza virological overview - Italy -

B Viruses

# Global circulation of influenza B viruses

Number of specimens positive for influenza by subtype



Data source: FluNet ([www.who.int/flu-net/](http://www.who.int/flu-net/)), GISRS

© World Health Organization 2014

WHO Information Meeting on the Composition of Influenza Virus Vaccines for the Northern Hemisphere 2015 – 2016

26 February 2015, WHO Geneva, Switzerland



World Health Organization

35



# Influenza virological overview

## - Italy -

Phylogenetic comparison  
of **B** HA genes

**Vaccine virus 2015/16**

Vaccine virus 2014/15

Reference viruses

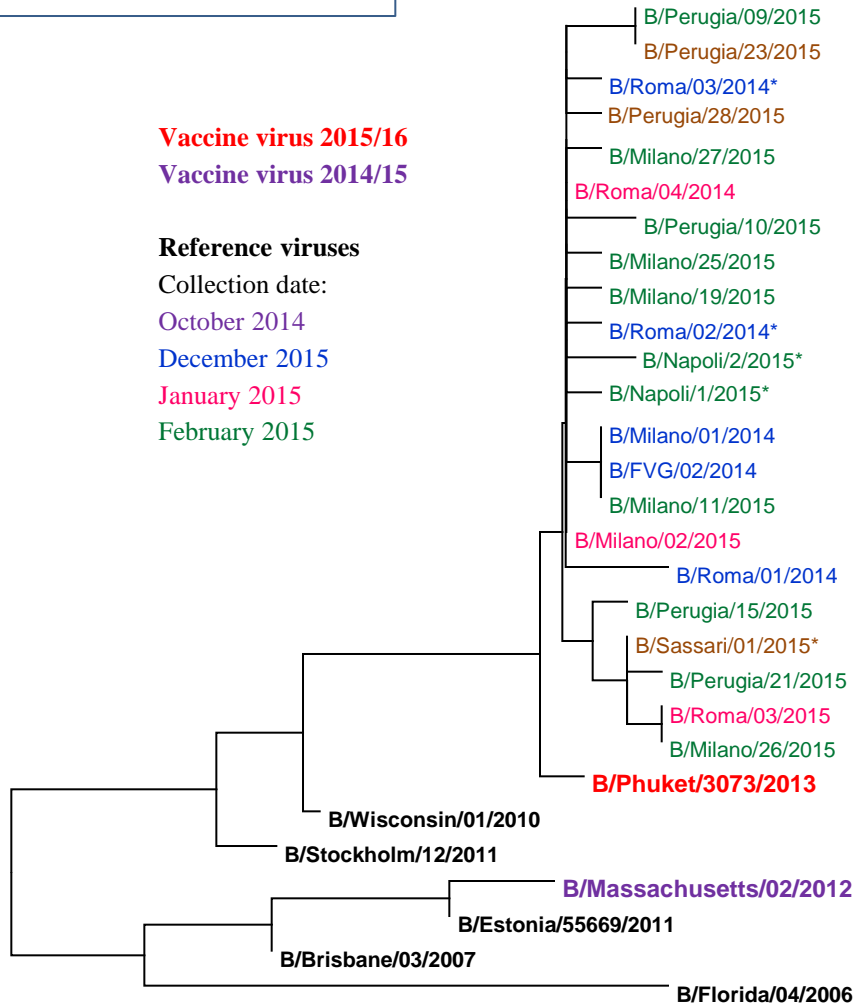
Collection date:

October 2014

December 2015

January 2015

February 2015



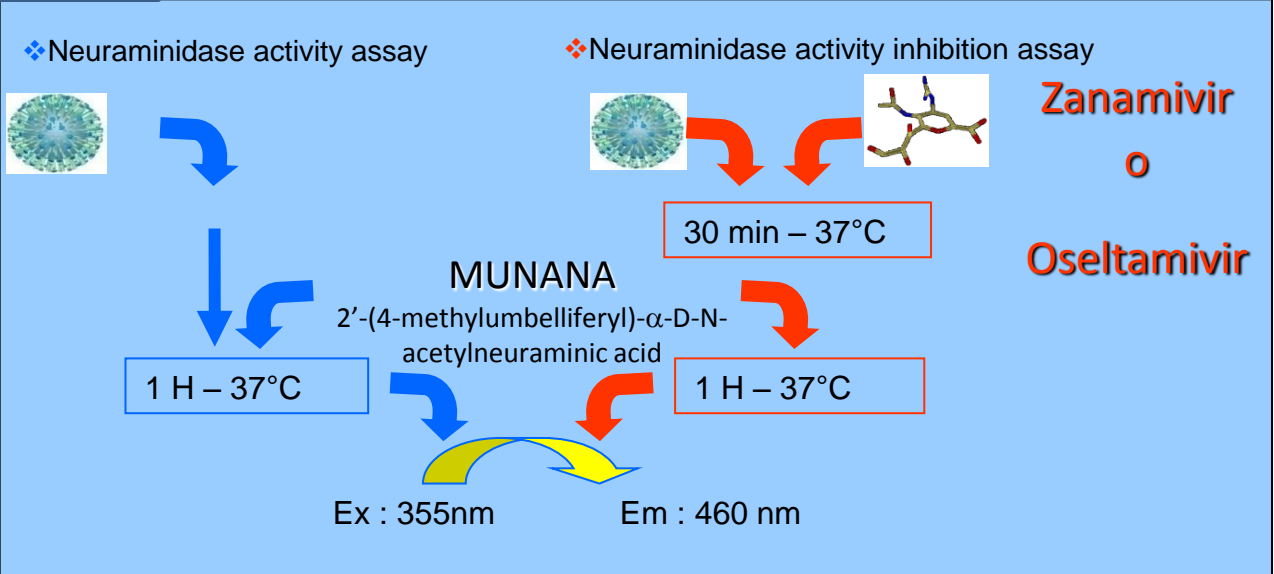
*antigenic drift*

# Antiviral resistance

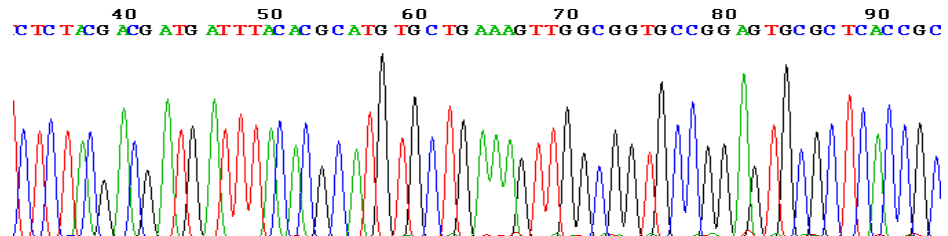


## Assays

1. phenotypic, IC50 values



2. genotypic, based on aa substitutions known to be associated with reduced susceptibility



# Antiviral resistance

Virus Type/Subtype	Susceptibility to Neuraminidase Inhibitors (phenotypic assay - MUNANA)					
	Oseltamivir			Zanamivir		
	Isolates tested	Mean IC <sub>50</sub>	Phenotypic interpretation	Isolates tested	Mean IC <sub>50</sub>	Phenotypic interpretation
A/H1N1	56	1.36	NI	56	0.6	NI
A/H3N2	19	0.6	NI	19	0.4	NI
B	17	27	NI	17	2.4	NI

Category	Fold IC50 change *	
	Type A viruses	Type B viruses
Normal inhibition (NI)	< 10	< 5
Reduced inhibition (RI)	10-100	5-50
Highly reduced inhibition (HRI)	>100	>50

\* Fold change against the median/mean IC50 for the (sub)type previous or current season after removal of obvious outliers, or against a known wild type virus of the same subtype.

# Influenza virological overview for Italy

- Over the course of the 2014-15 influenza season **A(H3N2)** and **A(H1N1)pdm09** and **type B viruses** have co-circulated in Italy. In particular, high-intensity influenza activity by both **A(H3N2)** and **A(H1N1)pdm09** was reported.
- The **A(H1N1)pdm09** viruses characterized, as those circulating worldwide, belonged to genetic subgroup **6B** and were antigenically similar to the vaccine strain **A/California/7/09** virus.
- Many of the **A(H3N2)** viruses characterized genetically, fell in genetic subgroups **3C.3a** and **3C.2a** and were antigenically distinct from the vaccine virus **A/Texas/50/2012**.
- Influenza **B viruses** of the **B/Yamagata** lineage predominated over those of the **B/Victoria** lineage, and were antigenically closely related to the new variant **B/Phuket/3073/2013**.
- All viruses tested were susceptible to NA inhibitors.

# WHO recommendation on the composition of influenza virus vaccines for the northern hemisphere **2015 – 2016**

- Geneva, Switzerland, February 2015 -

2014-2015	2015-2016
A/California/7/2009 (H1N1)pdm09	A/California/7/2009 (H1N1)pdm09
A/Texas/50/2012 (H3N2)	<b>A/Switzerland/9715293/2013 (H3N2)</b>
B/Massachusetts/2/2012 (Yamagata lineage)	<b>B/Phuket/3073/2013 (Yamagata lineage)</b>

*antigenic drift*

*antigenic drift*

## Quadrivalent vaccines

B/Brisbane/60/2008 (Victoria lineage)	B/Brisbane/60/2008 (Victoria lineage)
---------------------------------------	---------------------------------------

# Zoonotic Influenza

**WHO Information Meeting  
on the composition of influenza virus vaccines  
for the northern hemisphere  
2015 - 2016  
and  
Round-table discussion**

26 February 2015  
WHO HQ, Geneva

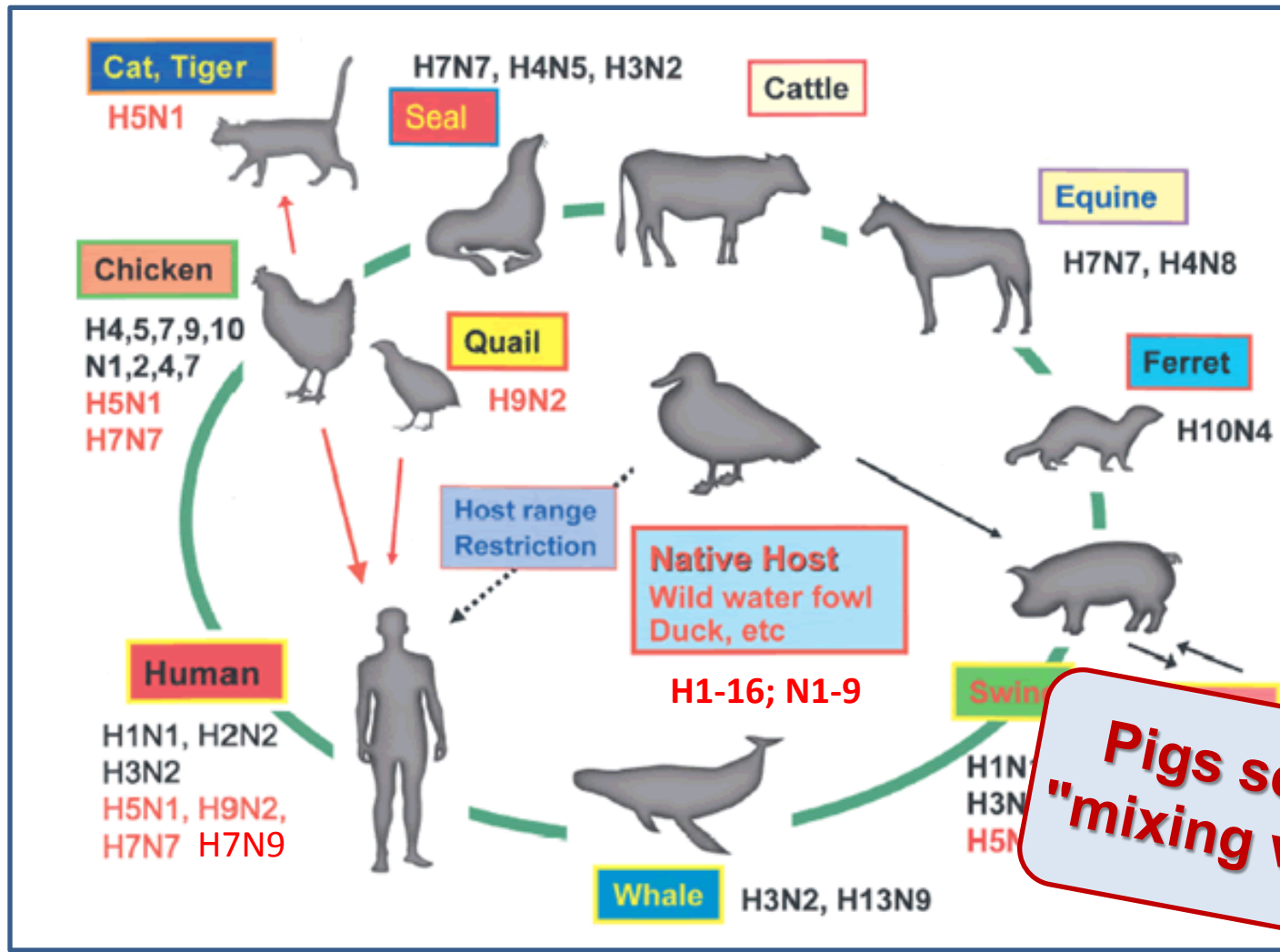


**Zoonotic influenza viruses  
September 2014 – January 2015**

**Richard Webby  
Director, WHOCC ST JUDE, USA**



# Influenza A virus in nature



**Pigs serve as "mixing vessels"**

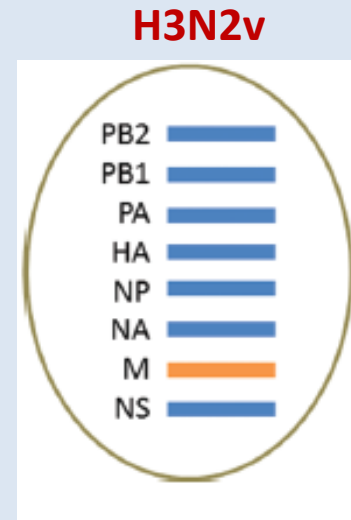


**Pigs represent a continual public health threat**

# Human infections with influenza A(H3N2) variant virus (H3N2v) in USA



- As of May 2015, CDC received reports of **351 human infections** with H3N2v virus
- This virus is similar to triple-reassortant viruses detected in US swine since the 1990s, but had also acquired the **M** gene from the pdm09 virus
- Pre-existing antibody-mediated immunity against seasonal H3N2 viruses appears to provide little or no protection against infection with the new antigenic H3N2v.



The potential for this H3N2v virus to transmit efficiently is of concern

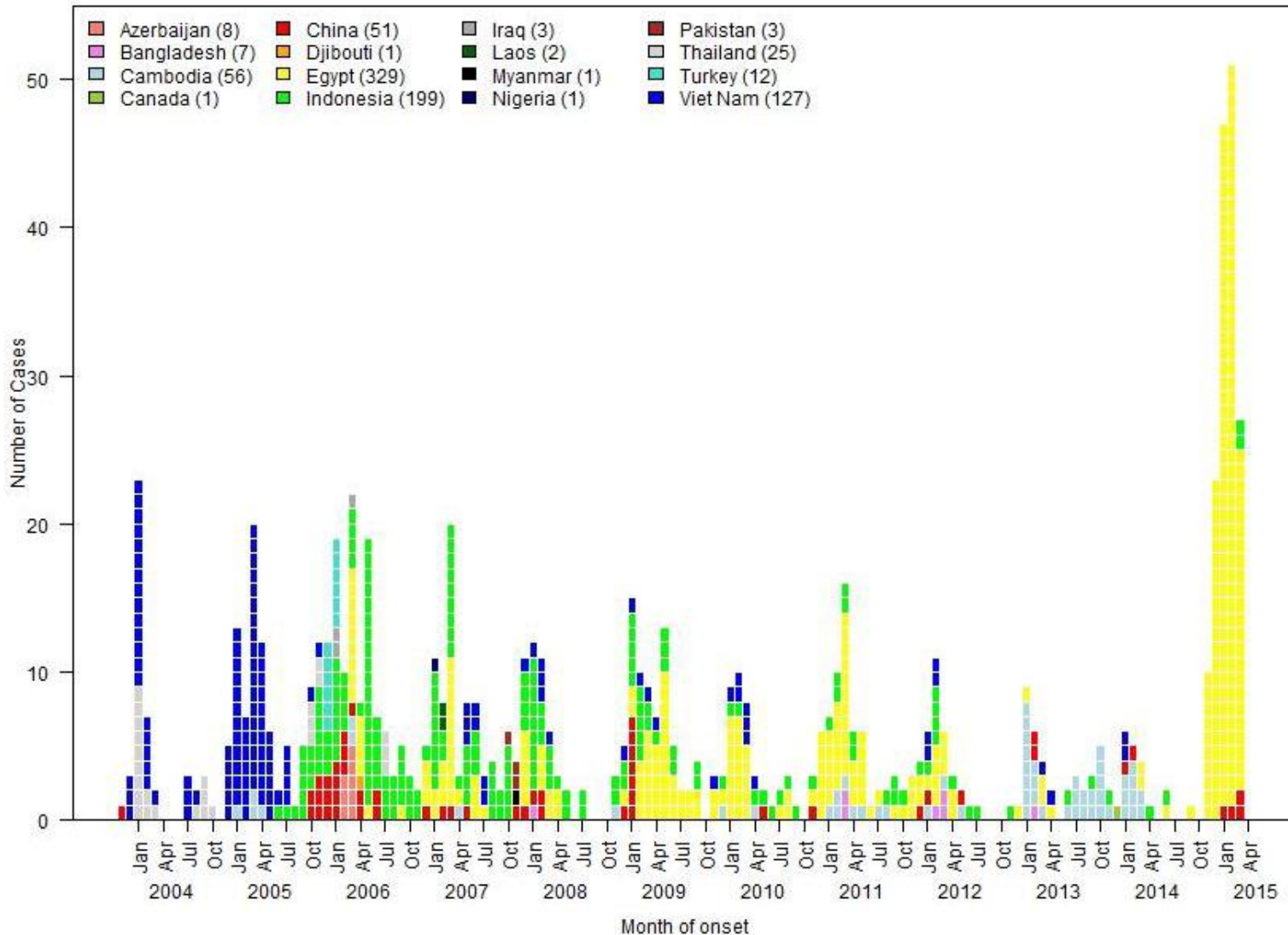
**Human infection  
with avian  
influenza viruses**

Subtype	Pathogenicity in chickens	Country reporting/year of first report in human	Lab-confirmed human cases	Clinical severity	Viruses found in birds
<b>A(H5N1)</b>	HPAI	Azerbaijan/2006 Bangladesh/2008 Cambodia/2005 Canada/2014 China/1997 Djibouti/2006 Egypt/2006 Indonesia/2005 Iraq/2006 Lao People's Democratic Republic/2007 Myanmar/2007 Nigeria/2007 Pakistan/2007 Thailand/2004 Turkey/2006 Viet Nam/2004	18 in 1997, 784 since re-emergence in 2003	Severe, high fatality	Enzootic in some countries
<b>A(H5N6)</b>	HPAI	China/2014	3	Severe	Detected in poultry in China
<b>A(H6N1)</b>	LPAI	China/2013	1	Moderate	Circulates in bird populations worldwide
<b>A(H7N2)</b>	LPAI	United Kingdom/2007 USA/2003	5	Mild to moderate	Detected in poultry
<b>A(H7N3)</b>	LPAI/HPAI	Canada/2004 Mexico/2012 United Kingdom/2006	5	Mild	Circulates in bird populations worldwide
<b>A(H7N7)</b>	LPAI/HPAI	Italy/2013 Netherlands/2003 United Kingdom/1995	96	Mild	Circulates in bird populations worldwide
<b>A(H7N9)</b>	LPAI	China/2013 Canada/2015 Malaysia/2014	602	Severe, high fatality	Detected in chickens and in poultry markets in China
<b>A(H9N2)</b>	LPAI	Bangladesh/2011 China/1998 Egypt/2015	19	Usually mild	Endemic in poultry in Africa, Asia and the Middle East
<b>A(H10N7)</b>	LPAI	Australia/2010 Egypt/2004	4	Mild	Circulates in bird populations worldwide
<b>A(H10N8)</b>	LPAI	China/2013	3	Severe, fatal	Limited information on circulations in birds

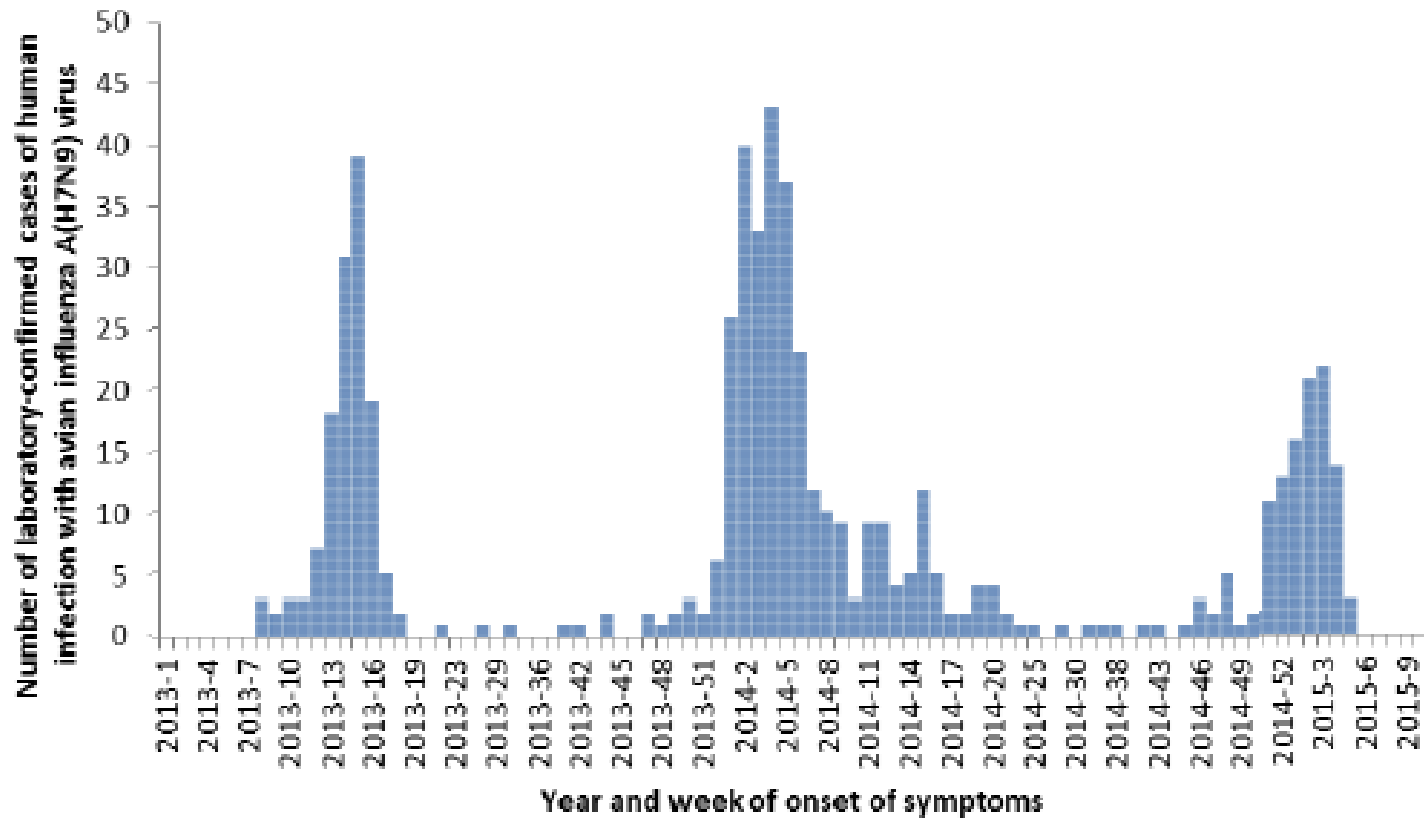
# Influenza A/H5N1 virus



826 lab-confirmed hu cases (413 deaths) reported from 16 countries



# Influenza A/H7N9 virus, China

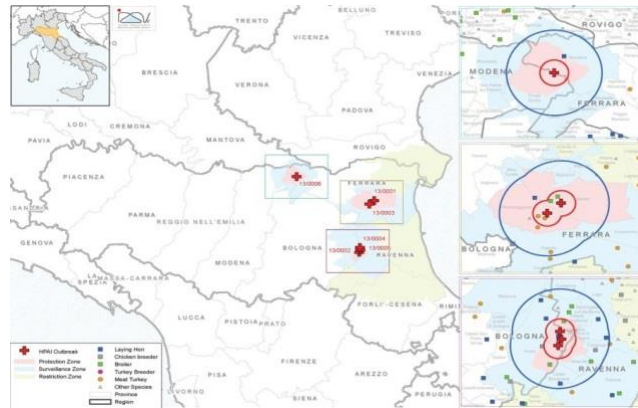


H5N1: 826 infections (since 1997)

H7N9: 631 infections (since 2013)

# Avian influenza A/H7N7 virus - Italy, 2013 -

- August 9, 2013
- 6 farms with infected poultry
- Culling: > 1 million chickens



- **3 poultry workers with conjunctivitis**
- **the viruses from humans were closely related to those from chickens**

## Short Communication

### Highly pathogenic H7N7 avian influenza in Italy

L. Bonfanti, I. Monne, M. Tamba,  
U. Santucci, P. Massi, T. Patregnani,  
L. Loli Piccolomini, S. Natalini, G. Ferri,  
G. Cattoli, S. Marangon

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 10, October 2014

## Human Infection with Highly Pathogenic A(H7N7) Avian Influenza Virus, Italy, 2013

Simona Puzelli, Giada Rossini, Marzia Facchini,  
Gabriele Vaccari, Livia Di Trani,  
Angela Di Martino, Paolo Gaibani,  
Caterina Vocale, Giovanni Cattoli,  
Michael Bennett, John W. McCauley,  
Giovanni Rezza, Maria Luisa Moro,  
Roberto Rangoni, Alba Carola Finarelli,  
Maria Paola Landini, Maria Rita Castrucci,  
Isabella Donatelli, and the Influenza Task Force

# Warning signals from the volatile world of influenza viruses (February 26, 2015)



The current global influenza situation is characterized by a number of trends that must be closely monitored. These include:

- an increase in the **variety of influenza viruses co-circulating** and exchanging genetic material, giving rise to novel strains
- continuing cases of **human H7N9** infections in China
- recent increase of **human H5N1** cases in Egypt



Additional adaptive mutations and/or reassortment with circulating human viruses may enable **H5N1** or **H7N9** viruses to efficiently infect humans and transmit among them, resulting in an influenza pandemic.



# Human-Animal Interface

Zoonotic outbreaks



Human exposure



Early warning for an impending emergence of a virus  
with pandemic potential



Evaluate the extent of infection

Systematic investigations of close contacts of infected  
patients and into the transmission potential of the new  
virus



# Acknowledgments



## **NIC - MIPI**

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