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Published in:
Eurosurveillance (Online Edition)

DOI:
10.2807/1560-7917.ES.2016.21.13.30184

Publication date:
2016

Document version:
Final published version

Predominance of influenza A(H1N1)pdm09 virus genetic subclade 6B.1 and influenza B/Victoria lineage viruses at the start of the 2015/16 influenza season in Europe

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Citation style for this article:
Broberg E, Melidou A, Prosenc K, Bragstad K, Hungnes O, on behalf of the WHO European Region and the European Influenza Surveillance Network members of the reporting countries. Predominance of influenza A(H1N1)pdm09 virus genetic subclade 6B.1 and influenza B/Victoria lineage viruses at the start of the 2015/16 influenza season in Europe. Euro Surveill. 2016;21(13):pii=30184. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.13.30184

Article submitted on 09 March 2016 / accepted on 31 March 2016 / published on 31 March 2016

Influenza A(H1N1)pdm09 viruses predominated in the European influenza 2015/16 season. Most analysed viruses clustered in a new genetic subclade 6B.1, antigenically similar to the northern hemisphere vaccine component A/California/7/2009. The predominant influenza B lineage was Victoria compared with Yamagata in the previous season. It remains to be evaluated at the end of the season if these changes affected the effectiveness of the vaccine for the 2015/16 season.

For the current northern hemisphere season, several reports have indicated intense influenza activity [1-5]. We analysed virological surveillance data from 20 European countries to study the genetic and antigenic characteristics of the circulating influenza viruses and compare them with the vaccine viruses and previously circulating strains.

Virological influenza surveillance in Europe, influenza season 2015/16

Virological influenza surveillance data in the World Health Organization (WHO) European Region are collected on a weekly basis and reported to The European Surveillance System (TESSy), a database hosted by the European Centre for Disease Prevention and Control (ECDC), as previously described [6]. From week 40/2015 to week 4/2016, 49 Member States of the Region reported influenza virus detections to TESSy, including 20 Member States (Belgium, Croatia, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Latvia, Netherlands, Norway, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom (UK)) that also reported antigenic or genetic characterisation data.

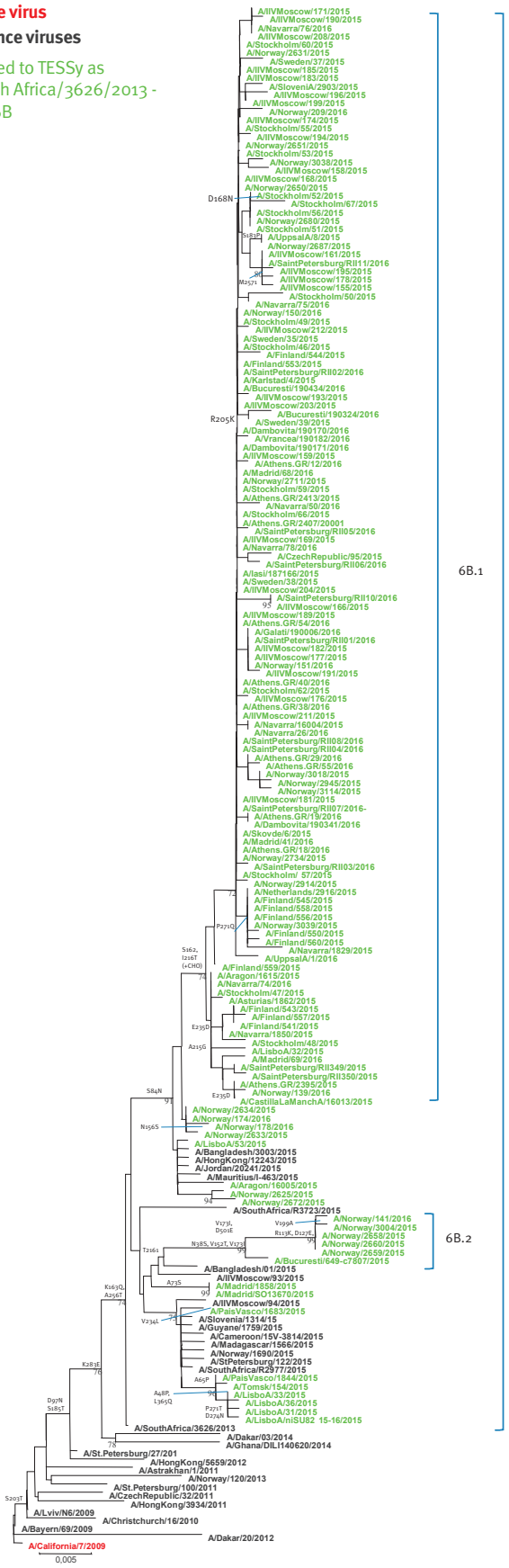
The antigenic and genetic reporting categories for TESSy are predefined by the WHO Collaborating Centre for Reference and Research on Influenza, London, for each influenza season. For antigenic characterisation, to denote a virus isolate as being like a vaccine or reference virus its haemagglutination inhibition (HI) titre with post-infection ferret antiserum raised against the reference virus should differ by no more than fourfold. For genetic characterisation, the allocation to reporting category is based on the phylogenetic and amino acid sequence analyses of haemagglutinin (HA) gene.

The summary analysis of the data are presented weekly in the Joint ECDC–WHO Regional Office for Europe weekly 'Flu News Europe' (http://flunewseurope.org/). Data on detections, antigenic and genetic characterisations were extracted on 8 February 2016 for analysis.

Between week 40/2015 and week 4/2016, influenza viruses were detected in 1,879 (19%) of 9,882 sentinel specimens tested in the 20 countries also reporting on virus characterisation. Of these 1,879 specimens, 1,512 (80%) were positive for type A influenza virus and 367 (20%) for type B. Of 1,441 subtyped influenza A viruses, 1,268 (88%) were A(H1N1)pdm09. Of 129 type B viruses with known lineage, 115 (89%) were of the B/Victoria/2/1987 lineage.

Figure 1

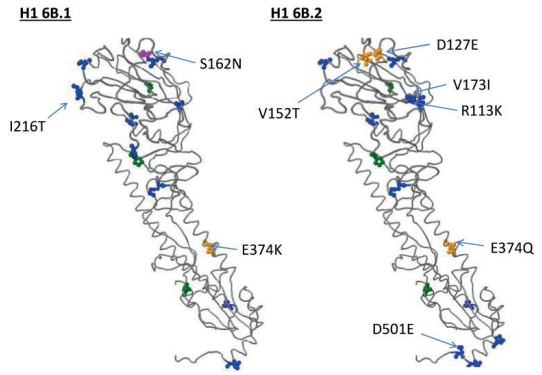
Phylogenetic analysis of A(H1N1)pdm09 haemagglutinin (HA) nt sequences reported from European countries, between week 40/2015 and 4/2016



Some sequences obtained in this study were not used to construct the phylogenetic tree because they were identical and redundant. The sequences used for the phylogenetic analysis were moreover only those of suitable length, and encode HA1 amino acids 3–327. These included sequences reported by the Czech Republic, Finland, Greece, Netherlands, Norway, Portugal, Romania, Russia, Slovenia, Spain and Sweden as well as sequences from reference A(H1N1)pdm09 viruses. The tree was constructed with the neighbour-joining method, using Kimura-2 parameter-corrected distances and bootstrapped with 1,000 replicates, Molecular Evolutionary Genetics Analysis (MEGA) software version 5.0.

Figure 2

Protein structure model (FluSurver-JSmol) of the haemagglutinin protein monomer of A(H1N1)pdm09 subclade 6B.1, represented by A/Norway/2650/2015 (left), and subclade 6B.2, represented by A/Norway/2658/2015 (right)



Amino acid differences compared with A/California/07/2009 are indicated in colour. Well-known differences are marked in blue. Common variant marker positions are indicated in green. Amino acid involved in virulence or antigenic drift is marked in orange. Amino acid not previously associated with a specific feature is marked in grey. Amino acid that creates a new potential N-glycosylation site is marked in magenta.

Virus characterisation

Between weeks 40/2015 and 4/2016, 447 (24%) of 1,879 influenza viruses were attributed to a genetic group by 16 countries (Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Netherlands, Norway, Portugal, Romania, Russia, Slovenia, Spain, Sweden and UK), and 429 (23%) were attributed to an antigenic category by also 16 reporting countries (Croatia, Czech Republic, Denmark, Finland, Germany, Greece, Latvia, Netherlands, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Switzerland and UK) (Table 1).

The majority (68%) of all genetic characterisations were reported from Norway (n=84), Spain (n=66), Germany (n=54), Russia (n=54) and Sweden (n=46). The majority (70%) of antigenic reports were from Russia (n=124), Portugal (n=99) and Germany (n=78). For 150 viruses, reported in strain-based manner, both genetic and antigenic data were available.

All 313 A(H1N1)pdm09 viruses characterised genetically fell in clade 6, subgroup 6B, represented by A/South Africa/3626/2013. Viruses falling in this genetic subgroup, were all attributed to an antigenic category A/California/7/2009 that corresponds to the component included in the 2015/16 northern hemisphere vaccines.

Of the 77 A(H3N2) viruses attributed to a genetic group, 50 (65%) fell into genetic subgroup 3C.2a (represented by A/Hong Kong/4801/2014) that has been shown to be antigenically similar to A/Hong Kong/4801/2014 and also to the current A(H3N2) vaccine virus A/Switzerland/9715293/2013 (Table 1). Twenty-six A(H3N2) viruses fell into the vaccine virus category of 3C.3a subgroup. Viruses in subgroup 3C.3b (represented by A/Stockholm/28/2014) constituted a substantial part (98/401) of the A(H3N2) viruses in Europe in the 2014/15 season [7], but none were yet reported by week 4/2016 (Table 1). Of 20 A(H3N2) viruses attributed to an antigenic category, 14 were A/Switzerland/9715293/2013-like and thus similar to the northern hemisphere 2015/16 vaccine component and six were A/Hong Kong/4801/2014-like, similar to the southern hemisphere 2016 vaccine component and recommendation for northern hemisphere 2016/17 season.

All of the 44 B/Victoria lineage viruses characterised genetically to date fell in the clade 1A, represented by B/Brisbane/60/2008 which is included in quadrivalent vaccines for northern hemisphere 2015/16. The 13 B/Yamagata lineage viruses all genetically resembled B/Phuket/3073/2013 recommended for inclusion in trivalent vaccines for northern hemisphere 2015/16. Thirty influenza B viruses were antigenically characterised, 29 as B/Brisbane/60/2008-like and one as B/Phuket/3073/2013-like.

Analysis of A(H1N1)pdm09 HA gene sequences from 12 countries (Czech Republic, Finland, Greece, Ireland, Netherlands, Norway, Portugal, Romania, Russia, Slovenia, Spain and Sweden) reported to TESSy, with provision of accession numbers in publicly accessible databases, confirmed that all these analysed viruses possessed the signature amino acid variations that define subgroup 6B viruses: D97N, K163Q, S185T, K283E and A256T [7-9]. All 215 analysed sequences, apart from two viruses isolated in Russia, also carried P83S and I321V substitutions in HA1.

The majority of sequences (173 of 215 TESSy-reported viruses) also possessed the amino acid signature of subclade 6B.1 and formed a separate branch in the phylogenetic analysis (Figure 1, Figure 2). The 6B.1 subclade is characterised by the amino acid substitutions S84N (present in a wider subgroup), S162N and I216T [8]. Six viruses carried amino acid substitutions V152T, V173I, D501E (the latter in HA2) characterising 6B.2 subclade. In addition the five most recently sampled of these six 6B.2 viruses all possessed the R113K, D127E and E374Q substitutions (Figure 1).

The highest number of accumulated variations in the known antigenic sites were observed in the antigenic site Ca. All subgroup 6B viruses possessed the K163Q substitution, while the vast majority (173/215; 80%) also possessed the S162N substitution in HA1, resulting in a gain of a potential glycosylation site. Additional

Table 1

Viruses attributed to genetic and antigenic groups[a], weeks 40/2015–04/2016

Genetic group	Number of viruses	Antigenic group	Number of viruses
A(H1N1)pdm09 A/South Africa/3626/2013 (subgroup 6B)[b]	313	A(H1N1)pdm09 A/California/7/2009-like	379
A(H3N2) A/Hong Kong/4801/2014 (subgroup 3C.2a)[b]	50	A(H3N2) A/Hong Kong/4801/2014-like	6
A(H3N2) A/Samara/73/2013 (subgroup 3C.3)[c]	1	No separate antigenic category; expected to resemble A/Stockholm/28/2014	–
A(H3N2) A/Stockholm/28/2014 (subgroup 3C.3b)[c]	0	A(H3N2) A/ Stockholm/28/2014-like	0
A(H3N2) A/Switzerland/9715293/2013 (subgroup 3C.3a)[b]	26	A(H3N2) A/Switzerland/9715293/2013	14
B/Phuket/3073/2013 (Yamagata lineage clade 3)[b]	13	B/Phuket/3073/2013 (Yamagata lineage) -like	1
B/Brisbane/60/2008 (Victoria lineage clade 1A)[d]	44	B/Brisbane/60/2008 (Victoria lineage) -like	29

The viruses which were genetically characterised are not necessarily the same than the viruses that were antigenically characterised.

[a] Genetic and antigenic groups used for reporting into The European Surveillance System are defined by World Health Organization Collaborating Centre for Reference and Research on Influenza for each influenza season. For antigenic characterisation, to denote a virus isolate as being like a vaccine or reference virus its haemagglutination inhibition (HI) titre with post-infection ferret antiserum raised against the reference virus should differ by no more than fourfold. For genetic characterisation, the allocation to reporting category is based on the phylogenetic and amino acid sequence analyses of haemagglutinin (HA) gene.

[b] These genetic groups contain viruses with antigenic properties similar to the viruses included in the trivalent influenza vaccine for 2015/16.

[c] These genetic groups contain viruses with antigenic properties dissimilar to the viruses included in the trivalent influenza vaccine for 2015/16.

[d] Viruses in this genetic group have antigenic properties similar to those of the vaccine component (B/Brisbane/60/2008) recommended for use in quadrivalent influenza vaccines for 2015/16.

variations observed were S162K, D168N, K170E, R205K, A215G, E235D and a partial A139D. Cb antigenic site variation A73S was observed in four viruses from Spain, one of which also possessed substitution N156K in Sa antigenic site. Another Norwegian virus had a N156S substitution in Sa antigenic site. Notably, all 6B.2 viruses and also two of the 6B viruses not belonging to any of the newly identified subgroups possessed substitutions affecting the loop that consists of amino acid positions 151 to 159 located adjacent to the receptor binding site.

When comparing the A(H1N1)pdm09 strains with the corresponding strain in the current northern hemisphere influenza vaccine, A/California/7/2009, the HA1 sequences (nt 1–981, amino acids 1–327) exhibited nt similarity of 96.8 to 98.0% and deduced amino acid similarity of 95.4 to 96.3%. Viruses within subclade 6B.1 exhibited higher HA nt heterogeneity, with similarities ranging between 98.8 and 100%, while within subclade 6B.2 strains exhibited higher nt similarity, ranging between 99.3 and 100%, as the group consists of fewer sequences and most of them from one region only. The viruses analysed phylogenetically are listed in Table 2.

Discussion

Continuous surveillance of influenza viruses is essential for detecting emerging new variant strains and providing viruses for vaccine production [10]. In Europe, within the detected A subtypes, influenza A(H1N1)pdm09 predominated during 2010/11, 2012/13 and 2013/14 seasons and concerned 97% [11], 62% [12] and 53% [13] of subtyped influenza viruses respectively, with variation in country-specific proportions. The A(H1N1)pdm09 vaccine component A/California/7/2009 has not been changed since the 2009 pandemic and the circulating A(H1N1)pdm09 viruses have remained antigenically similar to the virus included in the vaccines throughout the influenza 2009/10 to 2015/16 seasons. However, since 2013, several reports have indicated the emergence of an expanding subgroup of A(H1N1)pdm09 viruses, designated 6B [1,8,9]. This subgroup appeared in 2012/13 and became predominant in 2013/14 [14].

In this study, we observe the further emergence of a subclade within the 6B subgroup, designated 6B.1 [15], which accounted for the majority of the A(H1N1)pdm09 viruses detected across the WHO European Region during the first weeks of the 2015/16 influenza season. In addition, the surveillance data show a change in the predominant B virus lineage from B/Yamagata which predominated in the preceding three seasons in Europe to B/Victoria.

Our data are preliminary for this season and are based on influenza surveillance without detailed reporting of clinical symptoms or vaccination status. Our genetic analysis was only based on the HA gene and does not extend to changes e.g. in genes encoding internal proteins of influenza viruses. The data reported to TESSy do not include antigenic titres and therefore no direct analysis of antigenic properties was possible. However, the antigenic reports rely on national influenza centres' antigenic analysis that the viruses reported as like to vaccine virus were not more than fourfold different in HI titres from the vaccine or reference viruses.

Table 2a

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI685415	Netherlands	A/Netherlands/2916/2015	6/11/2015	National Institute for Public Health and the Environment (RIVM)	National Institute for Public Health and the Environment (RIVM)
EPI674853	Sweden	A/Stockholm/46/2015	9/10/2015	–	Swedish Institute for Infectious Disease Control
EPI674745	Sweden	A/Stockholm/47/2015	22/10/2015	–	Swedish Institute for Infectious Disease Control
EPI674753	Sweden	A/Stockholm/48/2015	24/10/2015	–	Swedish Institute for Infectious Disease Control
EPI674841	Sweden	A/Karlstad/4/2015	25/10/2015	–	Swedish Institute for Infectious Disease Control
EPI674777	Sweden	A/Stockholm/49/2015	7/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686820	Sweden	A/Skovde/6/2015	18/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686772	Sweden	A/Stockholm/ 57/2015	18/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674785	Sweden	A/Stockholm/50/2015	11/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674793	Sweden	A/Stockholm/51/2015	11/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674801	Sweden	A/Stockholm/52/2015	11/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674847	Sweden	A/Stockholm/53/2015	12/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674809	Sweden	A/Stockholm/55/2015	10/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686764	Sweden	A/Stockholm/56/2015	18/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686799	Sweden	A/Stockholm/59/2015	19/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686828	Sweden	A/Stockholm/60/2015	25/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686844	Sweden	A/Stockholm/62/2015	26/11/2015	–	Swedish Institute for Infectious Disease Control
EPI687173	Sweden	A/Stockholm/66/2015	23/11/2015	–	Swedish Institute for Infectious Disease Control
EPI687199	Sweden	A/Stockholm/67/2015	21/11/2015	–	Swedish Institute for Infectious Disease Control
EPI674825	Sweden	A/Sweden/35/2015	12/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686852	Sweden	A/Uppsala/8/2015	27/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686892	Sweden	A/Sweden/37/2015	26/11/2015	–	Swedish Institute for Infectious Disease Control
EPI686900	Sweden	A/Sweden/38/2015	2/12/2015	–	Swedish Institute for Infectious Disease Control
EPI686908	Sweden	A/Sweden/39/2015	2/12/2015	–	Swedish Institute for Infectious Disease Control
EPI694343	Sweden	A/Uppsala/1/2016	11/1/2016	–	Swedish Institute for Infectious Disease Control
EPI671518	Norway	A/Norway/2625/2015	21/10/2015	Sorlandet Sykehus HF, Dept. of Medical Microbiology	Norwegian Institute of Public Health
EPI675750	Norway	A/Norway/2659/2015	3/11/2015	Drammen Hospital / Vestreviken HF, Department for Medical Microbiology section Drammen	Norwegian Institute of Public Health
EPI675751	Norway	A/Norway/2660/2015	3/11/2015	Drammen Hospital / Vestreviken HF, Department for Medical Microbiology section Drammen	Norwegian Institute of Public Health

ID: identity; SAR: Special Administrative Region; WHO: World Health Organization.

Table 2B

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI675754	Norway	A/Norway/2672/2015	1/11/2015	Oslo University Hospital, Ulleval Hospital, Dept. of Microbiology	Norwegian Institute of Public Health
EPI675756	Norway	A/Norway/2680/2015	12/11/2015	Ostfold Hospital - Fredrikstad, Dept. of Microbiology	Norwegian Institute of Public Health
EPI675760	Norway	A/Norway/2687/2015	13/11/2015	–	Norwegian Institute of Public Health
EPI695284	Norway	A/Norway/2711/2015	18/11/2015	–	Norwegian Institute of Public Health
EPI695299	Norway	A/Norway/2914/2015	14/12/2015	Sorlandet Sykehus HF, Dept. of Medical Microbiology	Norwegian Institute of Public Health
EPI695310	Norway	A/Norway/3004/2015	15/12/2015	Innlandet Hospital Trust, Division Lillehammer, Department for Microbiology	Norwegian Institute of Public Health
EPI695311	Norway	A/Norway/3018/2015	26/12/2015	–	Norwegian Institute of Public Health
EPI695313	Norway	A/Norway/3038/2015	26/12/2015	Aalesund sjukehus	Norwegian Institute of Public Health
EPI695343	Norway	A/Norway/174/2016	7/1/2016	St. Olavs Hospital HF, Dept. of Medical Microbiology	Norwegian Institute of Public Health
EPI695344	Norway	A/Norway/178/2016	6/1/2016	Health Forde, Department of Microbiology	Norwegian Institute of Public Health
EPI695349	Norway	A/Norway/209/2016	8/1/2016	Stavanger Universitetssykehus, Avd. for Medisinsk Mikrobiologi	Norwegian Institute of Public Health
EPI677648	Finland	A/Finland/541/2015	9/11/2015	Helsinki University Central Hospital, Laboratory Services (HUSLAB)	National Institute for Health and Welfare
EPI677651	Finland	A/Finland/543/2015	19/11/2015	Helsinki University Central Hospital, Laboratory Services (HUSLAB)	National Institute for Health and Welfare
EPI678232	Finland	A/Finland/544/2015	13/11/2015	Helsinki University Central Hospital, Laboratory Services (HUSLAB)	National Institute for Health and Welfare
EPI696158	Russia	A/Tomsk/154/2015	19/11/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696470	Russia	A/IIV-Moscow/211/2015	23/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696478	Russia	A/IIV-Moscow/212/2015	23/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI690291	Spain	A/Aragon/16005/2015	21/12/2015	Servicio de Microbiología Hospital Miguel Servet	Instituto de Salud Carlos III
EPI671520	Norway	A/Norway/2631/2015	26/10/2015	Sorlandet Sykehus HF, Dept. of Medical Microbiology	Norwegian Institute of Public Health
EPI671521	Norway	A/Norway/2633/2015	27/10/2015	Haukeland University Hospital, Dept. of Microbiology	Norwegian Institute of Public Health
EPI671522	Norway	A/Norway/2634/2015	27/10/2015	Haukeland University Hospital, Dept. of Microbiology	Norwegian Institute of Public Health
EPI671525	Norway	A/Norway/2650/2015	3/11/2015	Ostfold Hospital - Fredrikstad, Dept. of Microbiology	Norwegian Institute of Public Health
EPI675748	Norway	A/Norway/2651/2015	2/11/2015	Mikrobiologisk laboratorium, Sykehuset i Vestfold	Norwegian Institute of Public Health
EPI675749	Norway	A/Norway/2658/2015	4/11/2015	Drammen Hospital / Vestreviken HF, Department for Medical Microbiology section Drammen	Norwegian Institute of Public Health
EPI695334	Norway	A/Norway/139/2016	4/1/2016	Haukeland University Hospital, Dept. of Microbiology	Norwegian Institute of Public Health
EPI695336	Norway	A/Norway/141/2016	4/1/2016	Unilabs Telelab, Laboratory for Medical Microbiology	Norwegian Institute of Public Health

ID: identity; SAR: Special Administrative Region; WHO: World Health Organization.

Table 2c

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI695339	Norway	A/Norway/150/2016	12/1/2016	Stavanger Universitetssykehus, Avd. for Medisinsk Mikrobiologi	Norwegian Institute of Public Health
EPI695340	Norway	A/Norway/151/2016	12/1/2016	Stavanger Universitetssykehus, Avd. for Medisinsk Mikrobiologi	Norwegian Institute of Public Health
EPI695287	Norway	A/Norway/2734/2015	13/11/2015	Innlandet Hospital Trust, Division Lillehammer, Department for Microbiology	Norwegian Institute of Public Health
EPI695304	Norway	A/Norway/2945/2015	16/12/2015	–	Norwegian Institute of Public Health
EPI695314	Norway	A/Norway/3039/2015	28/12/2015	Aalesund sjukehus	Norwegian Institute of Public Health
EPI695326	Norway	A/Norway/3114/2015	28/12/2015	Drammen Hospital / Vestreviken HF, Department for Medical Microbiology section Drammen	Norwegian Institute of Public Health
EPI678234	Finland	A/Finland/545/2015	19/11/2015	Helsinki University Central Hospital, Laboratory Services (HUSLAB)	National Institute for Health and Welfare
EPI678238	Finland	A/Finland/550/2015	4/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI678240	Finland	A/Finland/553/2015	6/12/2015	NordLab Oulu	National Institute for Health and Welfare
EPI693689	Finland	A/Finland/556/2015	16/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI687734	Finland	A/Finland/557/2015	15/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI693690	Finland	A/Finland/558/2015	19/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI693691	Finland	A/Finland/559/2015	14/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI693692	Finland	A/Finland/560/2015	18/12/2015	National Institute for Health and Welfare	National Institute for Health and Welfare
EPI674284	Portugal	A/Lisboa/31/2015	19/11/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI674285	Portugal	A/Lisboa/32/2015	18/11/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI678690	Portugal	A/Lisboa/33/2015	25/11/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI678691	Portugal	A/Lisboa/36/2015	2/12/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI692997	Portugal	A/Lisboa/53/2015	22/12/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI678693	Portugal	A/Lisboa/niSU82_15–16/2015	2/12/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal
EPI699780	Greece	A/Athens.GR/18/2016	4/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699778	Greece	A/Athens.GR/19/2016	4/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699774	Greece	A/Athens.GR/29/2016	7/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699772	Greece	A/Athens.GR/38/2016	7/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699770	Greece	A/Athens.GR/40/2016	7/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699766	Greece	A/Athens.GR/54/2016	8/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699764	Greece	A/Athens.GR/55/2016	8/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI670326	Romania	A/Iasi/187166/2015	13/10/2015	Cantacuzino Institute	Cantacuzino Institute
EPI690111	Romania	A/Bucuresti/649-c7807/2015	22/12/2015	Cantacuzino Institute	Cantacuzino Institute
EPI699023	Romania	A/Bucuresti/190460/2016	19/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI696174	Russia	A/IIV-Moscow/158/2015	12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation

ID: identity; SAR: Special Administrative Region; WHO: World Health Organization.

Table 2d

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI696182	Russia	A/IIV-Moscow/159/2015	12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696198	Russia	A/IIV-Moscow/161/2015	14/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696246	Russia	A/IIV-Moscow/169/2015	17/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696270	Russia	A/IIV-Moscow/174/2015	16/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696278	Russia	A/IIV-Moscow/176/2015	15/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696286	Russia	A/IIV-Moscow/177/2015	16/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696326	Russia	A/IIV-Moscow/183/2015	21/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696382	Russia	A/IIV-Moscow/191/2015	20/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696414	Russia	A/IIV-Moscow/195/2015	22/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI687093	Russia	A/Saint-Petersburg/RII349/2015	25/11/2015		WHO National Influenza Centre Russian Federation
EPI696574	Russia	A/Saint-Petersburg/RII350/2015	30/11/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696486	Russia	A/Saint-Petersburg/RII01/2016	19/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696494	Russia	A/Saint-Petersburg/RII02/2016	21/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696502	Russia	A/Saint-Petersburg/RII03/2016	21/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696510	Russia	A/Saint-Petersburg/RII04/2016	21/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696166	Russia	A/IIV-Moscow/155/2015	7/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696518	Russia	A/Saint-Petersburg/RII05/2016	14/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696526	Russia	A/Saint-Petersburg/RII06/2016	14/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696534	Russia	A/Saint-Petersburg/RII07/2016	21/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696542	Russia	A/Saint-Petersburg/RII08/2016	22/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696558	Russia	A/Saint-Petersburg/RII10/2016	23/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696566	Russia	A/Saint-Petersburg/RII11/2016	24/12/2015	WHO National Influenza Centre Russian Federation	WHO National Influenza Centre Russian Federation
EPI696222	Russia	A/IIV-Moscow/166/2015	16/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696238	Russia	A/IIV-Moscow/168/2015	15/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation

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Table 2e

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI696254	Russia	A/IIV-Moscow/171/2015	17/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696294	Russia	A/IIV-Moscow/178/2015	17/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696318	Russia	A/IIV-Moscow/182/2015	18/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696334	Russia	A/IIV-Moscow/185/2015	18/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696366	Russia	A/IIV-Moscow/189/2015	19/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696374	Russia	A/IIV-Moscow/190/2015	20/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696398	Russia	A/IIV-Moscow/193/2015	21/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696406	Russia	A/IIV-Moscow/194/2015	20/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696422	Russia	A/IIV-Moscow/196/2015	22/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696430	Russia	A/IIV-Moscow/199/2015	22/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696446	Russia	A/IIV-Moscow/203/2015	22/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696454	Russia	A/IIV-Moscow/204/2015	22/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI696462	Russia	A/IIV-Moscow/208/2015	23/12/2015	D.I. Ivanovsky Research Institute of virology MoPH of RF,Moscow	WHO National Influenza Centre Russian Federation
EPI686526	Spain	A/Madrid/1858/2015	22/12/2015	Servicio de Microbiología Hospital Ramón y Cajal	Instituto de Salud Carlos III
EPI690296	Spain	A/Madrid/1859/2015	23/12/2015	Servicio de Microbiología Hospital Ramón y Cajal	Instituto de Salud Carlos III
EPI672780	Spain	A/Madrid/SO13656/2015	21/10/2015	Instituto de Salud Carlos III	Instituto de Salud Carlos III
EPI674599	Spain	A/Madrid/SO13670/2015	20/10/2015	Instituto de Salud Carlos III	Instituto de Salud Carlos III
EPI680490	Spain	A/Madrid/SO13763/2015	8/12/2015	Instituto de Salud Carlos III	Instituto de Salud Carlos III
EPI699957	Spain	A/Madrid/41/2016	13/1/2016	Instituto de Salud Carlos III	Instituto de Salud Carlos III
EPI699959	Spain	A/Madrid/68/2016	12/1/2016	Servicio de Microbiología Hospital Ramón y Cajal	Instituto de Salud Carlos III
EPI699960	Spain	A/Madrid/69/2016	12/1/2016	Servicio de Microbiología Hospital Ramón y Cajal	Instituto de Salud Carlos III
EPI690298	Spain	A/Navarra/16004/2015	27/12/2015	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI686527	Spain	A/Navarra/1829/2015	15/12/2015	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI686528	Spain	A/Navarra/1850/2015	17/12/2015	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III

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Table 2f

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI690302	Spain	A/Navarra/26/2016	3/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI699967	Spain	A/Navarra/50/2016	11/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI699973	Spain	A/Navarra/74/2016	14/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI699974	Spain	A/Navarra/75/2016	12/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI699975	Spain	A/Navarra/76/2016	14/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI699977	Spain	A/Navarra/78/2016	14/1/2016	Servicio de Microbiología Complejo Hospitalario de Navarra	Instituto de Salud Carlos III
EPI672781	Spain	A/PaisVasco/1683/2015	21/10/2015	Servicio de Microbiología Hospital Donostia	Instituto de Salud Carlos III
EPI686529	Spain	A/PaisVasco/1844/2015	15/12/2015	Servicio de Microbiología Hospital Donostia	Instituto de Salud Carlos III
EPI687827	Slovenia	A/Slovenia/2903/2015	26/10/2015	Laboratory for Virology, National Institute of Public Health	Crick Worldwide Influenza Centre
KU558983	Czech Republic	A/Czech Republic/95/2015	1/12/2015	National Institute of Public Health	National Institute of Public Health
EPI699832	Greece	A/Athens.GR/2395/2015	23/12/2015	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699830	Greece	A/Athens.GR/2407/2015	28/12/2015	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699827	Greece	A/Athens.GR/2413/2015	29/12/2015	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI699824	Greece	A/Athens.GR/12/2016	5/1/2016	Hellenic Pasteur Institute	Hellenic Pasteur Institute
EPI698911	Romania	A/Dambovita/190170/2016	18/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI698910	Romania	A/Galati/190006/2016	8/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI699021	Romania	A/Vrancea/190182/2016	18/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI699023	Romania	A/Bucuresti/190324/2016	19/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI699059	Romania	A/Bucuresti/190434/2016	23/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI698912	Romania	A/Dambovita/190171/2016	18/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI699024	Romania	A/Dambovita/190341/2016	21/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI699000	Romania	A/Vrancea/190181/2016	11/1/2016	Cantacuzino Institute	Cantacuzino Institute
EPI672779	Spain	A/Aragon/1615/2015	29/9/2015	Servicio de Microbiología Hospital Miguel Servet	Instituto de Salud Carlos III
EPI690293	Spain	A/Asturias/1862/2015	17/12/2015	Servicio de Microbiología Hospital Central Universitario de Asturias	Instituto de Salud Carlos III
EPI699955	Spain	A/Baleares/16036/2015	30/12/2015	Servicio de Microbiología Hospital Universitario Son Espases	Instituto de Salud Carlos III
EPI699956	Spain	A/Baleares/35/2016	5/1/2016	Servicio de Microbiología Hospital Universitario Son Espases	Instituto de Salud Carlos III
EPI690295	Spain	A/CastillaLaMancha/16013/2015	30/12/2015	Instituto de Salud Carlos III	Instituto de Salud Carlos III
EPI624748	Russia	A/St-Petersburg/122/2015	26/2/2015	WHO National Influenza Centre Russian Federation	Crick Worldwide Influenza Centre
EPI624673	Cameroon	A/Cameroon/15V-3814/2015	7/5/2015	Centre Pasteur du Cameroun	Crick Worldwide Influenza Centre
EPI624730	Norway	A/Norway/1690/2015	17/3/2015	WHO National Influenza Centre	Crick Worldwide Influenza Centre

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Table 2G

Details of the A(H1N1)pdm09 sequences retrieved from the Global Initiative on Sharing All Influenza Data (GISAID)'s EpiFlu Database or GenBank, for haemagglutinin-gene-based phylogenetic analysis in this study

ID	Country	Strain name	Collection date	Originating laboratory	Submitting laboratory
EPI630638	Mauritius	A/Mauritius/I-463/2015	18/5/2015	Central Health Laboratory	Crick Worldwide Influenza Centre
EPI621835	Madagascar	A/Madagascar/1566/2015	15/4/2015	Institut Pasteur de Madagascar	Crick Worldwide Influenza Centre
EPI630634	Hong Kong SAR	A/Hong Kong/12243/2015	14/6/2015	Government Virus Unit	Crick Worldwide Influenza Centre
EPI630684	South Africa	A/South Africa/R3723/2015	29/6/2015	Sandringham, National Institute for Communicable D	Crick Worldwide Influenza Centre
EPI630676	South Africa	A/South Africa/R2977/2015	5/6/2015	Sandringham, National Institute for Communicable D	Crick Worldwide Influenza Centre
EPI630652	Slovenia	A/Slovenia/1314/15	5/3/2015	Laboratory for Virology, National Institute of Public Health	Crick Worldwide Influenza Centre
EPI624706	Russia	A/IIV-Moscow/94/2015	12/3/2015	Ivanovsky Research Institute of Virology RAMS	Crick Worldwide Influenza Centre
EPI624704	Russia	A/IIV-Moscow/93/2015	10/3/2015	Ivanovsky Research Institute of Virology RAMS	Crick Worldwide Influenza Centre
EPI589565	Jordan	A/Jordan/20241/2015	22/3/2015	Laboratory Directorate	Crick Worldwide Influenza Centre
EPI253705	Germany	A/Bayern/69/2009	1/1/2009	Robert-Koch-Institute	Robert-Koch-Institute
EPI278607	New Zealand	A/Christchurch/16/2010	12/7/2010	Canterbury Health Services	WHO Collaborating Centre for Reference and Research on Influenza
EPI319590	Russia	A/Astrakhan/1/2011	28/2/2011	WHO National Influenza Centre Russian Federation	National Institute for Medical Research
EPI319527	Russia	A/St. Petersburg/27/2011	14/2/2011	WHO National Influenza Centre Russian Federation	National Institute for Medical Research
EPI416411	Norway	A/Norway/120/2013	2/1/2013	WHO National Influenza Centre	National Institute for Medical Research
EPI574439	Ghana	A/Ghana/DILI-14–0620/2014	7/7/2014	University of Ghana	National Institute for Medical Research
EPI390473	Hong Kong SAR	A/Hong Kong/5659/2012	21/5/2012	Government Virus Unit	National Institute for Medical Research
EPI326206	Hong Kong SAR	A/Hong Kong/3934/2011	29/3/2011	Government Virus Unit	National Institute for Medical Research
EPI466626	South Africa	A/South Africa/3626/2013	6/6/2013	Sandringham, National Institute for Communicable D	National Institute for Medical Research
EPI539472	Senegal	A/Dakar/04/2014	3/2/2014	Institut Pasteur de Dakar	National Institute for Medical Research
EPI417122	Senegal	A/Dakar/20/2012	9/12/2012	Institut Pasteur de Dakar	National Institute for Medical Research
EPI319447	Czech Republic	A/Czech Republic/32/2011	18/1/2011	National Institute of Public Health	National Institute for Medical Research
EPI215957	Ukraine	A/Lviv/N6/2009	27/10/2009	Ministry of Health of Ukraine	National Institute for Medical Research
EPI320141	Russia	A/St. Petersburg/100/2011	14/3/2011	Russian Academy of Medical Sciences	Centers for Disease Control and Prevention
EPI626148	Bangladesh	A/Bangladesh/3003/2015	4/5/2015	Institute of Epidemiology Disease Control and Research (IEDCR) and Bangladesh National Influenza Centre (NIC)	Centers for Disease Control and Prevention
EPI626140	Bangladesh	A/Bangladesh/01/2015	10/5/2015	Institute of Epidemiology Disease Control and Research (IEDCR) and Bangladesh National Influenza Centre (NIC)	Centers for Disease Control and Prevention
EPI176620	United States	A/California/07/2009	9/4/2009	Naval Health Research Center	Centers for Disease Control and Prevention
EPI624468	French Guiana	A/Guyane/1759/2015	9/4/2015	Institut Pasteur	Institut Pasteur

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The data supporting the predominance of the 6B.1 subclade stem from the subset of 12 European countries that reported virus characterisation data referring to sequences available in publically accessible databases. These countries are well spread across Europe which corroborates the conclusion of widespread 6B.1 subclade circulation. Data from the WHO Collaborating Centres indicate that the new subgroup remains antigenically similar to the vaccine component A/California/7/2009 [1], but some recent A(H1N1)pdm09 viruses within the 6B.1 and 6B.2 subclades reacted poorly with sera from individuals vaccinated with A/California/7/2009-like-strain-containing vaccine [15].

The emergence of a new A(H1N1)pdm09 subclade may eventually affect the susceptibility of the population to the currently circulating A(H1N1)pdm09 viruses, e.g. by viruses drifting closer to become immune escape variants. It is not clear whether the emergence and predominance of subclade 6B.1 has been driven by immune selection or what its impact on vaccine effectiveness may be and this needs assessment e.g. by generating lineage-specific estimation of vaccine effectiveness. Early vaccine effectiveness estimates for A(H1N1)pdm09 this season compared with the previous ones are not significantly different [16] from previous seasons. As to the severity observed this season [1-4], similar observations have been made also in earlier seasons e.g. in 2010/11 in the United Kingdom, which experienced notably severe A(H1N1)pdm09 impact in the first post-pandemic season.

Notably, recent studies have demonstrated that antigenic change in A(H1N1)pdm09 viruses is mainly caused by single amino acid substitutions affecting the loop located adjacent to the receptor binding site [17]; eight of the 215 analysed 2015/16 viruses possessed such substitutions, all six of the viruses in subclade 6B.2 and two in 6B subgroup, that do not belong to any of the newly emerged subclades.

Further enhancement of the antigenicity and virulence of influenza virus has been attributed to shielding of the major antigenic epitopes by alteration of N-linked glycosylation sites [18]. D127E substitution seen in 6B.2 has been associated with antigenic change of other influenza viruses through modelling [17]. The change at position 173 (V173I) also in the 6B.2 subclade of viruses is located in antigenic site Ca1 (position 169–173), and therefore a change here could contribute to antigen drift. It has been proposed that the evolution of A(H1N1)pdm09 will involve the acquisition of additional glycosylations, as for former seasonal A(H1N1) HA [19]. Noteworthy, 80% of the analysed HA sequences have gained a potential glycosylation site S162N. No D222G/E/N substitutions were detected, nor N129D which was recently identified in India in two severe or fatal cases [9]. If the emerging groups continue to diversify from the vaccine component, their antigenic properties may change and the vaccine effectiveness might be reduced. WHO recommended not to change the vaccine component of A(H1N1)pdm09 for the northern hemisphere 2016/17 season [20].

Early vaccine effectiveness estimates for 2015/16 are not yet available for A(H3N2) and B viruses which have been detected in lower numbers in most countries. The B/Victoria virus component is available only in the quadrivalent vaccines in the northern hemisphere for this season. As the majority of the countries use trivalent vaccines, the lineage switch from B/Yamagata to B/Victoria may contribute to lower vaccine effectiveness against influenza B. For A(H3N2), the current component of influenza vaccines is expected to have improved vaccine effectiveness compared with the two previous seasons [21,22]. In the southern hemisphere, seasonal influenza vaccine has been demonstrated to have an overall effectiveness against A(H3N2) of 36% (95% confidence interval (CI): 11–54)) for general practice encounters and 50% (95%-CI: 20–68) for hospitalisations in 2015 [23]. Despite the changes in the genetic makeup of influenza A(H1N1)pdm09 viruses and the predominance of B/Victoria lineage over B/Yamagata lineage, seasonal influenza vaccine remains the single most effective measure to prevent severe outcomes of influenza.

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Phin, Richard Pebody, Simon de Lusignan, Simon Cottrell, Jim McMenamin, Lucy Jessop; European Centre for Disease Prevention and Control: Cornelia Adlhoch, Adrian Prodan, René Snacken, Pasi Penttinen; WHO Collaborating Centre for Reference and Research on Influenza London: John McCauley, Rod Daniels; WHO Regional Office for Europe: Dmitriy Pereyaslov, Sergejs Nikišins.

Acknowledgements

We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu Database on which the phylogenetic analysis is based (Figure 1; Accession numbers shown in Table 2). All submitters of data may be contacted directly via the GISAID website www.gisaid.org.

We thank Julien Beauté, Phillip Zucs, Denis Coulombier and Piotr Kramarz (ECDC) for improving this article, and Torstein Aune (Norway) for technical assistance in the analysis. We would also like to thank Caroline Brown from the WHO Regional Office for Europe for our joint collaboration on influenza surveillance.

We would additionally like to acknowledge all members of the Spanish Influenza Surveillance System (SISS) for the contribution in this study. Sequences from Spain were obtained in the Centro Nacional de Microbiología (ISCIII) from influenza viruses sent by the following laboratories: Hospital Miguel Servet de Zaragoza-Aragón, Hospital Universitario Central de Asturias, Hospital Universitario Son Espases de Palma de Mallorca-Baleares, Hospital San Pedro de Alcántara Cáceres-Extremadura, Hospital Donostia-País Vasco, Hospital San Pedro Logroño-La Rioja, Complejo Hospitalario Universitario de Vigo-Galicia.

Conflict of interest

None declared.

Authors' contributions

Eeva Broberg: Data extraction, data maintenance, first draft of the manuscript, study design, revisions of the article. Angeliki Melidou: data processing, phylogenetic analysis and text. Katarina Prosenc: data processing, analysis, text. Karoline Bragstad: data processing, amino acid analysis, text. Olav Hungnes: data processing, analysis, text. ECDC and WHO Regional Office for Europe staff: influenza surveillance data maintenance, management and analysis. Country experts: surveillance systems, data collection, data analysis at national level and reporting to TESSy.

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