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Type: Rapid communication: around 1,200 words, and have a minimum of eight and up to about 20 references and four illustrations (figures or tables). The abstract should not exceed 80 words.

### Title: Antigenic changes in influenza A(H3N2) driven by genetic evolution: Insights from EU/EEA virological surveillance, EU/EEA, week 40, 2023 – week 9, 2024

Short title: Genetic and antigenic diversification of influenza A(H3N2), EU/EEA, 2023-2024

Keywords: influenza, surveillance, Europe, genetic

### Authors

Eeva K. Broberg1, Maja Vukovikj1, Olov Svartström1, Iris Hasibra2, Maximilian Riess1 and Angeliki Melidou1, Members of the ERLI-Net network3 that contributed virus detection and/or characterisation data or were involved in weekly surveillance activities.

### Affiliations

1European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

2World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark

3Members of the ERLI-Net that contributed virus detection and/or characterisation data or were involved in weekly surveillance activities are listed under collaborators; see list in the end of article.

### Abstract, max 80 words

During 2023-24 influenza season in EU/EEA, there was co-circulation of A(H1N1)pdm09, A(H3N2) and B/Victoria viruses. The genetic diversification of these viruses continued and clade 5a.2a.1 of A(H1N1)pdm09, 2a.3a.1 of A(H3N2) and V1A.3a.2 of B/Victoria-lineage viruses dominated. 23% of A(H3N2) 2a.3a.1 viruses were antigenically distinct from current vaccine virus. B/Yamagata-lineage was not detected. The WHO's vaccine recommendations for the 2024-25 season in the northern hemisphere were updated to include a new A(H3N2) component, while maintaining the current A(H1N1)pdm09 and B/Victoria-lineage components.

Seasonal influenza viruses evolve constantly both genetically and antigenically and influenza vaccine components need to be evaluated regularly. Therefore, continuous virological surveillance of influenza virus strains is necessary. This report summarises influenza virological surveillance data in the European Union and Economic Area, for weeks 40/2023 through 9/2024, as reported by national influenza reference laboratories to The European Surveillance System (TESSy) hosted at the European Centre for Disease Prevention and Control (ECDC) and discusses the results in context of the WHO vaccine composition recommendation for northern hemisphere (NH) 2024-25 influenza season.

The data sources and methods were as described earlier [1] .

*Detections*

In the EU/EEA, within the reporting period, 154718 influenza virus detections (sentinel and non-sentinel combined), were reported from 29 countries of which 97% (150692) were type A and 3% (4026) were type B virus (Table 1, Figure 1).

Of the subtyped influenza A viruses, 30463 (75%) were influenza A(H1)pdm09 and 10174 (25%) were influenza A(H3). Of the 4026 reported influenza type B viruses, the lineage for 809 (20%) was determined, with all viruses falling into the B/Victoria/2/87-lineage. No B/Yamagata/16/88-lineage virus was reported (Table 1, Figure 1).

*Genetic characterisation*

Within the reporting period, 2567 (2% of all surveillance source detections; 6% of sentinel source detections) viruses from 15 countries were reported with sequence identifier, out of which 2544 sequences could be retrieved and included in the phylogenetic analysis. The 1083 (60%) of the 1815 A(H1N1)pdm09 viruses fell in clade 5a.2a, while 732 (40%) belonged to clade 5a.2a.1 where 710 (97%) to C.1.1.1 subclade defined by T216A and represented by A/Victoria/4897/2022, the virus component for 2023-24 NH egg-based vaccine (Table 1, Supplemental Figure 1). Genetically, 728 (67%) of 5a.2a viruses fell into a subgroup with T120A and additionally K169Q or V47I (within subclade C.1). In 5a.2a.1 viruses, 317 (43%) carried R113K (within C.1.1.1) with or without S85P and 243 (33%) R45K (within C.1.1.1).

All 639 A(H3N2) viruses fell into clade 2a.3, a subclade of 2a represented by A/Darwin/9/2021, the recommended vaccine strain for egg-based vaccines for 2023-24 NH influenza season (Figure 2). Within 2a.3, 98% (n=628) were clade 2a.3a.1, represented by A/Thailand/8/2022 which has been recommended for NH 2024-25 vaccine. Most (n=346, 55%) of A(H3N2) in 2a.3a.1 belonged to J.2 subclade defined by the amino acid substitutions N122D (potential loss of glycosylation site, antigenic site A) and K276E (in antigenic site C). Within 2a.3a.1, also smaller subclade J.1 with I25V (n=212, 33%) was present. (Table 1, Figure 2)

All 90 B/Victoria viruses belonged to clade V1A.3a.2, represented by B/Austria/1359417/2021, the recommended vaccine virus strain for the 2023-24 NH influenza season (Table 1, Supplemental Figure 2). However, 32% (n=29) of the viruses fell in a branch with an E128G substitution.

*Antigenic characterisation*

Antigenic characterisation data from eight countries were available for 675 viruses (Table 1). Of the 512 characterised A(H1)pdm09 viruses the majority (262, 51%) were A/Sydney/5/2021-like, 248 (48%) were similar to the vaccine virus A/Victoria/4897/2022-like virus, and two were reported as A/Wisconsin/67/2022-like viruses. The majority of the 103 antigenically characterised A(H3) viruses (76, 74%) were reported as A/Darwin/9/2021-like, 24 (23%) as A/Thailand/8/2022-like, and three were not attributed to any of the reporting categories.

Among 60 antigenically characterised influenza B/Victoria viruses, the majority (58, 97%) were similar to the vaccine virus for the 2023/24 NH influenza season (B/Austria/1359417/2021). Two (3%) B/Victoria viruses were not attributed to any of the reporting categories. (Table 1)

*Antiviral susceptibility*

Since the beginning of the season, 2003 viruses were assessed for antiviral susceptibility to oseltamivir and zanamivir (87% by genomic analysis and 13% by phenotypic analysis) and 1553 viruses to baloxavir marboxil (all by genomic analyses) from in total 14 EU/EEA countries (Table 2). In total, five viruses with reduced or highly reduced inhibition or susceptibility were detected based on genetic analyses: three A(H1)pdm09 viruses carried genetic markers associated with either reduced (NA:I223T) or highly reduced inhibition (NA:H275Y) by oseltamivir; two A(H3) viruses carried amino acid substitutions associated with reduced susceptibility to baloxavir (PA:L28P) (Table 2). For polymerase acidic protein associated to reduced inhibition genotypic susceptibility assessment was performed based on WHO table [2].

### Conclusions and discussion

### Based on our dataset, this influenza season was characterised by co-circulation of influenza A(H1N1)pdm09, A(H3N2) subtypes and B/Victoria-lineage viruses, with A(H1N1)pdm09 being the predominant virus overall in EU/EEA.

Regarding the antigenic similarity of circulating A(H1N1)pdm09 viruses to the 2023-24 NH vaccine component (A/Victoria/4897/2022-like clade 5a.2a.1 virus (egg-based)), the circulating viruses appeared to be overall antigenically similar. The early European vaccine effectiveness results showed 53% (95% CI: 41 to 63) protection against influenza in all ages in the primary care [3]. Some genetic diversification was observed in the 5a.2a viruses with branches having defined amino acid substitutions with a significant number of viruses such as T120A with K169Q or V47I in 5a.2a and S85P/R113K and R45K in 5a.2a.1. Despite the genetic heterogeneity of recently circulating A(H1)pdm09 viruses, the WHO recommended to maintain the same A(H1)pdm09 component for the 2024/25 influenza season as previous season, based on human serology study results confirming that the NH 2023/24 vaccine post-vaccination serum titres were not significantly reduced for most circulating viruses [4]. Lower VE was, however, observed in the European study against clade 5a.2a.1 viruses (39%, 95% CI: -44 to 74) compared to clade 5a.2a viruses (52%, 95% CI: -7 to 78) [3]; this is also supported by the Canadian Sentinel Practitioner Surveillance Network VE studies (56% vs 67%) [5]. Reduced inhibition by oseltamivir was detected in only three A(H1)pdm09 viruses with the large majority of tested viruses remaining susceptible.

For A(H3N2), almost all circulating viruses fell genetically in clade 2a.3a.1 represented by A/Thailand/8/2022, which was recently recommended as the vaccine component for NH influenza season 2024-25 [4]. It was shown by human serology studies using post-vaccination human sera, that reduced reactivity was seen against some recent viruses expressing HA genes from subclade 2a.3a.1 [4]. Noteworthy, in EU/EEA, the majority (346, 54%), of A(H3N2) viruses belonged genetically to this divergent clade 2a.3a.1 with additional amino acid substitutions in antigenic sites at N122D and K276E (J.2) and another subgroup with I25V (J.1). Early European vaccine effectiveness results in primary care for all ages indeed showed reduced protection of 30% (95% CI: −3 to 54) by the influenza vaccine from the circulating A(H3N2) viruses and in hospital studies 14% (95% CI: −32 to 43). This indicated that many of the currently circulating 2a.3a.1 subclade strains in the EU/EEA had diversified antigenically from the NH 2023-24 vaccine virus A/Darwin/9/2021 [4]. In our EU/EEA data, only 23% of antigenically characterised viruses were A/Thailand/8/2022-like which would indicate that they were less well recognised by the vaccine virus A/Darwin/9/2021 antisera. It needs, however, to be noted that antigenic characterisations were not performed for all circulating 2a.3a.1 viruses and that antigenic characterisation data do not necessarily reflect the proportion of different (sub)clades among circulating viruses. Furthermore, partially differences in the antigenic and/or human serology data in comparison with the VE data could possibly be explained by the fact that in the EU/EEA, as elsewhere, some available vaccines are produced in eggs rather than in cell lines [6-9]. Reduced susceptibility to baloxavir marboxil was reported in only two A(H3) viruses from two different countries with the large majority of tested viruses remaining susceptible.

For the B/Victoria -lineage, all antigenically characterised viruses were V1A.3a.2 B/Austria/1359417/2021-like, which is the current vaccine component in tri- and quadrivalent vaccines in the NH 2023/24. Even if genetic diversification continues within this lineage, the currently circulating viruses in the EU/EEA have been still well covered by the vaccine virus antigenically and no update to the vaccine component was proposed by WHO [4].

There are some additional limitations to these data. The specimen sources (sentinel GPs, hospital, ICU, outbreak investigations) and selection processes for the viruses that undergo characterisation vary from country to country. Only a small percentage (0.4% antigenically and 2% genetically; 3% and 6% of the sentinel source viruses, respectively) of detected viruses were characterised overall. ECDC and WHO Regional Office for Europe have previously recommended to sequence all influenza viruses detected from sentinel sources and we are still far from this target [10].

Despite the challenges in collecting influenza surveillance data collection, the detection and characterization of influenza viruses within the EU/EEA play a vital role in identifying which viruses should be sent to a WHO Collaborating Centre for in-depth analysis. These analyses are essential for guiding the decision-making process during the biannual WHO influenza vaccine composition meetings.

### Figures and tables

### Table 1. Influenza virus detections in sentinel and non-sentinel source specimens by type and subtype cumulatively for the weeks 40/2023-9/2024

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sentinel** | | **Non-sentinel** | |
| **Detections by virus (sub)type** | **Number** | **%** | **Number** | **%** |
| **Influenza A** | 12 397 | 96 | 138 295 | 98 |
| ***A(H1)pdm09*** | 8 296 | 81 | 22 167 | 73 |
| ***A(H3)*** | 2 136 | 19 | 8 038 | 27 |
| ***A not subtyped*** | 1 965 | - | 108 090 | - |
| **Influenza B** | 561 | 4 | 3 465 | 2 |
| ***B/Victoria -lineage*** | 256 | 100 | 553 | 100 |
| ***B/Yamagata -lineage*** | 0 | 0 | 0 | 0 |
| ***Unknown lineage*** | 305 | - | 2 912 | - |
| **Total detections**  **(total tested)** | **12 958**  **(66 596)** | **19** | **141 760**  **(1 168 394)** | **12** |
|  |  |  |  |  |
| **Antigenic characterisations** | **Number** | **%** |
| **Influenza A** |  |  |
| ***A(H1)pdm09*** |  |  |
| 5a.2a A/Sydney/5/2021-like3 | 262 | 51.2 |
| 5a.2a.1 A/Victoria/4897/2022-like4,5 | 248 | 48.4 |
| 5a.2a.1 A/Wisconsin/67/2022-like4,5 | 2 | 0.4 |
| *Subtotal* | 512 | 100.0 |
| ***A(H3)*** |  |  |
| 2a A/Darwin/9/2021-like1-4 | 76 | 73.8 |
| 2a.3a.1 A/Thailand/8/2022-like5 | 24 | 23.3 |
| Not categorised | 3 | 2.9 |
| *Subtotal* | 103 | 100.0 |
| **Influenza B** |  |  |
| ***B/Victoria-lineage*** |  |  |
| V1A.3a.2 B/Austria/1359417/2021-like1-5 | 58 | 96.7 |
| Not categorised | 2 | 3.3 |
| *Subtotal* | 60 | 100.0 |
|  |  |  |
| **Phylogenetic analysis** | **Number** | **%** |
| **Influenza A** |  |  |
| ***A(H1)pdm09*** |  |  |
| 5a.2a (C.1) | 1029 | 56.7 |
| 5a.2a + T216A (C.1.7) | 54 | 3.0 |
| 5a.2a.1 (C.1.1) | 22 | 1.2 |
| 5a.2a.1+T216A (C.1.1.1) | 710 | 39.1 |
| *Subtotal* | 1815 | 100.0 |
|  |  |  |
| ***A(H3)*** |  |  |
| 2a.3a (G.1.3.1) | 10 | 1.6 |
| 2a.3a.1 (J) | 50 | 7.8 |
| 2a.3a.1 + I25V (J.1) | 212 | 33.2 |
| 2a.3a.1 + N122D, K276E (J.2) | 346 | 54.1 |
| 2a.3a.1 Q173R, K276E (J.4) | 20 | 3.1 |
| 2a.3b (G.1.3.2) | 1 | 0.2 |
| *Subtotal* | 639 | 100.0 |
|  |  |  |
| **Influenza B** |  |  |
| ***B/Victoria-lineage*** |  |  |
| V1A.3a.2 (C.2) | 1 | 1.1 |
| V1A.3a.2 (C.3) | 2 | 2.2 |
| V1A.3a.2 (C.5) | 9 | 10.0 |
| V1A.3a.2 (C.5.1) | 35 | 38.9 |
| V1A.3a.2 (C.5.6) | 14 | 15.6 |
| V1A.3a.2 + E128G (C.5.7) | 29 | 32.2 |
| *Subtotal* | 90 | 100.0 |

*1 WHO recommended vaccine virus for the 2022 southern hemisphere influenza season (Trivalent vaccine)*

*2 WHO recommended vaccine virus for the 2022-2023 northern hemisphere influenza season (Trivalent vaccine)*

*3 WHO recommended vaccine virus for the 2023 southern hemisphere influenza season (Trivalent vaccine)*

*4 WHO recommended vaccine virus for the 2023-2024 northern hemisphere influenza season (Trivalent vaccine)*

*5 WHO recommended vaccine virus for the 2024 southern hemisphere influenza season (Trivalent vaccine)*

#### Table 2. Influenza subtypes and lineages with and without reduced inhibition following antiviral susceptibility testing to oseltamivir reported to TESSy, weeks 40/2023 through 9/2024, EU/EEA. NI: Normal inhibition; NS: Normal susceptibility; HRI: Highly reduced inhibition; RI: Reduced inhibition; RS: Reduced susceptibility; prefix ‘AA’: Amino acid, refers to genotypic testing result.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Oseltamivir susceptibility** | NI n (%) | AANI n (%) | AAHRI n (%) | AARI n (%) | **Total** |
| **Influenza A** |  |  |  |  |  |
| A(H1)pdm09 | 185 (13%) | 1239 (87%) | 2 (0.1%)a | 1 (0.1%)b | 1427 |
| A(H3) | 54 (11%) | 458 (89%) | 0 (0%) | 0 (0%) | 512 |
| **Influenza B** |  |  |  |  |  |
| B/Victoria lineage | 21 (33%) | 43 (67%) | 0 (0%) | 0 (0%) | 64 |
| **Total** | 260 (13%) | 1740 (87%) | 2 (0.1%) | 1 (0%) | 2003 |
| **Zanamivir susceptibility** | NI n (%) | AANI n (%) | AAHRI n (%) | AARI n (%) | **Total** |
| **Influenza A** |  |  |  |  |  |
| A(H1)pdm09 | 185 (13%) | 1242 (87%) | 0 | 0 | 1427 |
| A(H3) | 54 (11%) | 458 (89%) | 0 | 0 | 512 |
| **Influenza B** |  |  |  |  |  |
| B/Victoria lineage | 21 (33%) | 43 (67%) | 0 | 0 | 64 |
| **Total** | 260 (13%) | 1743 (87%) | 0 | 0 | 2003 |
| **Baloxavir marboxil**  **susceptibility** | | **AANS n (%)** | **AARS n (%)** | | **Total** |
| **Influenza A** | |  |  | |  |
| A(H1)pdm09 | | 1113 (100%) | 0 (0%) | | 1113 |
| A(H3) | | 400 (99.5%) | 2 (0.5%)c | | 402 |
| **Influenza B** | |  |  | |  |
| B/Victoria lineage | | 38 (100%) | 0 (0%) | | 38 |
| **Total** | | 1551 (100%) | 2 (0.1%) | | 1553 |

a: These viruses carried mutation NA:H275Y

b: This viruses carried mutation NA:I223T

c: These viruses carried mutation PA:L28P

#### Figure 1. Number of detections in the A) sentinel and B) surveillance system by subtype and proportion positive of all tested by week, EU/EEA, weeks 40/2023 through 9/2024.

### A.

### 

### 

### B.

### 

#### Figure 2. Phylogenetic comparison of influenza A(H3N2) HA genes. The vaccine strains are red, reference strains black and sequences reported to TESSy coloured according to the virus collection date by month (2023: October red, November yellow, December grey; 2024: January green, February, turquoise).

A computer screen shot of a number

Description automatically generated

### Supplemental materials

#### Supplemental Figure 1 SF1. Phylogenetic comparison of influenza A(H1N1)pdm09 HA genes. The vaccine strains are red, reference strains black and sequences reported to TESSy coloured according to the virus collection date by month (2023: October red, November yellow, December grey; 2024: January green, February, turquoise).

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#### Supplemental Figure 2 SF2. Phylogenetic comparison of influenza B/Victoria-lineage HA genes. The vaccine strains are red, reference strains black and sequences reported to TESSy coloured according to the virus collection date by month (2023: October red, November yellow, December grey; 2024: January green, February, turquoise).

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### Ethical statement

Ethical approval was not required for this study as Individuals are not identifiable and only virus data are included.

### Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

The authors affiliated with the World Health Organization (WHO) are alone responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the WHO.

Data are publicly available through [www.erviss.org](http://www.erviss.org) and/or upon data access request from ECDC and sequences publicly accessible through GISAID (see acknowledgement).

### Conflict of interest

None declared.

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### Collaborators and affiliations

Austria:

Belgium:

Bulgaria:

Croatia:

Czech Republic:

Denmark: Amanda Bolt Botnen and Ramona Trebbien, Statens Serum Institut, Copenhagen

Estonia:

Finland: Niina Ikonen and Erika Lindh, Finnish Institute for Health and Welfare (THL), Helsinki

France: Vincent Enouf, National Reference Center of Respiratory Viruses - Institut Pasteur, Paris, and Laurence Josset, National Reference Center of Respiratory Viruses - Hospices Civils de Lyon, Lyon.

Germany: Ralf Duerrwald and Marianne Wedde, Robert Koch Institute, Berlin

Greece: Maria Exindari, National influenza Centre for N. Greece, Thessaloniki and Emmanouil Mary, Research Staff Scientist, National Reference Laboratory for S. Greece, Hellenic Pasteur Institute, Athens

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Iceland:

Ireland: Elaine Brabazon, Health Service Executive, Health Protection Surveillance Centre, Dublin, and Charlene Bennett, National Virus Reference Laboratory, University College Dublin

Italy: Simona Puzelli and Antonino Bella, Institute of Health (Istituto Superiore di Sanità), Rome

Liechtenstein:

Lithuania:

Luxembourg:

Latvia:

Malta:

Netherlands: Ron Fouchier, Erasmus University Medical Center, Rotterdam, and Adam Meijer, Dutch National Institute for Public Health and the Environment (RIVM), Bilthoven

Norway: Andreas Rohringer and Karoline Bragstad , Norwegian Institute of Public Health, Oslo

Poland:

Portugal: Raquel Guiomar, National Reference Laboratory for Influenza and Other Respiratory Viruses, Infectious Diseases Department, and Ana Paula Rodrigues, Department of Epidemiology, National Institute of Health Doctor Ricardo Jorge

Romania: Mihaela Lazar, “Cantacuzino” National Medical-Military Research-Development Institute, Rodica Popescu, National Institute of Public Health Romania.

Slovak Republic:

Slovenia: Nataša Berginc, National Laboratory for Health, Environment and Food, Ljubljana; and Maja Sočan, National Institute of Public Health, Ljubljana,

Spain: Francisco Pozo and Inmaculada Casas, National Centre for Microbiology, Institute of Health Carlos III, Madrid. Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP).

Sweden: Annasara Carnahan and Neus Latorre-Margalef, Public Health Agency of Sweden, Stockholm

ECDC:

WHO European Region:

### Authors’ contributions

EB Conceptualisation, methodology, validation, data curation (lead); writing – original draft (lead); formal analysis (lead); visualisations (lead); writing – review and editing (equal);

MV, IH, MR, OS and AM data curation, analysis, visualisation (equal) – writing – review and editing (equal);

OS phylogenetic analysis and visualisation;

Members of the network coordinated national surveillance activities, collection of specimens and epidemiological data, analysed the specimens and provided data to TESSy and GISAID, reviewed the analysis and approved the final manuscript. All authors contributed to the work, reviewed and approved the manuscript before submission.

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Spain: Sara Sanbonmatsu, Servicio de Microbiología Hospital Virgen de las Nieves, Granada; Ana María Milagro, Servicio de Microbiología Hospital Universitario Miguel Servet, Zaragoza; Asunción del Valle, Servicio de Microbiología Hospital Universitario de Cabueñes, Gijón; Jordi Reina, Servicio de Microbiología Hospital Son Espases, Palma de Mallorca; Melisa Hernández, Servicio de Microbiología Hospital Universitario Doctor Negrín, Gran Canaria; Carlos Salas, Servicio de Microbiología Hospital Universitario Marqués de Valdecilla, Santander; Andrés Antón, Servicio de Microbiología Hospital Universitario Vall d’Hebron, Barcelona; Salomé Hijano, Servicio de Microbiología Hospital Universitario de Ceuta; Montserrat Ruiz, Servicio de Microbiología Hospital General Universitario de Elche, Alicante; Guadalupe Rodríguez, Servicio de Microbiología Hospital San Pedro de Alcántara, Cáceres; Sonia Pérez, Servicio de Microbiología Hospital Meixoeiro, Vigo; Juan García, Servicio de Microbiología Hospital Santa María Nai, Orense; Darío García de Viedma, Servicio de Microbiología Hospital General Universitario Gregorio Marañón, Madrid; Sergio Román, Servicio de Microbiología Hospital Comarcal de Melilla; Laura Moreno, Servicio de Microbiología Hospital Virgen de la Arrixaca, Murcia; Ana Blázquez, Servicio de Microbiología Hospital General Universitario Santa Lucía, Cartagena; Ana Navascués, Servicio de Microbiología Hospital Universitario de Navarra, Pamplona; Gabriel Reina, Servicio de Microbiología Clínica Universitaria de Navarra, Pamplona; Marta Adelantado, Servicio de Microbiología Hospital Reina Sofía, Tudela; Gustavo Cilla, Servicio de Microbiología Hospital Donostia, San Sebastián; Concepción Delgado, Clara Mazagatos and Amparo Larrauri, National Centre of Epidemiology (Instituto de Salud Carlos III), Madrid. We would like to thank all the participants in the Acute Respiratory Infection System in Spain (SiVIRA), including everyone involved in data collection and notification, epidemilogists and public health units of all participating Autonomous Regions.

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