TITLE: Impact of the COVID-19 pandemic on influenza circulation during the 2020/21 and 2021/22 seasons, in Europe

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Acknowledgments

The authors would like to gratefully acknowledge and thank colleagues from the European Center for Disease Prevention and Control (ECDC) Maja Vukovikj, Favelle Lamb, Angeliki Melidou, Cornelia Adlhoch and Edoardo Colzani for their contributions to this work and Catia Cunha, Marius Valcu, Zsolt, Bartha, Pedro Jose Murillo and Georgios Maragonis at ECDC for their continued support with the development, improvement and data management support for the data collection and publication of the Flu News Europe weekly bulletin.

The authors would like to gratefully thank all Members of the WHO European Region and the European Influenza Surveillance Network (EISN in EU/EEA countries) working on influenza surveillance and their commitment to the collection and submission of surveillance data to The European Surveillance System (TESSy), including the following:

Belgium: BELSARI-NET group consisting of Department of Infectiology, UZ Brussel, Brussels (Lucie Seyler), Department of Infectious Diseases, Centre hospitalier Universitaire Saint-Pierre, Brussels (Nicolas Dauby, Benedicte Delaere, Marc Bourgeois), Department of Laboratory Medicine, Medical Microbiology, Algemeen Ziekenhuis Sint-Jan, Brugge-Oostende AV (Evelyn Petit, Marijke Reynders), Department of Microbiology and Infection control, UZ Brussel, Brussels (Els Van Nedervelde, Thomas Demuyser, Arne Witdouck, Siel Daelemans, Virgini Van Buggenhout, Caroline Wylock), Department of Microbiology, Jessa Ziekenhuis, Hasselt (Door Jouck, Koen Magerman, Marieke Bleyen), Epidemiology of Infectious Diseases, Sciensano, Brussels (Melissa Vermeulen, Sebastien Fierens), National Influenza Centre, Sciensano, Brussels (François Dufrasne, Sarah Denayer), Pediatrics Department, CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels (Marc Hainaut), Service of Clinical Biology, Grand Hôpital de Charleroi, Charleroi (Benédicte Lissoir) and Service of Infectiology, Grand Hôpital de Charleroi, Charleroi (Xavier Holemans, Catherine Sion).

Czechia: National Institute of Public Health, Prague (Alexander Nagy, Pavel Slezak, Timotej Suri, Jaromira Vecerova)

Latvia: Center for Disease Prevention and Control of Latvia (Raina Nikiforova)

Netherlands: we thank epidemiologists, Rianne van Gageldonk, Anne Teirlinck, Daphne Reukers and Liz Jenniskens from the RIVM, Bilthoven for weekly assessment of the influenza situation in the

Netherlands, epidemiologist Mariëtte Hooiveld from Nivel, Utrecht for coordinating the GP sentinel surveillance network and reporting epidemiological data and the GPs and patients in this network for reporting incidence data and taking swabs for virological analysis, the diagnostic hospital and peripheral laboratories in the Netherlands for weekly reports on influenza virus detections and submitting influenza virus positive specimens to Erasmus MC and RIVM, Ron Fouchier, Mark Pronk and Pascal Lexmond from Erasmus MC, Rotterdam and Sharon van den Brink and Lisa Wijsman representing the molecular team and Mariam Bagheri, Gabriel Goderski, John Sluimer and Chantal Herrebrugh from RIVM, Bilthoven for diagnostics and detailed genetic, antigenic and antiviral susceptibility analysis of influenza virus positive specimens.

Spain: SiVIRA. Surveillance and vaccine effectiveness Group in Spain(Grupo SiVIRA de vigilancia y efectividad vacunal en España Grupo SiVIRA de vigilancia y efectividad vacunal en España)

United Kingdom (UK) of Great Britain and Northern Ireland (England): UK Health Security Agency: Suzanne Elgohari

Ukraine: Public Health Center of the Ministry of Health of Ukraine (Oleksandr Matskov)

Abstract (word count 250)

The emergence of SARS-CoV-2 in late 2019 saw the implementation of public health and social measures (PHSM) by countries across Europe to reduce its transmission and impact on populations. Consequently, many countries reported changes in influenza virus circulation and extensive disruptions to routine surveillance systems. We describe the epidemiology of influenza in Europe between weeks 40/2020 and 39/2022 compared to the 2016/17 to 2019/20 seasons using sentinel, non-sentinel and Severe Acute Respiratory Infections (SARI) surveillance systems.

Low detections of influenza were observed through primary care sentinel sources during seasonal influenza periods (week 40 to 20); where 56 detections (<1% positivity) in 2020/21 and 7,261 (11% positivity) detections in 2021/22 were observed, compared to an average of 18,383 detections (36% positivity) in 2016/17 to 2019/20. Similarly, 11 (<1% positivity) and 1,488 (6% positivity) detections were noted through SARI surveillance sources in 2020/21 and 2021/22 respectively, compared to an average of 2,850 (27% positivity) detections in 2016/17 to 2019/20. However, the 2021/22 interseasonal period saw unusual increases in influenza detections through all surveillance site types. Negative correlations between PHSM stringency and detections were noted for 6 countries in the 2021/22 season, with R-values ranging from -0.60 to -0.75.

In conclusion, findings suggest that the restriction and easing of PHSM measures were associated with decreases and increases in influenza virus detections. Our observations of out-of-season influenza activity highlight the importance of an integrated respiratory surveillance strategy to monitor circulating respiratory viruses throughout the year to inform optimal prevention and control strategies.

Keywords

Influenza, sentinel, non-sentinel, severity, surveillance, epidemiology, Europe, COVID-19 pandemic

Introduction

Influenza surveillance is recognized to be of critical public health importance to monitor and assess the impact of seasonally circulating influenza viruses which significantly contribute to global morbidity and mortality[1]. Following the emergence of the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) in 2020 (officially declared as a public health emergency of international concern on 30 January 2020) [2], a substantial decline in the circulation of a range of respiratory viruses, including influenza virus, was observed. This was notable through long-established sentinel and non-sentinel surveillance systems in countries, territories and areas (hereafter referred to as countries) in the World Health Organization (WHO) European Region , the European Union (EU) and European Economic Area (EU/EEA) (hereafter referred to as Europe), in the 2019/20 and 2020/21 seasons [3,4].

Influenza surveillance in the European Region is jointly coordinated by the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe, where weekly epidemiological and virological influenza data are submitted by countries to The European Surveillance System database (TESSy; managed by ECDC). Regional surveillance data is used to determine the start, end, magnitude, and severity of the season as well as the dominant circulating influenza virus types, A subtypes and B lineages.

Sentinel surveillance systems remain the gold standard for the detection and monitoring of circulating respiratory viruses including influenza virus. In the European Region, sentinel surveillance for influenza is conducted by countries using a representative subset of primary care outpatient and, separately, hospital sites. These systems have centralised coordination and application of pre-defined case definitions such as influenza-like illness (ILI) and/or acute respiratory infection (ARI) and severe acute respiratory infections (SARI), as described previously[5].

Since the start of the Coronavirus Disease 2019 (COVID-19) pandemic, some countries have also integrated testing for SARS-CoV-2 and Respiratory Syncytial Virus (RSV) into these systems in line with influenza testing from sentinel sourced specimens, following the ECDC and WHO guidance from October 2020[3,6,4,7].

Existing sentinel systems in primary and secondary care have been negatively impacted by the COVID-19 pandemic as a result of a spectrum of factors including limited access to health care, redistribution of patients and specimens to COVID-19 testing centres, suspension of physical

consultation in primary care, or limited capacity to maintain or enhance these systems given other pandemic-related priorities[8].

To assess the impact of the COVID-19 pandemic on sentinel surveillance including laboratory confirmed hospitalizations for influenza, this study provides a descriptive epidemiological summary of influenza virus testing and detections in the European Region over the two main influenza seasons during the pandemic between weeks 40/2020-2021 and 40/2021-20/2022 and the 2021 and 2022 interseasonal periods (weeks 21-39) in comparison to the same in the previous four seasons (2016/17 to 2019/20).

Methods

This retrospective epidemiological analysis used data submitted to The European Surveillance System (TESSy) by countries in Europe. The influenza season is defined for the northern hemisphere as week 40 in a given year to week 20 of the following year. For the purposes of this analysis, each interseasonal period (ranging between weeks 21 and 39 of a given year) was also included. The study period ranges from week 40/2020 to week 39/2022 with comparisons to the four previous seasons (2016/17 to 2019/20), where appropriate.

Data sources

Qualitative indicator intensity is a measure of influenza activity that considers the level of ILI and/or ARI rates as well as influenza virus detections and is reported based on an individual country assessment according to set definitions[9].

Weekly aggregated data on number of sentinel tests and detections in primary care and hospital settings were extracted from TESSy during week 40/2022 (7 October 2022), including data from 47 reporting countries in Europe.

The distribution of influenza virological data derived from specimens taken in sentinel primary care outpatient (from ILI or ARI cases) and hospital inpatients (from Severe Acute Respiratory Illness (SARI) cases) sites, separately, was summarized by week and where available by influenza virus type, A-subtype or B-lineage. A subset of countries additionally monitor laboratory confirmed influenza cases hospitalized in intensive care units (ICU) and/or other wards. Data from non-sentinel sources (such as hospitals, schools, primary care facilities not involved in sentinel surveillance, or nursing homes and other institutions) were also summarized.

Statistical methods

Circulating viruses were classified as dominant by surveillance systems if at least 10 specimens were tested and ≥60% of influenza viruses were identified as a given type (A or B), A-subtype (A(H1)pdm09 (seasonal influenza subtype after the 2009 pandemic), A(H3)) or B-lineage (B/Victoria, B/Yamagata). If between 41% and 59% of viruses, inclusive, were assigned to more than one type or A-subtype or B-lineage, these viruses were classified as codominant. This methodology has been previously used and outlined in the TESSy guidance [5].

Positivity (proportion positive)

Positivity was calculated as the number of weekly influenza virus-positive specimens divided by the number of specimens tested for influenza virus, when at least 10 specimens were tested for a given week.

Epidemic influenza circulation is considered to have started when the first of two consecutive weeks with at least 10% of specimens from sentinel sources tested positive for influenza and the end of the epidemic as the last week with a percent positive of at least 10%.

Correlation with Public health and social measures (PHSM)

Stringency of PHSM was derived from the PHSM Severity Index[10], which was developed to capture a Severity Index for each country based on six standardized PHSM indicators (wearing of masks (face coverings), school closures, workplace closures, restrictions on gatherings, stay-at-home mandates and international travel limitations) as reported by countries, to mitigate the transmission of COVID-19 Stringency of PHSM was calculated[10] as the weekly mean percentage of the six composing measures from 15 January 2020 to 30 September 2022, with 0% defined as no restrictions imposed and 100% defined as all considered restrictions imposed. Data for the United Kingdom could not be disaggregated (England, Northern Ireland, Scotland and Wales) for this analysis and was therefore considered as one Member State of the WHO European Region.

Pearson's correlations were calculated using each country's sentinel and SARI positivity against each PHSM in turn and data were restricted to at least 100 detections, to allow for more robust correlations, which meant that only the 2021/22 seasonal period was included in these analyses as the 2020/21 seasonal period did not reach 100 detections. Only statistically significant ($p<0.05$) results are reported here. As previously described[5], the strength of relationships was defined using the following r value ranges: very strong (r ranging between -1 and -0.80), strong (between -0.79 and -0.60), medium (between -0.59 and -0.40), weak (between -0.39 and -0.20) and very weak (between -0.19 and 0) [5].

Geo-temporal correlations

Additionally, geo-temporal analyses were used to calculate Pearson's correlations to determine potential relationships between a country's central longitude and latitude in relation to the start of its epidemic period. This analysis could only be done for the 2021/22 seasonal period as this was the only time period with enough data.

Analyses were performed using R version 4.0.5[11].

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Results

Seasonal period (week 40/2020 to 20/2021 and week 40/2021 to 20/2022)

Intensity indicators

During the 2020/21 season, only 11 out of 54 countries (mainly in the eastern parts of the Region) reported at least one week of influenza intensity to be above baseline level, of which three countries (Kazakhstan, Kyrgyzstan and Ukraine) reported at least one week of medium intensity in this time period (Figure 1). In comparison, during the 2021/22 season, 42 out of 54 countries reported at least one week of influenza intensity above baseline, including seven countries reporting at least one week of high intensity in Eastern Europe and two countries (Finland and Luxembourg) reporting very high intensity (Figure 1).

Geo-temporal correlation

From the 31 countries in the 2021/22 seasons, with sufficient data to be included in the geo-temporal analysis, a medium negative (R = -0.52, 95% confidence intervals = -0.60 to -0.42) correlation was observed with latitude and a medium positive (R = 0.44, 95% confidence intervals = 0.34 to 0.53) correlation was observed with longitude.

Primary care sentinel surveillance

Between weeks 40/2020 and 20/2021, there was no notable seasonal trend in the circulation of influenza viruses compared to previous seasons with a small number (<10 except in week 42/2020) of sporadic weekly detections observed of both influenza virus types A and B through primary care sentinel surveillance sites. There were 40 influenza A virus (13 A(H1)pdm09, seven A(H3), 20 A(not subtyped)) and 16 influenza B virus (three B/Victoria lineage and 13 B with no known lineage; no B/Yamagata lineage) detections reported in these weeks from 44 countries (Tables 1, Table 2, SF1, SF3). The highest number of detections (n=11, all influenza A (not subtyped)) was noted in week 42/2020 and all reported by one country (Tajikistan) (Figure 2, SF1). This is in stark contrast with prior four seasons which had a mean of 18,382.2 detections and a range of 16,445 to 22,321 (Table 1). The highest positivity was also noted in week 42/2020 at 2%, which means that a seasonal influenza epidemic was not declared as the 10% positivity threshold was not exceeded during any week of the seasonal period. This percentage positivity differs greatly from that observed over the previous four

seasons (2016/17 to 2019/20) where the average peak positivity was calculated at 53% (range: 50%-59%) and often later in the seasonal period between weeks 51 and 5 (Figure 5B).

The 2021/22 season was characterized by two peaks in influenza activity with positivity peaking at 16% in week 52/2021 and 27% in week 12/2022 (Figure 5B, Table 1). A total of 7,261 influenza detections were noted with 99% characterized as influenza A; with the majority (5,626) detected as A(H3), and 1% characterized as influenza B during this period in the Europe (Table 2). The first wave of activity was mainly noted in the Eastern parts of the Region, whereas activity in the Western parts of the region was mainly noted during the second wave in the latter weeks of the season, with Finland observing the greatest positivity at 80% during week 17/2022 (Figure SF1).

The largest number of specimens tested were recorded during the 2021/22 season, with a total of 64,153 specimens tested, which was a 21% increase in comparison to the average of 50,543.5 specimens tested over the previous seasons, 2016/17 to 2019/20 (Table 1). However, the range of weekly tests performed was more uniform across the season rather than being characterized by a peak in testing when positivity increased (Figure 5A). In contrast, the 2020/21 season saw a total of 39,457 specimens tested, a 28% decrease in comparison to the average of 50,543.5 specimens tested over the previous seasons, 2016/17 to 2019/20 (Table 1).

Non-sentinel data

Between weeks 40/2020 and 20/2021, there was no notable seasonal trend in the circulation of influenza viruses compared to previous seasons with a small number (≤50 except in week 49/2020) of sporadic weekly detections observed of both influenza types A and B through primary care non-sentinel surveillance sites. There were 436 influenza A (49 A(H3), 26 A(H1)pdm09, 361 A (not subtyped) and 431 influenza B (12 B/Victoria lineage, one B/Yamagata lineage (derived from LAIV vaccines) and 418 B with no known lineage) detections reported in these weeks from 41 countries (Tables 1 and 3). A total of 24 countries reported at least one detection per week for the season; with the highest number of detections (n=50, 27 type B and 23 type A) was noted in week 49/2020, of which 72% (n=36) were from United Kingdom (England) (Figure 3). This is in stark contrast with pre-COVID-19 pandemic seasons where the number of detections ranged between 132,384 and 229,033.

The 2021/22 season was also characterized by two peaks in influenza non-sentinel activity with detections peaking in week 51/2021 (n= 5,420) and in week 12/2022 (n= 12,988), during each respective peak, albeit not to the same level as the average noted across the previous four seasons (range of 132,384 to 229,033) (Figure 5C, Table 1). Influenza A viruses were dominant in this season, accounting for 98% of detections, of which 91% were characterized as A(H3) (Table 3). The countries most affected by each wave was not as distinct as seen in sentinel surveillance, with some countries like Finland, Montenegro, Republic of Moldova, Spain, Sweden and Tajikistan experiencing two distinct waves of activity (Figure SF1).

The first peak of detections (week 51/2021) saw 15 countries reporting at least 10 detections, with Sweden and Russian Federation reporting the most, with 1,851 and 1,320 respectively. The second peak of detections (week 12/2022), saw 29 countries reporting detections, with Denmark and France reported 3,214 and 2,016 detections, respectively.

The largest number of influenza B virus detections were observed in Netherlands (Kingdom of the) (n=202), Russian Federation (n=256) and the United Kingdom (England) (n=950), with the Russian Federation reporting most of its detections (n=23, 79% of detections) as type B (no lineage ascribed). However, the biggest proportion of type B detections was reported by Kazakhstan (n=23, 64% of detections), followed by the United Kingdom (Northern Ireland) (n=125, 22% of detections) and Poland (n=33, 13% of detections) during the 2021/22 season.

SARI surveillance

In line with observations from the primary care surveillance sites, between weeks 40/2020 and 20/2021, very low influenza virus detections were noted through SARI surveillance sites reported by 19 countries. A total of 11 (<1% positivity) influenza A virus detections were reported from two countries (Armenia and Ukraine) (seven A(H3), three A(H1)pdm09 and one A not subtyped) and no influenza B virus detections reported (Table 4, SF2). Week 48/2020 was noted to be the week with the most detections during the 2020/21 season where four influenza A virus detections (three A(H1)pdm09 and one A (not subtyped)) were reported by one country (Ukraine) (Figure 4, SF2).

In contrast, a total of 1,488 (6% positivity) detections were reported from 22 countries during the 2021/22 season, with influenza A viruses (95%) accounting for most detections of which 96% were

influenza A(H3) (Tables 2, 4, Figure 4). Additionally, of the 77 influenza B virus detections, 10 were attributed to the B/Victoria lineage and none to the B/Yamagata lineage (Table 4). These detections were from 22 countries, of which both Lithuania and Serbia recorded the highest overall percentage positivity of 36%. Armenia recorded a peak of 70% positivity (week 51/2021), much higher than in any previous season (Figure SF4). Similarly, to sentinel surveillance, SARI detections saw two waves of activity, with a first peak of positivity in week 51/2021 (92 detections; 12% positivity) and in week 15/2022 (83 detections; 14% positivity) (Figures 4 and 5E).

During the 2021/22 season, the number of patients tested was higher than the 2020/21 season, with a total of 23,636 tests performed (Table 1). A peak in testing was observed in week 2/2022, with 1,039 tests compared to an average of 463.8 in prior seasons for the same week (Figure 5D).

The weekly number of SARI patients tested for influenza in both seasons was continuously greater than that of the average across the previous four seasons. During the 2020/21 season, a peak of 947 patients tested was noted in week 4/2021 in comparison to the average peak of 583.8 tests (range: 501-610) in the same week in prior seasons mainly reported by Turkmenistan and Albania (Figure 5D).

In the 14 countries where a comparison was possible, Republic of Moldova and Ukraine were the only countries where SARI positivity peaked later compared to sentinel positivity. In the other 12 countries, peaks of positivity in both systems occurred at a similar time (SF2, SF4).

Laboratory confirmed hospitalizations

During the 2020/21 season, three laboratory confirmed influenza hospitalizations (one influenza A(H1), one influenza A (not subtyped) and one influenza B (no lineage ascribed)) from ICU wards were reported from three countries (Czechia, Sweden and Ukraine) with no clear age group distinction (Table 5). Only two laboratory-confirmed infections were reported from non-ICU wards during the seasonal period (from Ukraine), both were patients infected with influenza A(H1)pdm09 viruses and aged between 15 and 64 years.

In contrast, during the 2021/22 season, 739 laboratory confirmed hospitalizations from ICU wards (from Czechia, France, Ireland, Sweden and the United Kingdom (England)), and 574 from non-ICU wards (from Czechia, Ireland and Ukraine) were reported. Of those reported from ICU wards, 732 (99%) were type A (of which 93 (13%) were A(H3), 59 (8%) were A(H1)pdm09 and 580 (79%) were not subtyped) and 7 were type B (no lineage ascribed). Of those with known age (559 patients, 69%), 250 (45%) were aged between 15 and 64 years, 198 (35%) were aged 65 years and older, 58 (10%) were aged four years or younger and 53 (9%) were aged between five and 14 years (Table 5). Of the 574 patients reported from the non-ICU wards, only three (<1%) were reported to be infected with type B viruses (no lineage ascribed), and of the type A viruses 155 (27%) were A(H3), three (1%) were A(H1)pdm09 and 413 (72%) were not subtyped. Of these non-ICU patients, 241 (42%) were aged 65 years and older, 223 (39%) were aged between 15 and 64 years, 72 (13%) were aged four and younger, and 38 (7%) were aged between five and 14 years (Table 5). The largest number of cases from ICU wards (n=81) were detected in week 15/2022, but in week 10/2022 from non-ICU wards (n=93).

PHSM correlation

When considering the PHSM used by countries during the 2021/22 season, statistically significant results were seen in 18 countries using the overall average of stringency, all experiencing negative correlations (Figure 6). An overall strong negative correlation could be found between the number of sentinel detections and the overall stringency of measures in Slovenia (r: -0.82, 95% confidence intervals (CI): -0.91 to -0.69), Georgia (r: -0.75, CI: -0.85 to -0.62), Poland (r: -0.75, 95%CI: -0.85 to -0.62), Luxembourg (r= -0.75 CI: -0.85 to -0.6), UK (r: -0.66, CI: -0.77 to -0.49), Hungary (r= -0.63 CI: -0.8 to -0.36), France (r= -0.62 CI: -0.75 to -0.44), Germany (r: -0.62, CI: -0.75 to -0.45), Kyrgyzstan (r= -0.62 CI: -0.8 to -0.33) and Italy (r= -0.6 CI: -0.76 to -0.38). Of the six measures considered here, restrictions on gatherings had the biggest impact on the number of sentinel detections, with Slovenia and Spain recording very strong correlations and eight countries (Denmark, Luxembourg, France, Georgia, Germany, Hungary, Poland, and Switzerland) recording strong correlation, followed by mask wearing (very strong in Georgia; strong in Denmark, Italy, Slovenia, Poland and United Kingdom) and workplace restrictions (strong correlation in Georgia, Luxembourg, Kyrgyzstan, Poland, Slovenia and

United Kingdom). School closures had strong correlation with sentinel number of cases in Georgia, Poland and Kyrgyzstan (Figure 6).

Data for only three countries was statistically significant when considering correlations between overall stringency of PHSM and SARI cases: Belgium (r= -0.59, CI: -0.74 to -0.37), Georgia (r= -0.67, CI: -0.80 to -0.49) and Russian Federation (r= 0.42, CI: 0.20 to 0.60). From these, a strong negative correlation could only be seen in Georgia with travel (r= -0.68, CI: -0.80 to -0.50), gatherings (r= -0.66, CI: -0.79 to -0.48) and masks (r= -0.43, CI: -0.64 to -0.18) restrictions and in Belgium with gatherings (r= -0.70, CI: -0.82 to -0.52) and workplace (r= -0.61, CI: -0.76 to -0.39) restrictions.

Interseasonal period (weeks 21 to 39/2021 and weeks 21 to 39/2022)

It is of note that not all countries report or monitor influenza activity out of the influenza seasonal weeks.

Intensity indicators

During the 2020/21 interseasonal period, only seven out of 31 countries reported influenza intensity to be above baseline level, of which Kazakhstan reported at least one week of medium intensity in this time period (Figure 1). In comparison, during the 2021/22 season, nine out of 34 countries reported influenza intensity above baseline, including Kazakhstan that reported very high intensity in one week (Figure 1).

Primary care sentinel surveillance

Between weeks 21 and 39/2021, there were 10 influenza type A viruses (eight A(H3) and two A (not subtyped)) reported from three countries (France, Germany and Kyrgyzstan) and no type B virus detections (Table 2, Figure 3). This total number of type A virus detections was lower than the average number of detections seen during prior interseasonal periods, but the lack of detection of type B viruses contrasted with their detection in prior interseasonal periods (Table 2). The total number of primary care sentinel specimens tested (n= 7,993) for influenza virus during this period was greater than those observed in the average number of specimens tested in the previous four seasons (average: 2,110.5) (Tables 1 and 2). Week 39/2021 saw the highest number of detections during the 2021 interseason with 5 detections (all influenza A(H3)); all detections were reported from

Kyrgyzstan. The overall positivity in week 39/2021 was 22%, which was greater than the average positivity of <1% noted in previous seasons for this period (Figure 5B).

Between weeks 21 and 39/2022, a total of 1,045 influenza virus detections were reported, with an overall positivity of 5%, which was higher than the average number of detections and positivity from any prior interseasonal periods (n=<1%). The majority (97%) of these detections were type A viruses, of which A(H3) accounted for 91% (n=855). Of the 33 type B viruses identified, six were B/Victoria and none of those subtyped were B/Yamagata (Tables 1 and 2). The largest number of detections were recorded in week 21/2022 (Figure 2), with 96 detections (of which 91 were type A(H3), two were A(H1)pdm09 and two were not subtyped) reported from 12 countries and the majority (n=62, 65%) were identified in Spain. From week 34 to 39/2022, percentage positivity ranged between 6 and 8%, which was higher than the same weeks in any previous seasons (Figure 5B).

Non-sentinel data

Between weeks 21 and 39/2021, there were 301 (84% of detections) influenza type A viruses (222 A(H3), six A(H1)pdm09 and 73 A (not subtyped) reported from 31 countries and 59 type B virus detections (only one was ascribed to a lineage, and it was B/Victoria) (Table 1 and 3, Figure 3). This total number of type A virus detections was within range of the average number of detections seen during prior interseasonal periods (Table 3). Week 37/2021 saw the highest number of detections during the 2021 interseason with 88 detections (52 influenza A(H3), one A(H1)pdm09, 20 influenza A unsubtyped and 15 type B viruses (no lineage ascribed)) with the majority of detections (n=43, all A(H3)) reported from Croatia. The maximum number of detections previously seen in pre-COVID-19 pandemic seasons during week 37 was 60 (Figure 5C).

Between weeks 21 and 39/2022, a total of 6,570 influenza virus detections were reported, which was higher than the average number of detections from any prior interseasonal periods (maximum number of detections = 1,422). The majority (94%) of these detections were type A viruses, of which A(H3) accounted for 83% (n=1,846). Of the 368 type B viruses identified, 32 were B/Victoria and none were B/Yamagata (Tables 1 and 3). The largest number of detections were recorded in week 21/2022 (Figure 3), with 1,145 detections (of which 288 were type A(H3), 14 were A(H1)pdm09, 784 were not subtyped and 59 were type B (three were B/Victoria)) reported from 21 countries and the largest

proportion (n=339, 30%) were identified in Norway. Between weeks 25 and 39/2022, the number of positive detections ranged between 152 and 365 which was higher than the same weeks in any of the four pre-COVID-19 pandemic seasons (Figure 3).

SARI surveillance

Between weeks 21 and 39/2021, there were no type B virus detections and 18 influenza virus type A detections (17 A(H3), and one A(not subtyped) (Tables 3 and 4) reported from three countries (Croatia, Kyrgyzstan and Russian Federation). The average weekly number of SARI patients tested for influenza during this period was greater than the average number of patients tested in previous seasons: 218.2 specimens tested compared to an average of 59 per week in prior seasons. The largest number of patients (n=280) were tested in week 37/2021 in comparison to an average of 69.8 tests (range: 28-105) in week 37 during the previous four seasons (Figure 5B).

Between weeks 21 and 39/2022, a total of 100 detections were reported, of which the majority (86%) were type A (52 were A(H3), four were A(H1)pdm09 and 30 were not subtyped) and 14 were type B (two B/Victoria, 12 did not have a lineage ascribed) (Tables 2 and 4). These detections were reported from seven countries (Georgia, Ireland, Kazakhstan, Kyrgyzstan, Malta, Russian Federation and Uzbekistan). A peak of 4% percentage positivity was seen in week 35/2022, with 10 detections from 280 tests. The average number of weekly patients tested for the 2022 interseason was 406.6, higher than in any prior season, with a peak in testing in week 30/2022 (n=532 patients tested performed) (Figure 5).

Laboratory confirmed hospitalizations

Only one case was identified from ICU wards during the 2021 interseasonal period. The patient was infected with a type B virus (no lineage ascribed). No cases were reported from other wards during this period (Table 5).

During the 2022 interseasonal period, 79 cases were reported from ICU wards from four countries (Czechia, Ireland, Sweden and United Kingdom (England)). The majority of which (n=71, 90%) were infected with type A viruses (60 were not subtyped, eight were A(H1)pdm09 and three were A(H3)) and eight were infected with type B viruses (no lineage ascribed). Of the cases with known age groups (n=9), five were aged 65 years and older, two were aged between 15 and 64 years, one was aged between five and 14 years and one was younger than four years (Table 5). During the same

period, 85 patients were identified from other wards, all reported from Ireland. Of these patients, 83 were infected with type A viruses (eight were infected with A(H3) and three with A(H1)pdm09) and two were infected with type B viruses (no lineage ascribed). Of these 85 patients, 67 were aged 15 years and older (36 were aged between 15 and 64 years and 31 were aged 65 years and older), three were aged 5 to 14 years and 15 were aged four or younger).

Discussion

Our study described substantially fewer detections and circulation of influenza during the 2020/21 (week 40 to 20) and during the 2021/22 seasonal period despite widespread testing, in comparison to those observed in the previous four influenza seasonal periods (2016/17 to 2019/20) in Europe. This further builds on evidence seen mid-season of 2020/21[3]. We also highlight that despite the subsequent resurgence in influenza activity in 2021/22 compared to the 2020/21 season, the circulation and timing were different to typical influenza annual epidemic activity observed before the COVID-19 pandemic, and seasons following the 2009 influenza pandemic. The study saw additional unusual interseasonal detections reported from sentinel, non-sentinel and SARI surveillance sites in 2022.

Our findings of low or no detections of influenza viruses through both primary and SARI systems in 2020/21 coincided with increased transmission of SARS-CoV-2 during the 2020/21 seasonal period and high levels of PHSM stringency implemented to reduce the transmission of SARS-CoV-2, but which also disrupted influenza virus transmission. . Indeed since the declaration of the COVID-19 pandemic in March 2020 and subsequent implementation of PHSM across the globe, decreases in influenza virus detections have been noted in the latter part of the 2019/20 influenza season, albeit past its peak, across Europe; a trend which was still evident mid-season of 2020/21[3,12,13]. The findings of decreased detections of influenza during the 2020/21 season are consistent with those observed in other countries of the Northern as well as then the Southern hemisphere, with influenza positivity not exceeding 10% throughout each hemisphere's seasonal period[14–17]This is also evidenced through our findings of decreased influenza virus detections when the PHSM were at their most stringent denoting the interference of the SARS-CoV-2 waves on influenza detections in the Region. With the reduced stringency of PHSM during the 2021/22 season, atypical late influenza activity was detected with two waves of activity, although this circulation was still lower than during the 2016/17 to 2019/20 seasons. Further aberrant circulation of influenza can still be anticipated.

Additionally, our findings highlighted a mix of influenza subtypes circulating and we noted that influenza B/Yamagata lineage viruses were not detected through primary, SARI or non-sentinel

563 sources throughout our study period. Possible extinction of B/Yamagata has been highlighted before
564 and has potential future implications for influenza vaccine composition[18].
565
566 It is also significant to note that our study of reduced influenza virus detections coincided with high
567 numbers of SARS-CoV-2 detections during the seasonal period in the SARI data and an increase in
568 influenza virus detections was noted when the circulation of SARS-CoV-2 detections decreased in
569 both interseasonal periods [19]. This was particularly evidenced through SARI sentinel sites during the
570 interseasonal period. It has been suggested these observations may be due to viral interference[20].
571 Further work is required to understand this phenomenon better.
572
573 The reduction in testing activity could be one factor that contributed to a lower detection of influenza
574 viruses. Most probably, a true reduction in influenza virus transmission occurred because some
575 countries sustained their sentinel surveillance at the same level as before. We demonstrate ongoing
576 testing for influenza through a range of surveillance systems, with actually greater number of
577 specimens tested for influenza than several seasons before, and through both primary care sentinel
578 and SARI surveillance schemes during the interseasonal period in 2022. This observation of
579 increased testing may have been due to the increased use of multiplex assays to test for influenza
580 viruses, SARS-CoV-2 and RSV. There was also the increased need to detect SARS-CoV-2 and its
581 variants at a time when PHSM were relaxed. Nonetheless, it is important to note that there were
582 changes in the number of reporting countries during the pandemic in comparison to pre-pandemic
583 seasons[21]. The main factor for the reduced transmission thus seems to be the impact of PHSM,
584 including travel measures across the Region. These measures aimed to mitigate the increasing
585 spread of SARS-CoV-2 variants, Alpha (B.1.1.529) and Beta (B.1.351) detected in December 2020,
586 however as measures were relaxed in the 2021/22 season and at a time when the Omicron variant,
587 with greater transmissibility, began circulating and as it was also usually a time of seasonal circulation
588 of influenza viruses, so the implementation of PHSM would have hypothetically also naturally reduced
589 transmission of influenza virus. Potential viral interference and competition of both influenza and
590 SARS-CoV-2 could have also been a factor[19]. Further work is required to disentangle these effects.
591

The reduced circulation of influenza virus for a prolonged period poses several uncertainties and implications for future seasons. Firstly, the reduced/lack of exposure to influenza viruses increases susceptibility among populations, particularly those in younger age groups, within whom late first exposure to such viruses, may impact future immune response, but also in older age-groups in whom immunity may then have waned. This could lead to a surge in rates of influenza once its circulation resumes and/or co-circulate with other respiratory viruses[22]. Indeed, the 2022/23 season has seen an unexpectedly early influenza season[23]. Secondly, the lack of circulation may impact on virus characterization for the annual recommendations of influenza vaccines' composition as predictions are heavily reliant on laboratory information from characterization of currently circulating viruses[6]. These characteristics, therefore, have been based on a reduced sample of circulating viruses available increasing the risk of suboptimal vaccine effectiveness, this issue is now reducing following the subsequent increase in circulation in 2021/23 and in subsequent seasons.

Some limitations to this study should be considered. Firstly, it is important to highlight the influence of the COVID-19 pandemic on the varying degrees of disruption to national sentinel surveillance systems, particularly influenza specific indicators such as ILI and ARI rates, due to changes in health seeking behaviors and limitations in the capacity of sites to receive cases and take specimens, impacting their ability to monitor respiratory viruses, including RSV. Secondly, not all countries who collate sentinel surveillance data report these data through the TESSy[21]. Furthermore, some countries do not maintain all-year-around surveillance therefore may not have reported data for the interseasonal periods, introducing the likelihood of underestimating our findings. Thirdly, not all countries have fully implemented an integrated approach with the inclusion of influenza and SARS-CoV-2 testing in NICs. Despite this, findings from sentinel surveillance, which has been considered to be the gold standard for the monitoring of influenza, correlate with those from non-sentinel sources, as described earlier[3]. Lastly, there is potential for differential reporting across countries, due to variations in population coverage; for example there may have been an increase in participating surveillance sites due to the COVID-19 pandemic, sampling approaches for example the use of antigen testing impacting health seeking behaviors during the COVID-19 pandemic and laboratory techniques used (for example multiplex assays).

In conclusion, the 2020/21 season observed exceptionally low detections of influenza virus, despite elevated testing, which was followed by unusual activity during the 2021 interseasonal period coinciding with the differing waves of SARS-CoV-2 circulation. The easing of PHSM was associated with a rise in influenza virus detections during the 2021/22 season in many countries. The circulation and timing of influenza activity during the 2021/22 season are not comparable to any influenza annual epidemic activity observed before the COVID-19 pandemic. As countries move towards integrating surveillance of SARS-CoV-2, influenza and other relevant respiratory viruses, underlying systems might change and reported data might not be comparable to historical data. Further work is also needed to understand the recent lack of circulation of influenza B/Yamagata lineage which could have implications on future vaccine composition[18]. Our study has highlighted the importance to ensure resources and strengthening and implementing integrated surveillance across the Region for the most commonly circulating respiratory viruses throughout the year, to identify unusual out of season detections as we move from the acute phase of the COVID-19 pandemic. It is, therefore, vital for countries to continue to plan towards the implementation of robust and agile integrated respiratory disease surveillance in line with the WHO European Region and ECDC guidelines[24] to vigilantly and simultaneously survey, sequence and report the circulation of the most commonly circulating respiratory pathogens such as influenza, RSV and SARS-CoV-2[8].

Funding

WHO Regional Office for Europe was supported for work on influenza by a cooperative agreement from the United States Center for Disease Control and Prevention (NU511P000876); the funder had no role in the analysis or interpretation of the data.

Conflicts of interest

No conflict of interest declared.

Disclaimer:

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 availability

TESSy data are available upon request (https://www.ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy)

Author contributions

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Piers Mook: Conceptualization, formal analysis, methodology, writing – original draft, writing- review & editing, supervision

Richard G. Pebody: Conceptualization, writing- review & editing, supervision

All authors: - review

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Figures

Figure 1. Qualitative indicator influenza intensity, by week and West (W) to East (E), between weeks 40/2020 to 39/2022, Europe
Note: Seasonal weeks: 40/2020 to 20/2021 and 40/2021 to 20/2022; interseasonal weeks: 21 to 39/2021 and 21 to 39/2022.

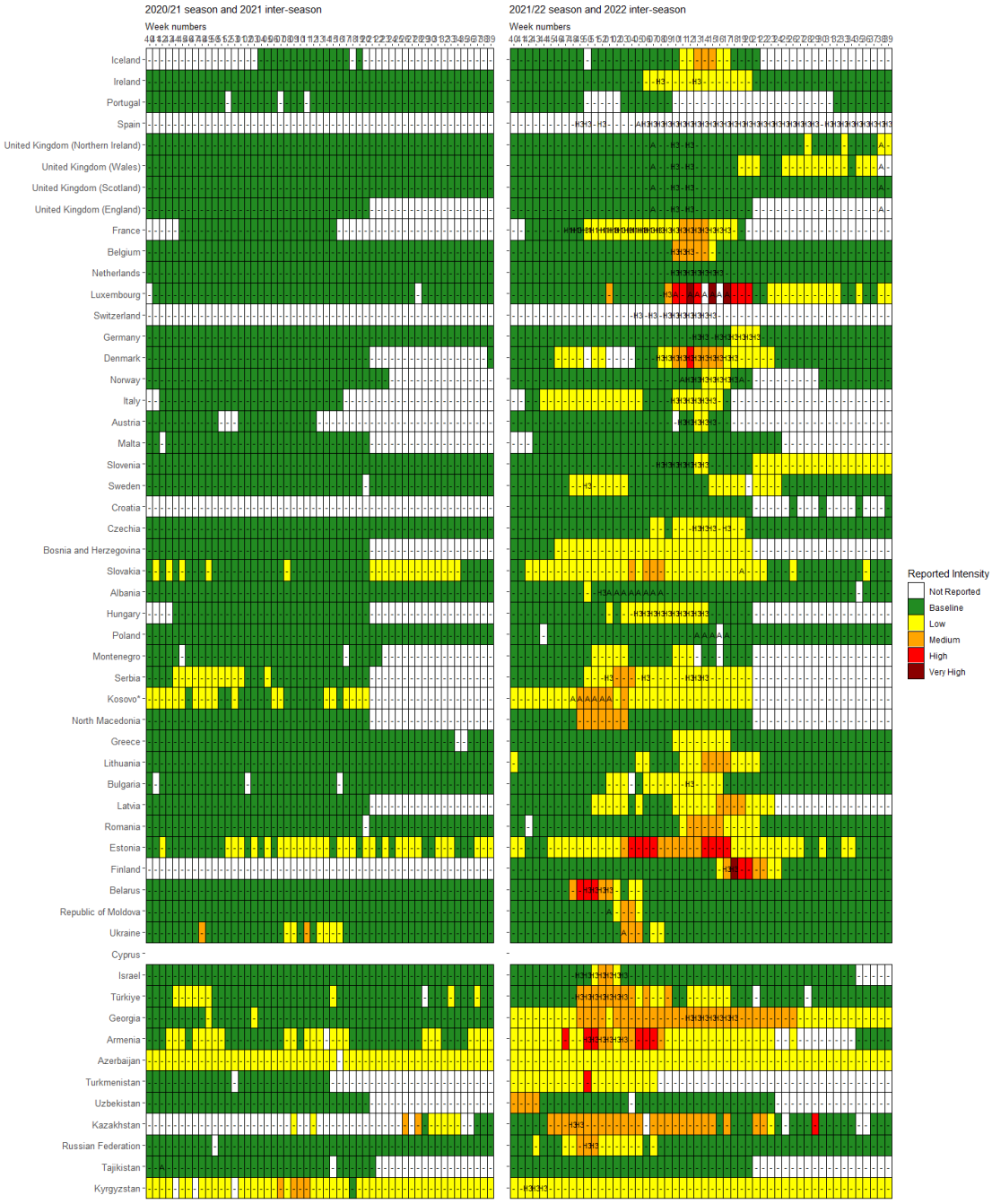


Figure 2. Weekly number of laboratory-confirmed positive tested influenza specimens in sentinel primary care with percentage positivity (upper figure) and % of stringency of public health and social measures (PHSM) (lower graph), by week, between weeks 40/2020 to 39/2022, Europe

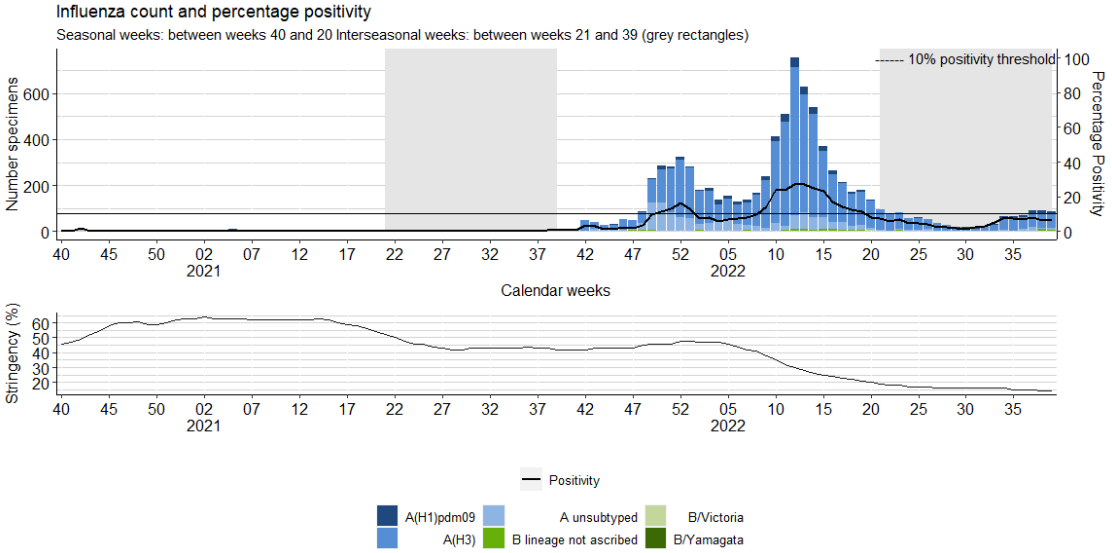


Figure 3. Weekly number of laboratory-confirmed positive tested influenza specimens in non-sentinel primary care with percentage positivity (upper figure) and % of stringency of public health and social measures (PHSM) (lower graph), by week, between weeks 40/2020 to 39/2022, Europe

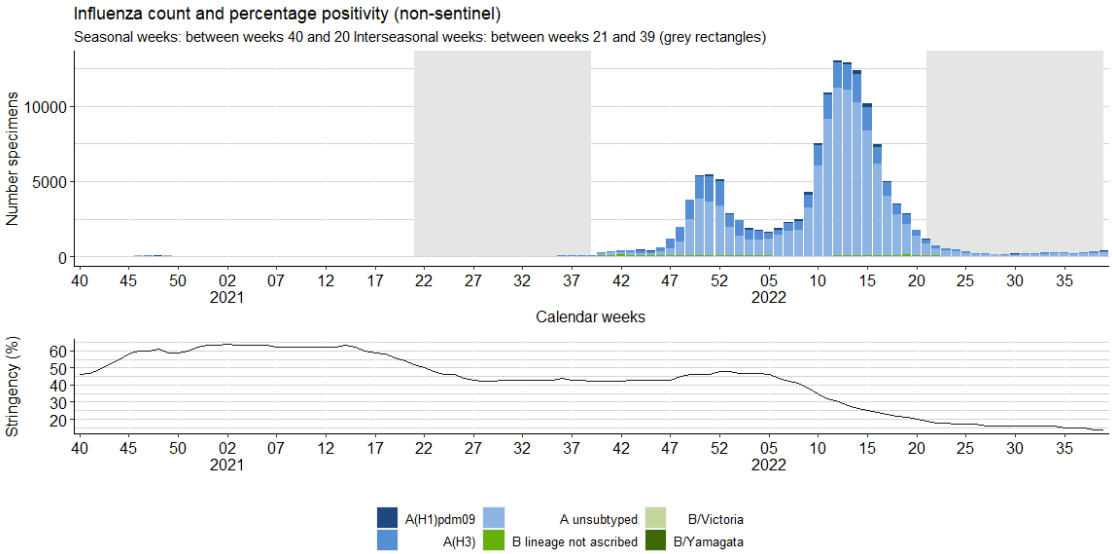


Figure 4. Weekly number of laboratory-confirmed positive tested influenza specimens in hospitalized patients with severe acute respiratory illness (SARI) and percentage positivity (upper graph) and % of stringency of public health and social measures

(PHSM) (lower graph), by week, between weeks 40/2020 and39/2022, Europe

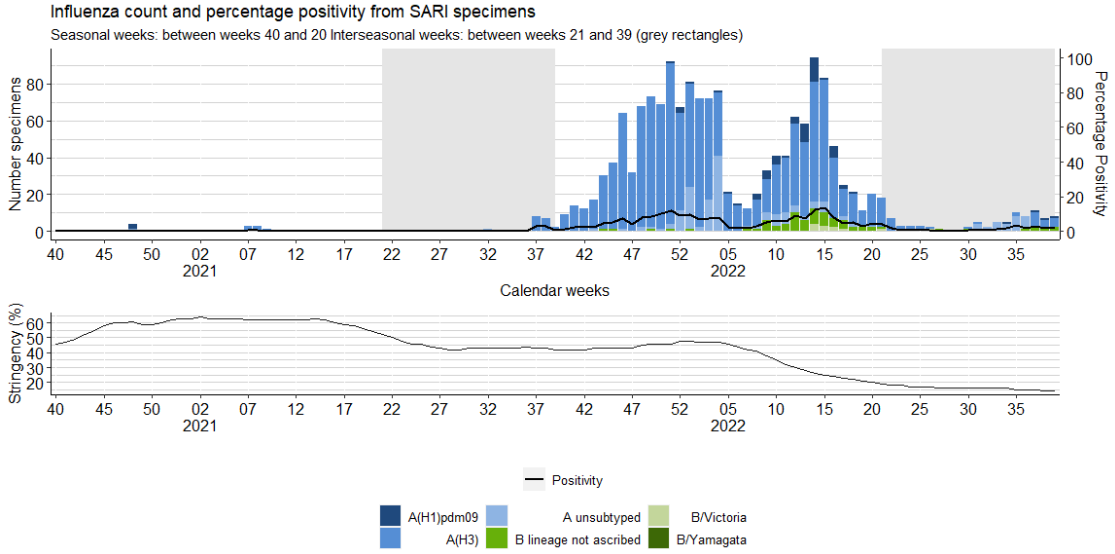


Figure 5. Top row: Count of specimens tested (A), and percentage positivity (B) of influenza specimens per week from sentinel sources compared to the mean, minimum (Min) and maximum (Max) from pre-COVID-19 pandemic seasons; Middle row: count of non-sentinel influenza detections compared to the mean, minimum (Min) and maximum (Max) from pre-COVID-19 pandemic seasons (C); Bottom row: count of specimens tested for influenza (D), and percentage positivity (E) from SARI sites compared to the mean, minimum (Min) and maximum (Max) from pre-COVID-19 pandemic seasons, Europe. Note: percentage positivity was calculated when at least ten specimens were

tested.

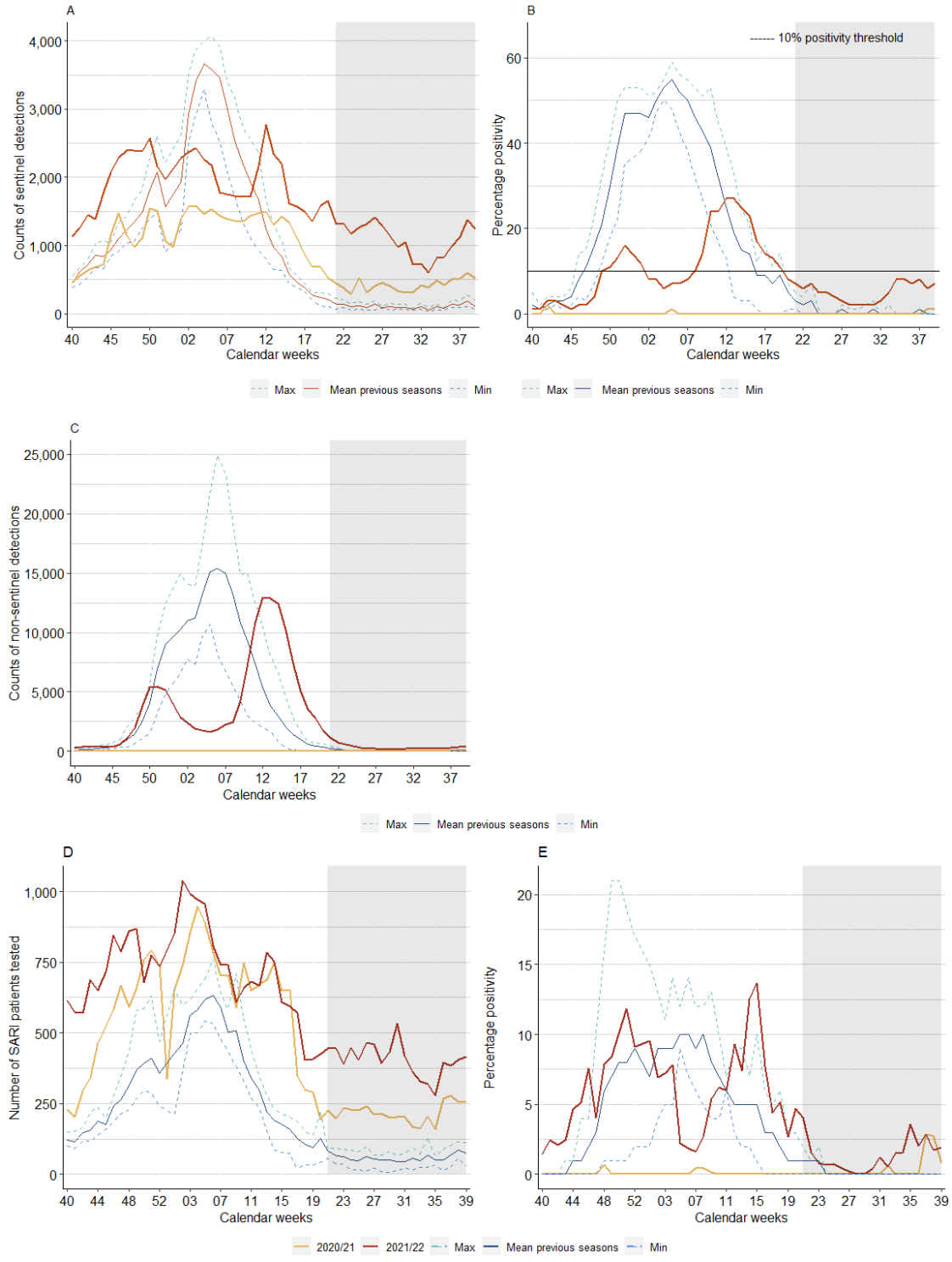
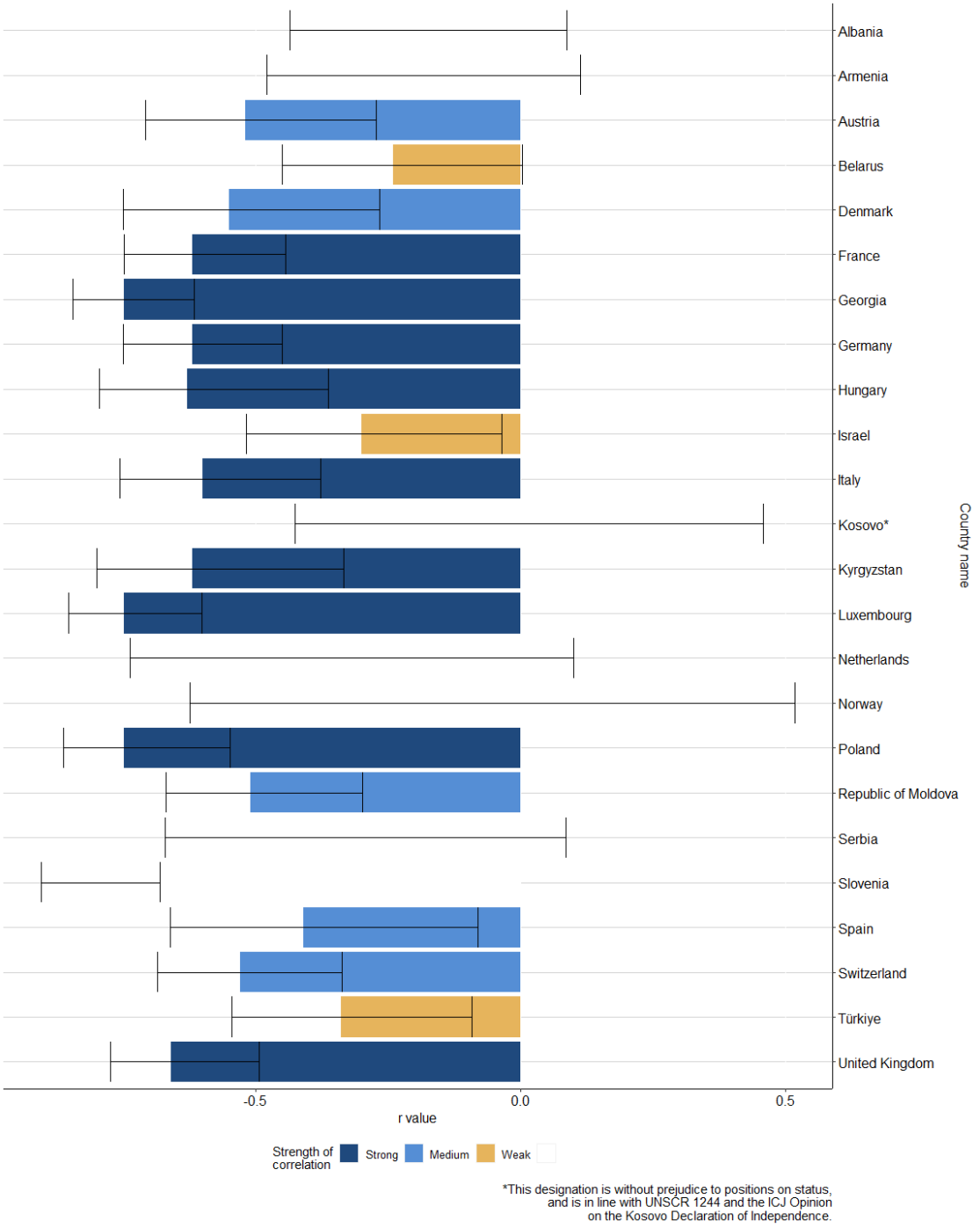

A
Counts of sentinel detections
4,000
3,000
2,000
1,000
0
40 45 50 02 07 12 17 22 27 32 37
Calendar weeks
B
------ 10% positivity threshold
Percentage positivity
60
40
20
0
40 45 50 02 07 12 17 22 27 32 37
Calendar weeks
Max Mean previous seasons Min
Max Mean previous seasons Min
C
Counts of non-sentinel detections
25,000
20,000
15,000
10,000
5,000
0
40 45 50 02 07 12 17 22 27 32 37
Calendar weeks
Max Mean previous seasons Min
D
Number of SARI patients tested
1,000
750
500
250
0
40 44 48 52 03 07 11 15 19 23 27 31 35 39
Calendar weeks
E
Percentage positivity
20
15
10
5
0
40 44 48 52 03 07 11 15 19 23 27 31 35 39
Calendar weeks
2020/21 2021/22 Max Mean previous seasons Min

Figure 6. Summary of correlations between public health and social measure (PHSM) and sentinel surveillance systems for the 2021/22 season, Europe



Tables

Table 1. Number of countries reporting by reporting systems with total number of tested specimens and overall positivity for seasons 2020/21 and 2021/22 compared to the median and range of seasons 2016/17-2019/20, by season (weeks 40-20) and interseason (weeks 21-39), Europe

	2021/22 season		2020/21 season		2016/17-2019/20 seasons			
	Seasonal period	**Interseasonal period**	**Seasonal period**	**Interseasonal period**	**Season (mean)**	**Season (range)**	**Inter-season (mean)**	**Inter-season (range)**
Sentinel surveillance								
Number of countries *	49	37	44	26	48	46 - 50	20.8	14 - 25
Specimens tested	64,153	20,709	39,457	7,993	50,543.5	46,234 - 55,171	2,110.5	1,519 - 2,904
Positive detections	7,261 (11.3%)	1,045 (5%)	56 (0.1%)	10 (0.1%)	18,382.5 (36.4%)	16,445 - 22,321	14.8 (0.7%)	3 - 37
Non sentinel surveillance								
Number of countries *	46	33	41	31	47.2	45 - 48	23	16 - 26
Specimens tested	2,600,987	575,538	869,347	332,582	767,305.5	597,413 - 860,610	62,868.8	52,138 - 73,658
Positive detections	134,493	6,650	867	360	176,715 (23%)	132,384 - 229,033	837 (1.3%)	48 - 1,422
SARI surveillance								
Number of countries *	22	16	19	12	17	15 - 18	6	4 - 7
Specimens tested	23,636	7,725	19,989	4,146	10,389.0	9,556 - 11,308	1,122.8	474 - 1,608
Positive detections	1,488 (6.3%)	100 (1.3%)	11 (<1%)	18 (0.4%)	2,849.8 (27.4%)	2,043 - 3,645	7.8 (<1%)	1 - 11

	2021/22 season		2020/21 season		2016/17-2019/20 seasons			
	Seasonal period	**Interseasonal period**	**Seasonal period**	**Interseasonal period**	**Season (mean)**	**Season (range)**	**Inter-season (mean)**	**Inter-season (range)**

* Reporting at least one specimen tested per season.

Table 2. Distribution of influenza virus (sub)types and lineages from primary care sentinel surveillance for 2020/21 and 2021/22 seasons and previous seasons for respective seasonal and interseasonal periods, Europe

	2021/22 season		2020/21 season		2016/17 - 2019/20 seasons			
Subtype /lineage	**Seasonal period**	**Interseasonal period**	**Seasonal period**	**Interseasonal period**	**Prev inter-season (mean)**	**Seasonal period (mean)**	**Prev inter-season (range)**	**Seasonal period (range)**
Positive samples	7,261 (11.3%)	1,045 (5%)	56 (0.1%)	10 (0.1%)	14.8 (0.7%)	18,382.5 (36.4%)	3 - 37	16,445 - 22,321
Influenza A	7,157 (99%)	1,012 (97%)	40 (71%)	10 (100%)	8.0 (54%)	12,737.5 (69%)	1 - 14	8,200 - 16,752
A(H1)	394 (7%)	85 (9%)	13 (65%)	0 (0%)	2.8 (40%)	4,884.8 (42%)	0 - 7	149 - 8,298
A(H3)	5,626 (93%)	855 (91%)	7 (35%)	8 (100%)	4.2 (60%)	6,864.5 (58%)	1 - 8	2,650 - 13,375
Influenza A not subtyped	1,137	72	20	2	1.0	988.2	0 - 2	579 - 1,265
Influenza B	104 (1%)	33 (3%)	16 (29%)	0 (0%)	6.8 (46%)	5,645.0 (31%)	1 - 23	248 - 14,121
B/Victoria	18	6	3	0	1.5	762.5	0 - 5	13 - 2,492
B/Yamagata	0	0	0	0	0.0	1,839.5	0 - 0	7 - 6,943
B lineage unknown	86	27	13	0	5.3	3,043.0	1 - 18	228 - 6,978
Total samples tested	64,153	20,709	39,457	7,993	2,110.5	50,543.5	1,519 - 2,904	46,234 - 55,171

For type percentage calculations, the denominator is total detections; for subtype and lineage, it is total influenza A subtyped and total influenza B lineage determined, respectively.

Table 3. Distribution of influenza virus (sub)types and lineages from non-sentinel surveillance for 2020/21 and 2021/22 seasons and previous seasons for respective seasonal and interseasonal periods, Europe

	2021/22 season		2020/21 season		2016/17 - 2019/20 seasons			
Subtype /lineage	**Seasonal period**	**Interseasonal period**	**Seasonal period**	**Interseasonal period**	**Prev inter-season (mean)**	**Seasonal period (mean)**	**Prev inter-season (range)**	**Seasonal period (range)**
Positive samples	134,493	6,650	867	360	837	176,715	48 - 1,422	132,384 - 229,033
Influenza A	132,117 (98%)	6,267 (94%)	436 (50%)	301 (84%)	503.2 (60%)	130,557.5 (74%)	30 - 1,147	102,528 - 194,096
A(H1)	2631 (9%)	398 (18%)	26 (35%)	6 (3%)	76.2 (25%)	18,588.2 (42%)	4 - 138	420 - 36,515
A(H3)	28,036 (91%)	1,869 (82%)	49 (65%)	222 (97%)	226.8 (75%)	25,729.8 (58%)	6 - 567	16,638 - 40,086
Influenza A not subtyped	101,450	4,000	361	73	200.2	86,239.5	20 - 445	65,107 - 131,578
Influenza B	2376 (2%)	383 (6%)	431 (50%)	59 (16%)	333.8 (40%)	46,157.5 (26%)	18 - 1,032	2,082 - 126,505
B/Victoria	98	32	12	1	9.5	675.8	0 - 23	46 - 2,067
B/Yamagata	2	0	1	0	47.2	2,644.8	0 - 179	65 - 8,919
B lineage unknown	2276	351	418	58	277.1	42,836.9	18 - 840	1,958 - 117,388
Total samples tested	2,600,987	575,538	869,347	332,582	62,868.8	767,305.5	52,138 - 73,658	597,413 - 860,610

For subtype and lineage percentage calculations, the denominator is the total influenza A subtyped and total influenza B lineage determined, respectively; as not all countries have a true non-sentinel testing denominator, no percentage calculations for total tested are shown.

Table 4. Influenza viral virus distribution by (sub)types and lineage from severe acute respiratory illness (SARI) surveillance for 2020/21 and 2021/22 seasons and previous seasons for respective seasonal and interseasonal periods, Europe

	2021/22 season		2020/21 season		2016/17-2019/20 seasons			
Subtype /lineage	**Seasonal period**	**Interseasonal period**	**Seasonal period**	**Interseasonal period**	**Prev inter-season (mean)**	**Seasonal period (mean)**	**Prev inter-season (range)**	**Seasonal period (range)**
Positive samples	1,488 (6.3%)	100 (1.3%)	11 (0.1%)	18 (0.4%)	7.8 (0.7%)	2,849.8 (27.4%)	1 - 11	2,043 - 3,645
Influenza A	1,411 (95%)	86 (86%)	11 (100%)	18 (100%)	4.0 (51%)	1,996.2 (70%)	0 - 10	893 - 2,770
A(H1)	59 (5%)	4 (7%)	3 (30%)	0 (0%)	2.0 (50%)	842.2 (46%)	0 - 7	7 - 1,978
A(H3)	1,208 (95%)	52 (93%)	7 (70%)	17 (100%)	2.0 (50%)	975.8 (54%)	0 - 3	301 - 2,564
Influenza A not subtyped	144	30	1	1	0.0	178.2	0 - 0	44 - 267
Influenza B	77 (5%)	14 (14%)	0 (0%)	0 (0%)	3.8 (49%)	853.5 (30%)	0 - 8	32 - 1,304
B/Victoria	10	2	0	0	0.2	214.8	0 - 1	0 - 673
B/Yamagata	0	0	0	0	0	123	0 - 0	1 - 341
B lineage unknown	67	12	0	0	3.6	515.7	0 - 8	31 - 770
Total samples tested	23,636	7,725	19,989	4,146	1,122.8	10,389.0	474 - 1,608	9,556 - 11,308

For type percentage calculations, the denominator is total detections; for subtype and lineage, it is total influenza A subtyped and total influenza B lineage determined, respectively.

Table 5. Influenza viral virus distribution by (sub)types and lineage from severe acute respiratory illness (SARI) surveillance for 2020/21 and 2021/22 seasons and previous seasons for respective seasonal and interseasonal periods, Europe

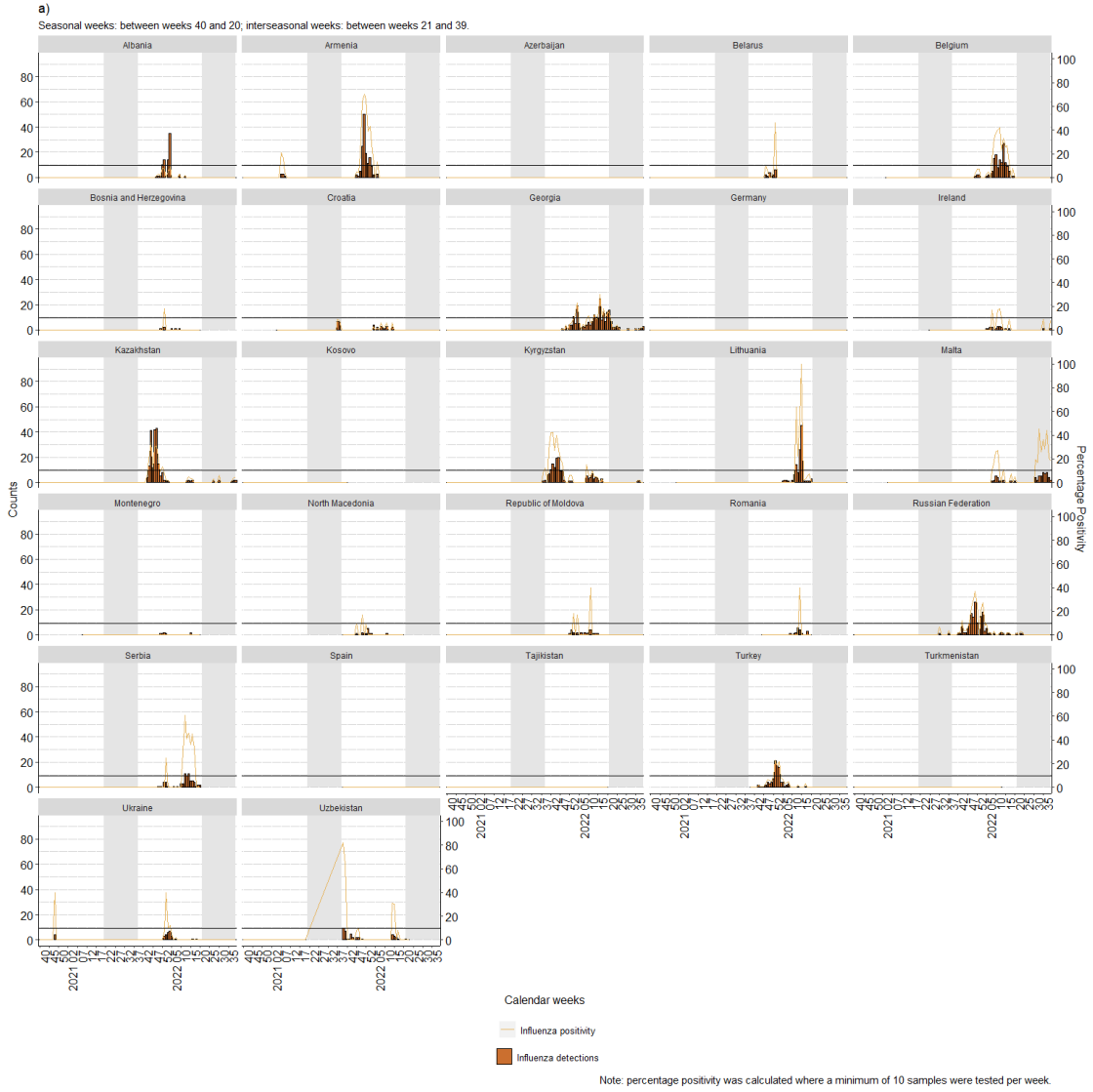
Hospital ward	Variable	2021/22 season	2022 interseason	2020/21 season	2021 interseason
ICU	A(H1)pdm09	59	8	1	0
	A(H3)	93	3	0	0
	A unsubtyped	580	60	1	0
	B	7	8	1	1
	Total (subtypes)	739	79	3	1
	00-04 years	58	1	0	0
	05-14 years	53	1	1	0
	15-64 years	250	2	1	1
	65+ years	198	5	1	0
	Age unknown	180	70	0	0
	Total (ages)	739	79	3	1
Other wards	A(H1)pdm09	3	3	2	0
	A(H3)	155	8	0	0
	A unsubtyped	413	72	0	0
	B	3	2	0	0
	Total (subtypes)	574	85	2	0

Hospital ward	Variable	2021/22 season	2022 intersea son	2020/21 season	2021 intersea son
	00-04 years	72	15	0	0
	05-14 years	38	3	0	0
	15-64 years	223	36	2	0
	65+ years	241	31	0	0
	Total (ages)	574	85	2	0

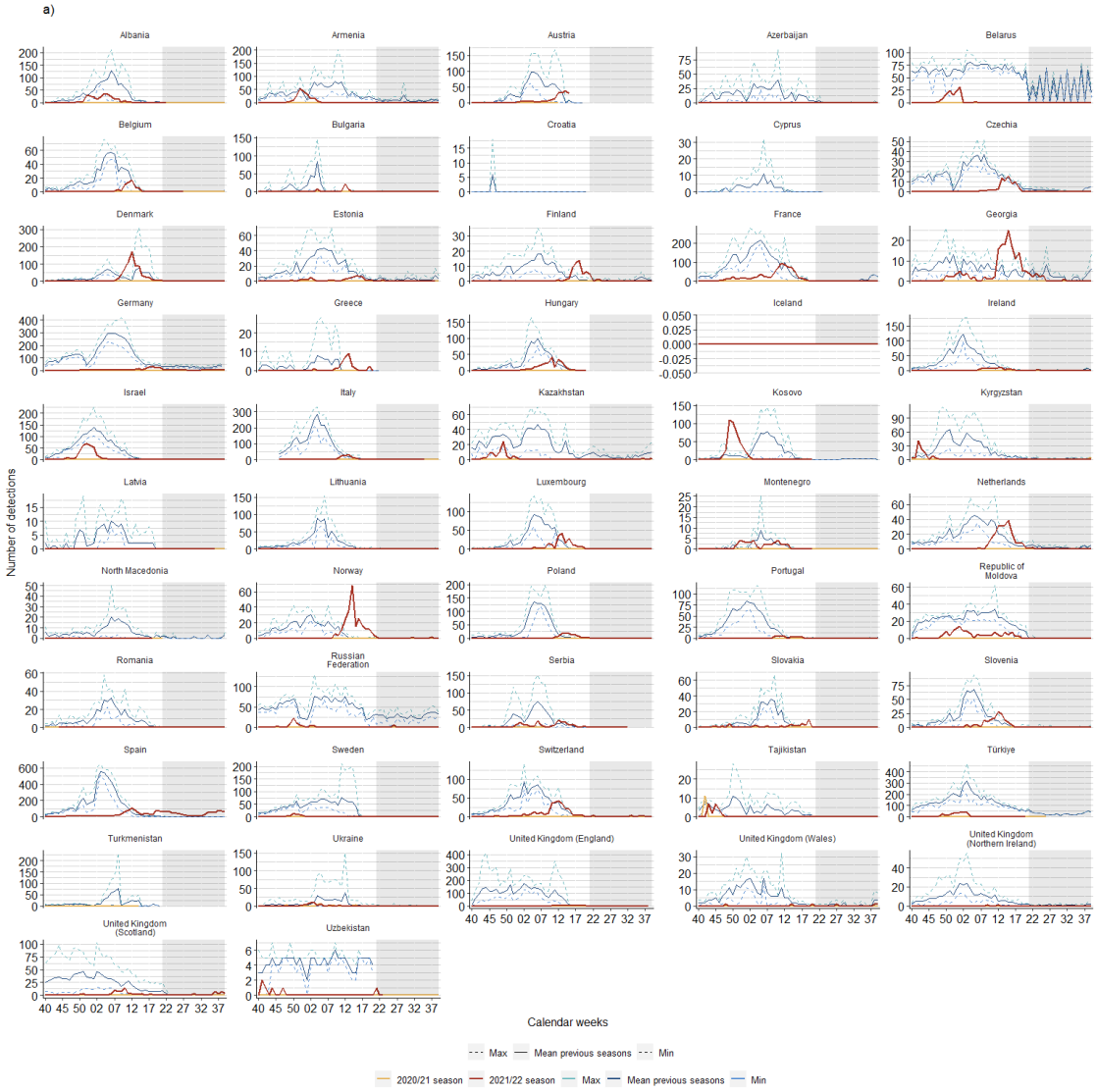
Supplementary Figures

Supplementary Figure 1 (SF1). Individual country-level weekly number and percentage positivity reported for influenza detections through sentinel primary care surveillance, between week 40/2020 and week 39/2021, Europe

Supplementary Figure 2 (SF2). Individual country-level weekly number and percentage positivity reported for influenza detections through SARI surveillance, between week 40/2020 and week 39/2021, Europe



Supplementary Figure 3 (SF3). Individual country-level percentage positivity for influenza, week 40/2020 and 39/2021 in comparison with the mean, minimum, maximum number of specimens in the previous four seasons (week 40 to 39, 2015/16 to 2019/20) through sentinel primary care surveillance, Europe



Supplementary Figure 4 (SF4). Individual country-level percentage positivity for influenza, week 40/2020 and 39/2021 in comparison with the mean, minimum, maximum number of specimens in the previous four seasons (week 40 to 39, 2015/16 to 2019/20) through SARI surveillance, Europe