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Probable extinction of influenza B/Yamagata and its public health implications: a systematic literature review and assessment of global surveillance databases

Saverio Caini, Adam Meijer, Marta C Nunes, Laetitia Henaff, Malaika Zounon, Bronke Boudewijns, Marco Del Riccio, John Paget

Early after the start of the COVID-19 pandemic, the detection of influenza B/Yamagata cases decreased globally. Given the potential public health implications of this decline, in this Review, we systematically analysed data on influenza B/Yamagata virus circulation (for 2020–23) from multiple complementary sources of information. We identified relevant articles published in PubMed and Embase, and data from the FluNet, Global Initiative on Sharing All Influenza Data, and GenBank databases, webpages of respiratory virus surveillance systems from countries worldwide, and the Global Influenza Hospital Surveillance Network. A progressive decline of influenza B/Yamagata detections was reported across all sources, in absolute terms (total number of cases), as positivity rate, and as a proportion of influenza B detections. Sporadically reported influenza B/Yamagata cases since March, 2020 were mostly vaccine-derived, attributed to data entry errors, or have yet to be definitively confirmed. The likelihood of extinction necessitates a rapid response in terms of reassessing the composition of influenza vaccines, enhanced surveillance for B/Yamagata, and a possible change in the biosafety level when handling B/Yamagata viruses in laboratories.

Lancet Microbe 2024; 5: 100851

Published Online May 7, 2024
https://doi.org/10.1016/S2666-5247(24)00066-1

Netherlands Institute for Health Services Research (NIVEL), Utrecht, Netherlands (S Caini PhD, B Boudewijns MSc, M Del Riccio MD, J Paget* PhD); **National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands** (A Meijer PhD); **Center of Excellence in Respiratory Pathogens (CERP), Hospices Civils de Lyon, Lyon, France** (Prof M C Nunes PhD, M Zounon MD); **Centre International de Recherche en Infectiologie, Team Public Health, Epidemiology and Evolutionary Ecology of Infectious Diseases, Université Claude Bernard 1, Inserm U1111, CNRS UMR5308, ENS de Lyon, Lyon, France** (Prof M C Nunes, L Henaff BSc, M Zounon MD); **South African Medical Research Council, Vaccines & Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (Prof M C Nunes); **Department of Health Sciences, University of Florence, Florence, Italy** (M Del Riccio)

*Dr Paget died in November, 2023

Correspondence to:
Saverio Caini, Netherlands Institute for Health Services Research (NIVEL), 3513 CR Utrecht, Netherlands
s.caini@nivel.nl

Introduction

The emergence of SARS-CoV-2 and the resulting COVID-19 pandemic, and the public health measures that were put in place to contain the spread of SARS-CoV-2, caused major disruptions to the circulation of influenza and other respiratory viruses.[1] Early in the course of the COVID-19 pandemic, there was a drastic reduction in the circulation of seasonal influenza viruses, with most countries reporting marked decline in influenza positivity rates, and, in some cases, only sporadic detections or even none at all, during the regular epidemic periods that followed.[2] In late 2021, during the regular northern hemisphere period, influenza viruses gradually resumed circulation;[3] however, whether the pattern of circulation and burden of disease observed before 2020 will be restored, or changes will persist due to the cocirculation of influenza viruses and SARS-CoV-2 is still unknown.

Although the high uncertainty makes predictions difficult, the obvious decrease in the number of influenza B/Yamagata cases has caught the attention of the scientific community. In the years before the emergence of SARS-CoV-2, the B/Victoria and B/Yamagata virus lineages tended to circulate simultaneously, with no clear or consistent pattern in the way the two lineages alternated from one influenza season to another.[4] Globally, during 2012–17, B/Yamagata viruses caused a larger proportion of infections than B/Victoria viruses, but in the 2 years before the COVID-19 pandemic, the B/Victoria lineage had become largely prevalent, with the B/Yamagata-to-B/Victoria ratio dropping to 1:4·5 in 2018 and 1:19·3 in 2019.[5] Early in the course of the COVID-19 pandemic (ie, from March, 2020), and even after influenza viruses started circulating again in late 2021, B/Yamagata lineage viruses were detected in only a few countries globally,[1,6,7] thereby giving rise to the question as to whether B/Yamagata lineage viruses were on the verge of extinction.

To declare the extinction of the B/Yamagata lineage would be premature, since there is a possibility that currently, the viral circulation might be at low levels (sub-threshold to the capabilities of existing surveillance systems) or might be happening in regions not well covered by surveillance systems, thereby leaving scope for a possible resurgence of the B/Yamagata lineage in the future. Indeed, during much of the 1990s, the B/Victoria lineage did not circulate in most regions of the world and was primarily confined to east Asia, before spreading globally again in the early 2000s.[8] The current epidemiological situation holds important implications for public health, particularly with respect to strategies for the development of influenza vaccination.[1,7] Since quadrivalent influenza vaccines contain virus strains from both the B/Yamagata and B/Victoria lineages, the question arises as to whether a vaccine targeting a virus that is currently not circulating is required. Moreover, there is a concern that the mechanistically attenuated replication of the B/Yamagata strains contained in the live attenuated influenza vaccine (LAIV), which is primarily administered to children, could lead to reintroduction of the haemagglutinin and neuraminidase genes of a potentially extinct virus through reassortment with a co-infecting wild-type B/Victoria lineage.[9] During shedding, LAIV retains its cold-adapted nature and a low scope for secondary infections after vaccine-derived influenza B/Yamagata infections, with no reports to date.[10] Therefore, continuous monitoring of viral circulation is essential so that influenza-prevention policies, especially those related to vaccine formulation and composition, can be adapted to the current epidemiological landscape.

Here, we aimed to study the circulation of B/Yamagata influenza viruses from 2020 onwards, to understand whether these viruses are extinct and how their extinction could have public health implications. For this purpose, we conducted an updated systematic review that builds upon

previous assessments and extends to multiple data sources pertaining to the circulation of B/Yamagata influenza viruses. To achieve this, our search (conducted in January, 2024) has been extended from global databases for influenza virological surveillance (FluNet, Global Initiative on Sharing All Influenza Data [GISAID], and GenBank),[7] to include one additional surveillance database (Global Influenza Hospital Surveillance Network [GIHSN]), biomedical literature databases (PubMed and Embase), and webpages of national surveillance systems worldwide.

For more on **FluNet** see https://www.who.int/tools/flunet

Methods

Search strategy and selection criteria

We performed this systematic review in accordance with PRISMA guidelines.[11] On Jan 2, 2024, we searched PubMed and Embase using the following search string: "([influenza OR flu] AND [Yamagata OR Victoria OR lineage OR Vic OR Yam]) OR (influenza b)". All articles published from Jan 1, 2020 onwards were subjected to a multistep selection process to evaluate their eligibility for inclusion in the literature review. The selection procedure consisted of an initial screening-out step in which two investigators (SC and BB) independently discarded irrelevant articles on the basis of their title and abstract, and a second step in which the full text of articles retained after the first step were read to evaluate their eligibility. We did not place any language restriction as long as an English title and abstract were available for the first step of the selection process. An attempt to contact the corresponding author was made when the full copy of an article was not available. Finally, we included articles focusing on influenza in which the collection of respiratory specimens for influenza testing extended from at least Feb 28, 2020, to Jan 2, 2024, when the search was performed, and the virus lineage was characterised in all or a subset of the detected influenza B cases. We excluded articles in which the data collection period was entirely before 2020 or was not specified; no respiratory specimens tested positive for influenza; all influenza detections were due to type A viruses, or the virus type was not characterised; none of the influenza B detections were tested to characterise the virus lineage; or there were no original data (eg, commentaries, editorials, or correspondence without data). Articles that were entirely based on data from FluNet, GISAID, or GIHSN study were not considered, since an extensive search of these databases was also conducted as part of the present study. We applied no restrictions in terms of study design: studies as diverse as surveillance reports, hospital-based clinical studies, vaccine-effectiveness studies, and phylogenetic analysis of influenza isolates (eg, to understand their genetic and antigenic characteristics) were all considered as potentially eligible for inclusion as long as they matched the criteria listed above.

For more on **GIHSN** see https://gihsn.org/

For more on **GISAID** see https://gisaid.org/

The data extracted from each eligible study included the study country, start and end of data collection, number of respiratory specimens that were collected and tested for influenza, and number of those specimens testing positive for influenza and specifically for type B influenza. Of the specimens that tested positive for type B influenza, the number of specimens characterised as having B/Yamagata lineage was also recorded.

Influenza B/Yamagata viruses reported in FluNet, GIHSN, GISAID, and GenBank

FluNet is a web-based database coordinated by WHO and freely available to researchers. The database contains information on the weekly number of laboratory-confirmed influenza detections that are uploaded from WHO regional databases or directly entered by national influenza centres and other influenza reference laboratories (a total of 194 countries and regions provided data for at least 1 week during the observation period) participating in the Global Influenza Surveillance and Response System initiative. Although a vast majority of the cases reported have information on the influenza virus type and the influenza A virus subtype, the proportion of influenza B cases for which the lineage is reported varies considerably across countries and regions, and years.[5] Influenza data for 2020–23 were downloaded from FluNet on Jan 21, 2024. The total number of influenza B/Yamagata detections and the number per 100 000 tested specimens, total influenza cases, and influenza B cases (overall and the subset of the overall cases that were characterised for lineage) were calculated for each of the following five periods: 2020 weeks 1–17 (January–April), 2020 weeks 18–53 (May–December), 2021, 2022, and 2023.

The GIHSN initiative was launched in 2012 as a partnership between industry partners, public health institutions, and sentinel hospitals in several countries and regions worldwide. The overarching objective of GIHSN is to collect data on the epidemiology of severe influenza, defined as a laboratory-confirmed influenza infection resulting in hospitalisation. Some of the authors of this Review are involved with GIHSN and requested access to the database (in addition, access to GIHSN data can be requested upon submission of research proposals). The database was queried for severe influenza B/Yamagata cases reported from week 1 of 2020 to week 52 of 2023, with 21 countries (Brazil, Canada, China, France, India, Côte d'Ivoire, Kenya, Lebanon, Mexico, Nepal, Pakistan, Peru, Romania, Russia, Senegal, Serbia, South Africa, Spain, Türkiye, Ukraine, and the USA) contributing data for at least one influenza season during this period.

GISAID is a publicly accessible repository established in 2008 to share viral genomic data for influenza (later expanded to include SARS-CoV-2 and other pathogens). The database includes genetic sequences for all influenza viruses and related epidemiological data, and provides password-protected access free-of-charge to users worldwide, to aid research and gain a better understanding of how influenza viruses evolve over time and spread globally. Although GISAID includes influenza virus sequences from other sequence databases such as GenBank, to ensure that the search was as comprehensive as possible, both the GISAID and GenBank databases were queried on Jan 14, 2024, to retrieve all sequences of B/Yamagata and

B/unknown lineages within the GISAID database and influenza B viruses within the GenBank database, with a collection date starting from Jan 1, 2020, onwards. Duplicate entries were removed on the basis of the standardised virus strain name provided in GISAID and GenBank records. These sequences were subjected to a GenBank BLAST analysis and phylogenetic analysis using MEGA version 7.0.21 (when taking into account sequences of all available segments) and Nextclade version 3.2.0 (for assessment of haemagglutinin and neuraminidase segments).

Review of the webpages of national respiratory virus surveillance systems

In January, 2024, we searched the webpages of the surveillance systems of the following countries and regions for influenza and respiratory viruses: England, France, Germany, Italy, the Netherlands, Portugal, Russia, and Spain (Europe); Argentina, Brazil, Canada, Mexico, and the USA (Americas); China, Hong Kong, Israel, Japan, and Türkiye (Asia); Australia and New Zealand (Oceania); and South Africa (Africa). These countries and regions were selected for a comprehensive geographical representation and on the basis of availability of web-based surveillance reports. The information extracted included the number of respiratory specimens tested for influenza, and the number of influenza detections, overall and by virus type (A and B), during 2020–23. If the virus lineage (Victoria, Yamagata, or not characterised) for influenza B viruses was reported, we recorded that information as well. Moreover, we retrieved the available information on the main features of the surveillance system and duration of the surveillance period (ie, whether year-round or limited to the regular epidemic period).

Results

Literature review

The literature search returned 2559 entries in PubMed and 4724 in Embase. There were 5152 non-duplicate articles, of which 4416 were not considered on the basis of the title and abstract (figure 1). Of the remaining 736 articles, 693 were excluded, leaving a total of 43 articles that were included in the systematic review; the main characteristics of these reports can be found in the appendix (pp 1–4).[3,12–53] Europe was the most represented area (n=17, of which four articles reported findings from multiple countries), followed by Asia (n=15), North America (n=6), South America (n=2), and Oceania (n=1). In addition, the paper by O'Neill and colleagues reported influenza-positive samples from countries in Oceania, Asia, and Africa that were subtyped at the WHO Collaborating Centre for Reference and Research for Influenza (CCRRI) in Melbourne during 2020–21 and the study by Diefenbach-Elstob and colleagues reported the same during 2022.[34,46]

In appendix (pp 1–4), studies have been arranged according to the start and end of the observation period. In three of these articles, data collection began several years before the start of the COVID-19 pandemic.[12–14] B/Yamagata viruses accounted for a large proportion of all characterised

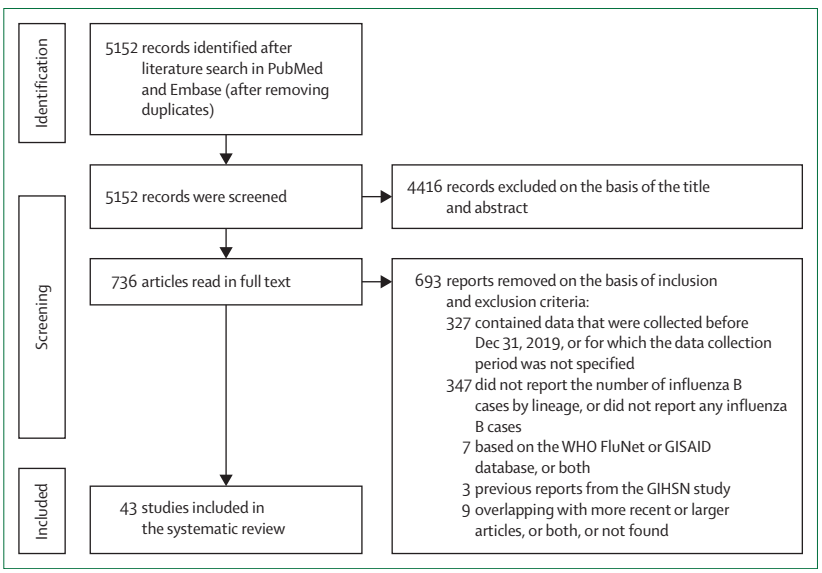


Figure 1: **PRISMA flow diagram reporting the number of influenza B/Yamagata virus detections from 2020 to 2023. The total number of duplicates was 2,297, so the total number of records was 7,449**

For more on **Nextclade** see https://clades.nextstrain.org/

influenza B-positive specimens, but since data stratified by year were not available in these studies, the number of specimens detected after March 1, 2020, could not be assessed. Eleven studies reported data for the 2019–20 influenza season in the northern hemisphere; B/Yamagata detections were reported in only three of these, which represented a minor percentage of all influenza-positive specimens, namely one of 1683 in the study by Panatto and colleagues, Italy;[16] six of 28 176 in the study by Hu and colleagues, USA;[19] and two of 171 in the study by Awadalla and colleagues, Saudi Arabia.[23] In three more studies, data collection started in 2019 and ended in 2021 or 2022.[26–28] Of these, B/Yamagata detections after the 2019–20 influenza season were reported only in the study by Tan and colleagues (three of 509 influenza cases).[28]

Three studies included data that were collected entirely in 2020: Melidou and colleagues analysed data from the European Surveillance System during weeks 1–20 of 2020 and reported a single influenza B/Yamagata case (1691 influenza detections overall, of which 397 were influenza B),[31] whereas in the other two studies, one conducted in Thailand and another in Brazil, the observation periods were between January and March, 2020, and no B/Yamagata detections were reported.[29,30] The observation period started in 2020 and extended to 2021 or 2022 in six studies, four of which reported no B/Yamagata detections. In China, the proportion of influenza-positive B/Yamagata lineage specimens reported to the Chinese National Influenza Surveillance Systems was 0·22% in 2020 and 0·07% in 2021.[29] Two B/Yamagata detections (2021 influenza cases) were reported by the WHO-CCRRI among samples collected in 2020.[34]

See **Online** for appendix

Finally, the observation periods of 17 studies started in 2021, 2022, or 2023, and ended as late as July, 2023. These reported no (n=15 studies) or few (n=2 studies) influenza

	Influenza B/Yamagata detections	Influenza B/Yamagata detections per 100 000				Detections by country and week
		Processed specimens*	Influenza-positive detections	Influenza B-positive detections	Lineage-characterised influenza B-positive detections	
2020, weeks 1–17	297	14·89	63·73	179·14	1175·68	117 (USA, weeks 1–13), 67 (Mexico, weeks 1–14), 18 (Norway, weeks 1–8), 14 (Dominican Republic, weeks 2–9), 10 (France, weeks 2–12), less than 10 (24 countries)
2020, weeks 18–53	9	0·40	187·54	421·55	1565·22	8 (USA, weeks 44–49), 1 (Afghanistan, week 45)
2021	10	0·51	8·57	29·23	34·25	3 (India, week 41), 1 each (Afghanistan, week 1; Niger, week 1; Ghana, week 4; Bulgaria, week 8; Côte d'Ivoire, week 8; Mexico, week 24; and USA, week 39)
2022	3	0·03	0·31	4·75	8·68	2 (Germany, weeks 12–13), 1 (North Korea, week 43)
2023	1	0·06	0·12	0·59	2·09	1 (Cuba, week 11)

*Calculated over all the countries and weeks in which the number of processed specimens was reported.

Table 1: **WHO FluNet: number of influenza B/Yamagata detections (overall and by country) in 2020 (weeks 1–17 and 18–53), 2021, 2022, and 2023, and rate of detections per 100 000 processed specimens, influenza-positive detections, influenza B-positive detections, and lineage-characterised influenza B-positive detections**

	Influenza-positive detections	Influenza B-positive detections	Lineage-characterised influenza B-positive detections	Influenza B/Yamagata detections by country and week
2020, weeks 1–17	3772	1449	639	6 (France, weeks 1 and 9; India, week 5; Mexico, weeks 6 and 9; and Russia, week 12)
2020, weeks 18–53	15	5	1	1 (India, week 51)
2021	875	149	33	0
2022	3072	246	175	0
2023, until week 29	1470	319	182	0

Table 2: **Global Influenza Hospital Surveillance Network: number of influenza detections (overall, type B, lineage-characterised influenza B, and B/Yamagata by country and week) in 2020 (weeks 1–17 and 18–53), 2021, 2022, and 2023 (until week 29)**

B/Yamagata detections, which, after sequencing, were partly linked to vaccination with quadrivalent LAIV (ie, containing a B/Yamagata lineage virus strain).[3,42]

In summary, we reviewed studies published up to December, 2023, and whose observation periods extended up to July, 2023. With the exclusion of the first 4 months of 2020, B/Yamagata detections were reported only in four countries globally, and that too accounted for a miniscule proportion (<2 in 1000) of all influenza B cases.

FluNet, GIHSN, GISAID, and GenBank

On Jan 21, 2024, we downloaded data for around 36·25 million respiratory specimens for the period 2020–23 from FluNet. In 2020, the weekly number (in thousands) dropped from approximately 138 in weeks 1–17 to 93 in weeks 18–53, and then rose to 159 in 2021, 222 in 2022, and 209 in 2023. Of the reported 2 376 287 influenza detections, 435 250 (18·3%) were of influenza type B; of these, 297 915 (68·4%) were not characterised, 137 015 (31·5%) were of B/Victoria lineage, and 320 (<0·1%) were of B/Yamagata lineage. The average number of influenza B/Yamagata detections per 100 000 processed specimens dropped from 14·9 in the weeks 1–17 of 2020 to less than 0·10 in 2022 and 2023 (table 1). Influenza B/Yamagata accounted for a substantially greater proportion of detections during the weeks 18–53 of 2020 than in the earlier weeks of the same year. This occurrence was followed by a major drop in the number of influenza B/Yamagata detections in subsequent years (table 1): from 306 in 2020 to ten in 2021, three in 2022 (two in Germany and one in North Korea), and one in 2023 (in Cuba). In summary, the rate of B/Yamagata detections in FluNet dropped markedly worldwide after 2020, both in absolute terms and as a percentage of the total number of influenza and influenza type B detections (table 1).

Of a total of 9204 influenza detections reported to the GIHSN between January, 2020, and December, 2023, 2168 (23·6%) were influenza B. Of the 1030 influenza B viruses that were characterised, seven (0·7%) were B/Yamagata, all detected during 2020 (two in France, two in Mexico, one in India, and one in Russia in the first 3 months of the year, and again one in India in week 51). No B/Yamagata influenza detections were reported from 2021 onwards (table 2).

The GISAID set of B/Yamagata sequences included a total of 88 unique viruses. The specimens for these virus sequences were collected in January, 2020 (n=44), February, 2020 (n=24), March, 2020 (n=14), November, 2021 (n=4, all from Kenya), June, 2022 (n=1, from Greece), and March, 2023 (n=1, from the UK). Of these, one virus obtained from Japan in 2020 had an haemagglutinin genome segment identical to that of a B/Yamagata-like vaccine strain (B/Phuket/3073/2013), and another virus obtained from Greece in 2022 had an haemagglutinin genome segment identical to that of another B/Yamagata-like vaccine strain

	Influenza B/Yamagata detections	Detections by country and week	Influenza-positive specimens by country and surveillance system
Week 40, 2019 to week 20, 2020	269	1 (Spain, week 1 [2020]; Netherlands, week 8 [2020]; England, week 6 [2020]; Portugal, week 48 [2019]; Russia, week †5 [2020]; Germany, week Ns), 239 (USA, week 40 [2019] to week 13 [2020]), 24 (France, week 48 [2019] to week 11 [2020])	2579 (Spain, virus characterisation), 207 (Netherlands, general practitioner surveillance), 1204 (England, virus characterisation), 303 (Germany, virus characterisation), 349 (Portugal, emergency and obstetrics wards), 16 649 (Russia, national influenza centres and network of regional base laboratories), 45 898 (USA, public health laboratories), 1195 (France, general practitioner surveillance)
Week 35, 2020 to week 39, 2021	10	1 (Australia, weeks 37–38 [2020]) 9 (USA, weeks 44–49 [2020], 39 [2021])	306 (Australia, WHO Collaborating Centre for Reference and Research on Influenza), 352 (USA, public health laboratories)
Week 40, 2021 to week 39, 2022	1	1 (USA, week 46 [2021])	26 322 (USA, public health laboratories)
Week 40, 2022 to week 52, 2023	1	1 (Spain, week NS)*†	2483 (Spain, virus characterisation)

*This B/Yamagata detection had the same sequence as the vaccine strain.†NS=not specified.

Table 3: **Number of influenza-positive specimens tested and influenza B/Yamagata detections from webpages of national influenza surveillance systems worldwide (see text for a complete list of countries that were included)**

(B/Jiangsu/10/2003), suggesting that both were vaccine-derived viruses. For the five viruses collected between 2021 and 2023, only the sequences of the polymerase acid (PA; n=3) or matrix protein (n=2) genome segments were available. Therefore, for three of the four viruses from Kenya (2021), the absence of information on most genome segments posed challenges in identifying whether these viruses were wild-type circulating B/Yamagata viruses; however, upon BLAST analysis of the available PA genome segments, these viral sequences displayed the closest match with B/Yamagata viruses from 2018. Upon BLAST analysis, the matrix protein genome segments for the remaining virus from Kenya and the one from the UK matched the most with those of B/Victoria lineage viruses, suggesting that these viruses had been incorrectly labelled B/Yamagata. The GISAID B/unknown lineage dataset included 218 unique viruses. BLAST and phylogenetic analyses revealed that, of the 99 of these viruses that had sequences available for the haemagglutinin genome segments, the majority (n=89) were current wild-type B/Victoria viruses and seven were derived from the study published in 2023 by Aslam and colleagues on historic B viruses for influenza vaccine virus construction.[54] The remaining three were either most likely vaccine-derived B/Yamagata (2020, South Korea) or B/Victoria (2021, USA) or belonging to the older B/Victoria lineage clade V1A from 2019 (2020, Saudi Arabia). Of the 119 unique viruses that did not have sequences available for the haemagglutinin genome segments, 111 were recognised to be of B/Victoria lineage on the basis of other genome segments. Seven waste-water specimens collected in March, 2020, in New York, USA had partial PB1 sequences, similar to the B/Yamagata lineage viruses observed in 2007 or 2008 and the B/Florida/4/2006 Yamagata lineage vaccine strain. No sequences for haemagglutinin and neuraminidase genome segments were available for one virus obtained from the USA in 2021, but all the other segments showed that the virus had the backbone of the cold-adapted B/Ann Arbor/1/66 virus used in LAIV. When we downloaded and analysed a little over 17 000 sequences labelled as derived from 1747 unique influenza B viruses from GenBank, no further B/Yamagata detections were identified apart from those already in the GISAID dataset. In conclusion, no sequences of wild-type viruses of the B/Yamagata lineage with a collection date after March, 2020 have been uploaded to GISAID and GenBank.

Review of the webpages of the national surveillance systems for respiratory viruses

The number of influenza B/Yamagata detections reported in the webpages of the respiratory virus surveillance systems included in this study were sorted by country and week, together with details of the surveillance system in which each case was observed and overall number of influenza cases reported (table 3). After week 35 of 2020, a total of 12 B/Yamagata detections were reported: one in Australia (week 37–38 of 2020), ten in the USA (nine in weeks 44–49 of 2021 and an additional case in week 46 of 2021), and one in Spain (in 2023; the sequence of this virus was identical to that of the vaccine strain).

The number of countries that reported the last B/Yamagata detections (from any of the sources that we explored) were nine in 2021, three in 2022, and two in 2023 (the total number of reported B/Yamagata detections, obtained by summing the data from all sources, was 40 in 2021, ten in 2022, and two in 2023; figure 2). In all other countries of the world (coloured grey in figure 2), there were no B/Yamagata detections after 2020.

Discussion

The early claims that the influenza B/Yamagata lineage might have gone extinct in the aftermath of the COVID-19 pandemic quickly caught the attention of policy makers and vaccine manufacturers, and epidemiologists and researchers, due to the key implications such an extinction would have on the formulation and development of influenza vaccines. Given the enormous public health relevance of such a development and the need for solid and updated epidemiological data, we undertook a comprehensive review of the available evidence on the topic, covering multiple complementary sources of information.

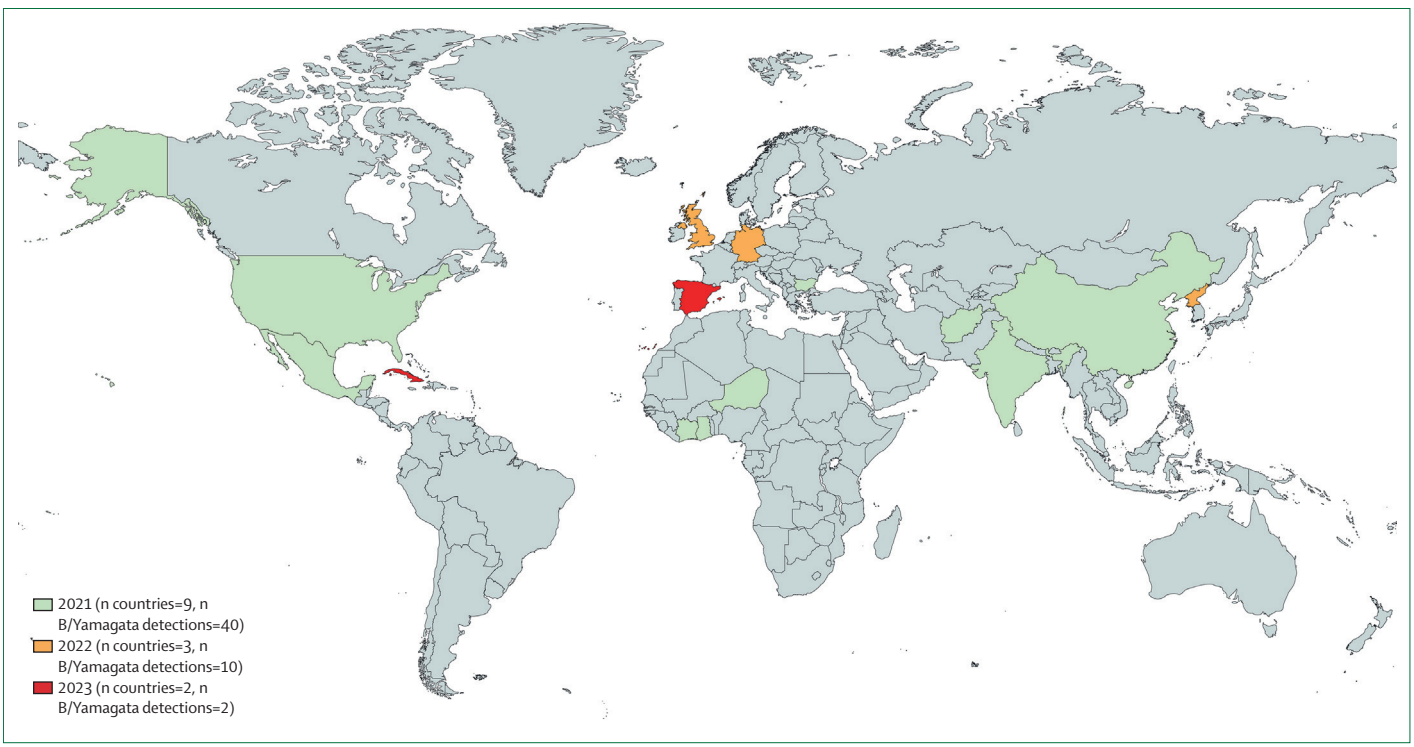


Figure 2: **Map depicting the countries in which the last reported B/Yamagata detections occurred in 2021, 2022, or 2023**

The different sources investigated concordantly showed that there was a considerable and progressive decline in the number of influenza B/Yamagata virus detections over the past 4 years (2020–23), compared with that in the period before the COVID-19 pandemic. Following the major B/Yamagata outbreak that started in 2017 and involved large parts of the world, the proportion of B/Yamagata viruses had fallen to one-twentieth of all influenza B cases in 2018–19.[5] This observation can explain (together with the absence of known zoonotic or environmental reservoirs, and the lower reproductive number of B/Yamagata lineage viruses than that of influenza B/Victoria lineage and influenza A subtype viruses)[55,56] why this virus is the only respiratory virus pushed towards extinction by the emergence of SARS-CoV-2. Since the different global regions are unevenly covered by respiratory virus surveillance systems, some caution is warranted in considering the B/Yamagata lineage actually to be extinct. However, the current epidemiological situation of the rapid global disappearance of an influenza B virus lineage is unprecedented, since in the early 1980s, influenza B viruses actually split into two lineages. In the 1990s, although the B/Victoria lineage had practically disappeared from most world regions (including Europe and North America), viral circulation persisted in the populous east Asia. Thus, the B/Victoria lineage might re-emerge globally at some point (which happened in 2001–02).[8,57] The current protracted and nearly undetectable viral circulation of the B/Yamagata lineage provides enough evidence to suggest that these viruses are on the verge of extinction, if they are not extinct already. In this context, B/Yamagata detections captured by surveillance systems or studies globally should be investigated to identify whether the cases are wild virus detections or vaccine-derived, and a much larger proportion of influenza B detections should be tested to characterise their lineage. Vaccine-derived detections can mostly be linked to sampling individuals vaccinated with quadrivalent LAIVs and indeed, several B/Yamagata viruses whose sequences are uploaded in GISAID and GenBank appeared to be vaccine-derived. Studies on sequencing of influenza B viruses should be supported and procedures should be put in place to detect wild-type B/Yamagata viruses, together with the collection of detailed virological (sequence confirmation) and epidemiological (ie, vaccination status, type and timing of vaccination) data and its subsequent sharing.

Besides pointing to the most likely extinction of the B/Yamagata viruses, the current epidemiological situation also highlights the need for a rapid revision in influenza-prevention practices, particularly with respect to the composition of vaccines. Such a step has been taken in the past, wherein an influenza viral strain, A(H2N2), was removed from influenza vaccines after the strain stopped circulating following the 1968 A(H3N2) pandemic.[58] The extinction of B/Yamagata viruses requires the appropriate regulatory bodies to decide whether quadrivalent influenza vaccines should be changed to trivalent influenza vaccines and, if so, whether this change should be applied simultaneously to both egg-based and cell-based inactivated influenza vaccines and quadrivalent LAIVs. Incidentally, in September, 2023,

and February, 2024, the WHO influenza vaccine composition advisory committee declared "that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible" (this decision applies to vaccines for 2024 in the southern hemisphere and for the 2024–25 season in the northern hemisphere).[59,60] This decision has regulatory and manufacturing implications for implementation over different timescales. From a public health perspective, close coordination between manufacturers and public health authorities is crucial to ensure that no country is confronted with influenza vaccine shortages. Concerns also exist about how the change from quadrivalent influenza vaccine to trivalent influenza vaccine should be communicated, as this could be confusing for the general public and have a negative effect on influenza vaccination campaigns. Moreover, if B/Yamagata viruses are considered extinct, then the safety level with which influenza laboratories worldwide are allowed to handle B/Yamagata viruses should be changed, to avoid the risk of an extinct influenza virus escaping the laboratories.

The sources of information that were researched in this Review deserve comment. The FluNet database is dynamic, ie, the data it contains can change over time; for example, a national influenza centre or reference laboratory in a given country might need to make corrections to data entered into this database over previous weeks. Moreover, the FluNet database does not have an option to report vaccine-derived detections separately. WHO proactively investigates all reports of B/Yamagata detections entered into their global surveillance databases, and these entries are sometimes removed at a later stage when laboratory analyses reveal that the detections are vaccine-derived. In preparing this Review, the 2020–23 data from the FluNet database were downloaded three times: on May 19, 2023; Aug 28, 2023; and Jan 21, 2024. In this time period, the number of reported B/Yamagata influenza cases decreased from 45 to ten for the year 2021, from eight to three for the year 2022, and from six to one for the year 2023. Hence, the number of B/Yamagata detections reported in 2021–23 might be an overestimation of the real numbers. A further limitation is the underrepresentation of tropical countries (particularly those in the populous regions of southeast Asia and Africa) in the data gathered from the review of scientific literature and webpages of the surveillance systems of respiratory viruses. This is an important limitation since we have previously shown that influenza B tended to circulate more in the tropical countries than in the temperate countries before the COVID-19 pandemic.[61]

Here, we have described the current epidemiological situation of B/Yamagata lineage viruses and outlined the most important public health implications of this situation, particularly with respect to the composition of influenza vaccines. The effect of the disappearance of B/Yamagata viruses on the circulation of other influenza viruses is currently difficult to predict. B/Yamagata viruses tend to infect adults and older individuals more often than the B/Victoria lineage, which mostly infect children and adolescents (specifically, the age distribution of B/Yamagata cases showed a secondary peak around age 25–50 years, in addition to the primary peak at 10–20 years, which was also seen for B/Victoria cases).[61] If B/Yamagata viruses actually became extinct, then the distribution of influenza B cases might shift towards younger age groups, resulting in a disease burden lower than that in the pre-COVID-19 era. However, this hypothesis is currently nothing more than a plausibility that will only be confirmed or refuted in time. These uncertainties imply that epidemiological and virological monitoring of influenza viruses, SARS-CoV-2, and other respiratory viruses for protecting human health is now more important than ever and will remain so for many years to come. In conclusion, with the rapid disappearance and potential extinction of the influenza B/Yamagata virus, international, regional (eg, the European Medicines Agency), and national public health authorities (both public health institutes and medical regulatory authorities) are confronted with several decisions concerning this unprecedented situation (a development they have not faced in the past 30 years), and this Review might contribute to the decision-making process.

Contributors

SC, AM, MCN, and JP contributed to the conceptualisation. SC, AM, MCN, LH, BB, MDR, and JP contributed to the methodology. SC, AM, MCN, LH, MZ, BB, MDR, and JP contributed to the investigation. SC, AM, LH, MZ, and BB curated the data. MZ and BB validated the data. SC, MDR, and JP wrote the original draft. SC contributed to the visualisation. SC, MCN, and JP supervised the study. AM, MCN, LH, MZ, and BB reviewed and edited the manuscript. MCN and JP were responsible for acquiring resources and funding. SC and BB were in charge of project administration. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MCN received grants from the Foundation for Influenza Epidemiology, Bill & Melinda Gates Foundation, European & Developing Countries Clinical Trials Partnership (EDCTP), Sanofi, AstraZeneca, and Pfizer; received payments or honoraria (for lectures, presentations, speakers bureaus, manuscript writing, or educational events) and support for attending meetings or travel, or both, from Sanofi; and had leadership or fiduciary role from Gavi Board. An unrestricted research grant from NIVEL (the employer) and Sanofi for JP funded the work carried out in this manuscript; JP also received grants or contracts from Sanofi and the Fondation de France; and support for attending meetings or travel, or both, from WHO and Sanofi. The other authors declare no conflicts of interest.

Acknowledgments

We would like to thank the investigators at all the sites participating in the GIHSN. We would also like to thank the FluNet and GISAID teams for access to their databases and all those who submitted data and sequences to these databases. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SC, AM, and LH received no specific funding for this work. JP, MDR, and BB were funded by a research grant from Sanofi to NIVEL (FluCov project). MCN and MZ work at the Center of Excellence in Respiratory Pathogens, a partnership between the Hospices Civils de Lyon, the Université Claude Bernard Lyon 1, under the Centre International de Recherche en Infectiologie (CIRI), and Sanofi.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps.

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