NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

PUBLIC HEALTH SURVEILLANCE BULLETIN
VOLUME 19. ISSUE 1- MAY 2022

Influenza Activity in South Africa - 2021

Nicole Wolter[1,2], Amelia Buys[1], Sibongile Walaza[1,3], Jocelyn Moyes[1,3], Mignon du Plessis[1,2], Thulisa Mkhencele[1], Fahima Moosa[1,2], Daniel Amoako[1], Dikeledi Kekana[1], Linda de Gouveia[1], Cheryl Cohen[1,3] and Anne von Gottberg[1,2]

[1]Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service, Johannesburg, South Africa

[2]School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Summary

This report summarises the results of influenza surveillance in South Africa for the period week 1 to week 52 of 2021. The report includes data from individuals satisfying syndromic case definitions within three respiratory illness surveillance programmes: Viral Watch influenza-like illness surveillance in outpatients (n=253) at private general practitioners, influenza-like illness surveillance in outpatients (n=1941) at public health clinics and pneumonia surveillance in hospitalised patients (n=6213). Together, the three surveillance programmes contributed data from all nine provinces in South Africa. Influenza activity was observed from weeks 9 through 52, with an overall detection rate in 2021 of 5% (414/8407). Increased influenza activity was observed during the late spring season (weeks 37 through 49) and fell outside of the timing of the usual winter influenza season. A comparable number of influenza cases were detected compared to the years prior to COVID-19 (2016-2019) although a larger number of specimens were tested. Using the Moving Epidemic Method (MEM), the levels of activity only reached moderate and low levels in the influenza-like illness and pneumonia surveillance programmes respectively. Influenza infections were dominated by influenza A(H1N1)pdm09 (56%, 215/383), followed by B/Victoria (27%, 102/383) and A(H3N2) 17% (66/383). Influenza B/Yamagata was not detected. Subtype/lineage could not be determined for 7% (31/414) of infections, due to low viral load. Cell culture-derived influenza virus isolates were obtained with an 87% (202/232) success rate. Haemagglutinin inhibition (HAI) assays demonstrated that 88% (44/50) of tested A(H1N1)pdm09, 70% (14/20) of A(H3N2) and 97% (61/63) of B/Victoria viruses were recognised by antisera raised against current and former vaccine strains. Genetic analysis of the haemagglutinin gene of South African 2021 influenza viruses was available for 34 A(H1N1)pdm09, 17 A(H3N2) and 80 B/Victoria viruses. All 2021 viruses belonged to the same clade as the corresponding southern hemisphere 2021 vaccine strains, as well as the 2020 South African strains (A(H1N1)pdm09, clade 6B.1A; A(H3N2), clade 3C.2a; Y/Victoria, V1A.3), although some drift was observed by detection of a number of different mutations and clustering in different subgroups. It is concluded that during 2021, South Africa experienced a period of increased influenza activity outside of the normal winter influenza season, likely due to the immunity gap created as a result of limited influenza circulation during the COVID-19 pandemic and easing of COVID-19 restrictions. Groups at an increased risk of severe complications of influenza are encouraged to receive the influenza vaccine. Clinicians are encouraged to consider influenza as a differential diagnosis when managing patients presenting with respiratory illness.

Epidemiology of the 2021 influenza season

South Africa has a temperate climate and influenza epidemics usually occur between April and October, with a peak during the winter months. The trivalent influenza vaccines in use in the southern hemisphere in 2021 comprised an A/Victoria/2570/2019 (H1N1)pdm09-like virus, an A/Hong Kong/2671/2019 (H3N2)-like virus and a B/Washington/02/2019 (B/Victoria lineage)-like virus. The quadrivalent vaccine also included B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Description of the surveillance systems

South Africa has three influenza surveillance programmes that are coordinated by the Centre for Respiratory Diseases and Meningitis (CRDM) of the National Institute for Communicable Diseases (NICD), which houses the National Influenza Centre (NIC). These programmes include (i) Viral Watch (VW) influenza-like illness surveillance in outpatients at private general practitioners, (ii) systematic influenza-like illness (ILI) surveillance in outpatients at public health clinics, and (iii) national pneumonia surveillance in public health hospitals (**Table 1**).

Table 1. Description of influenza and respiratory surveillance programmes in South Africa, 2021.

Programme	Viral Watch	Influenza-like illness surveillance	National syndromic surveillance for pneumonia
Start year	1984	2012	2009
Provinces*	EC, FS, GP, LP, MP, NC, NW, WC	KZ, NW, WC, MP	GP, KZ, MP, NW, WC
Number of sites	91	5	9
Type of site	General practitioners	Public primary health care clinics	Public hospitals
Case definition	An acute respiratory illness with fever (≥38°C) or reported fever, cough and symptom onset ≤10 days or **Suspected SARS-CoV-2:** Any person presenting with an acute (≤14 days) respiratory tract infection or other clinical illness compatible with COVID-19**	An acute respiratory illness with fever (≥38°C), cough and symptom onset ≤10 days or **Suspected SARS-CoV-2:** Any person presenting with an acute (≤14 days) respiratory tract infection or other clinical illness compatible with COVID-19**	Acute (symptom onset ≤10 days) or chronic (symptom onset >10 days) lower respiratory tract infection requiring hospitalisation or **Suspected SARS-CoV-2:** Any person admitted with a physician-diagnosis of suspected COVID-19 and not meeting SRI case definition
Specimens collected	Combined oropharyngeal and nasopharyngeal swabs or throat and/or nasal swabs	Combined oropharyngeal and nasopharyngeal swabs	Combined oropharyngeal and nasopharyngeal swabs

*EC: Eastern Cape; FS: Free State; GP: Gauteng; KZ: KwaZulu-Natal; LP: Limpopo; MP: Mpumalanga; NC: Northern Cape; NW: North West; WC: Western Cape ** Symptoms include ANY of the following respiratory symptoms: cough, sore throat, shortness of breath, anosmia (loss of sense of smell) or dysgeusia (alteration of the sense of taste), with or without other symptoms (which may include fever, weakness, myalgia or diarrhoea).

From 4 January 2021 (week 1) through 2 January 2022 (week 52), respiratory specimens from 8407 individuals were tested through the three surveillance programmes (**Table 2**), using the Allplex™ SARS-CoV-2/influenza/RSV commercial kit (Seegene, Seoul, Korea) and the CDC subtyping method (with reagents sourced through the International Reagent Resource). Influenza infections were identified in 414 individuals, resulting in an overall detection rate of 5% (414/8407). Influenza detections occurred from week 9 through 52. Influenza infections were dominated by influenza A(H1N1)pdm09 (56%, 215/383), followed by B/Victoria (27%, 102/383) and A(H3N2) 17% (66/383). Influenza B/Yamagata and dual infections were not detected. Inconclusive results for subtyping occurred in 7% (31/414) of samples. The latter samples had a primary identification reverse transcription real-time polymerase chain reaction (rRT-PCR) cycle threshold (C_t) value greater than 35 and subsequent characterisation PCR could not determine the subtype/lineage.

Table 2. Total number of influenza infections identified in all syndromic influenza surveillance programmes, South Africa, 4 January 2021 – 2 January 2022 (weeks 1-52).

Programme	Number of specimens tested	Number influenza positive (% of all specimens tested)	Influenza A				Influenza B			
			Total A	Subtype inconclusive*	A(H1N1) pdm09	A(H3N2)	Total B	Lineage inconclusive*	B/Victoria	B/Yamagata
			n (% of total influenza positives)				n (% of total influenza positives)			
Viral Watch	253	35 (14)	24 (69)	1 (3)	17 (49)	6 (17)	11 (31)	3 (9)	8 (23)	0
Influenza-like illness surveillance	1941	171 (9)	125 (73)	5 (3)	94 (55)	26 (15)	46 (27)	4 (2)	42 (25)	0
Pneumonia surveillance	6213	208 (3)	149 (72)	11 (5)	104 (50)	34 (16)	59 (28)	7 (3)	52 (25)	0
Total	**8407**	**414 (5)**	**298 (72)**	**17 (4)**	**215 (52)**	**66 (16)**	**116 (28)**	**14 (3)**	**102 (25)**	**0**

*Inconclusive: insufficient viral load in sample and unable to characterise further

Viral Watch Programme

Specimens from 253 patients were received and tested from VW practitioners located in 6 of the 8 provinces participating in surveillance (**Table 3**), with the majority of specimens received from Gauteng (180/253, 71%) and Western Cape (60/253, 24%) provinces. Influenza was detected in 35 (14%) patients, of which 69% (24/35) were influenza A and 31% (11/35) were influenza B (**Figure 1 , Table 3**). Among the influenza A infections for which a subtype could be determined, 74% (17/23) were A(H1N1)pdm09 and 26% (6/23) were A(H3N2). All influenza B infections for which a lineage was determined were B/Victoria (8/8).

Table 3. Number of influenza infections by subtype/lineage, and total number of specimens tested by province in the Viral Watch surveillance programme, South Africa, 4 January 2021 – 2 January 2022 (Weeks 1-52).

Province	A(H1N1)pdm09	A (H3N2)	A subtype inconclusive*	B /Victoria	B /Yamagata	B lineage inconclusive*	Total cases	Total specimens tested
Eastern Cape	0	0	0	2	0	0	2	4
Free State	1	0	0	0	0	0	1	4
Gauteng	6	2	0	5	0	3	16	180
Limpopo	0	0	0	0	0	0	0	0
Mpumalanga	0	0	0	0	0	0	0	3
Northern Cape	0	0	0	0	0	0	0	2
North West	0	0	0	0	0	0	0	0
Western Cape	10	4	1	1	0	0	16	60
Total	**17**	**6**	**1**	**8**	**0**	**3**	**35**	**253**

*Inconclusive: insufficient viral load in sample and therefore unable to characterise further.

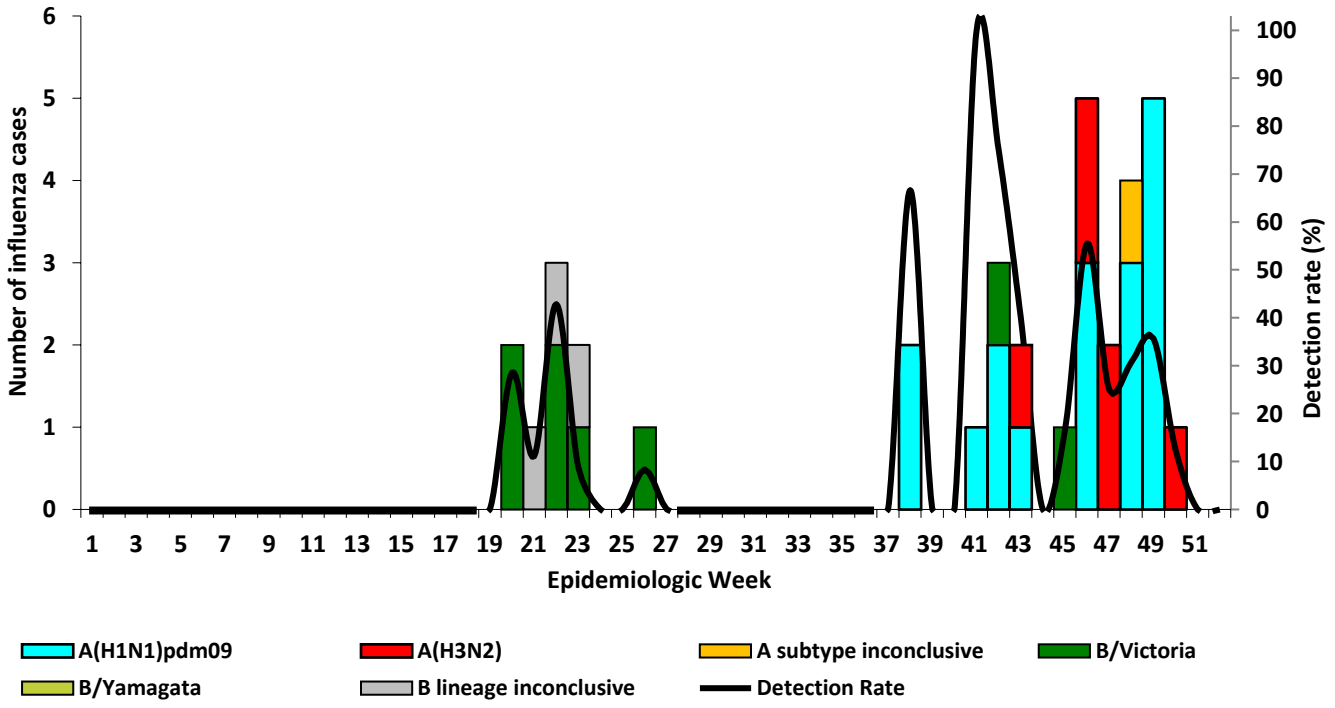

Figure 1. Number of influenza infections by influenza subtype/lineage and detection rate by epidemiologic week - Viral Watch programme for influenza-like illness surveillance, South Africa, Weeks 1 to 52, 2021 (N=35).
Inconclusive: insufficient viral load in sample and therefore unable to characterise further.

Influenza-like illness (ILI) surveillance programme at primary health care clinics

Specimens from 1941 patients with ILI were received from five primary health care clinics located in four provinces. In total, 171 (9%) individuals tested positive for influenza. Among the specimens which could be further

characterised, influenza A(H1N1)pdm09 accounted for 58% (94/162), influenza B/Victoria for 26% (42/162) and A(H3N2) for 16% (26/162) of cases. Influenza B/Yamagata was not detected in 2021 (**Table 4, Figure 2**). The influenza detection rate increased from week 35, peaking between weeks 44 (41%, 21/51) and 47 (40%, 22/55), and subsequently decreased (**Figure 3**). In 2021, the period of increased influenza activity in the ILI programme during the late spring season fell outside of the timing of the usual winter influenza season. The mean onset of influenza season in South Africa in 2005-2019 was week 17 (3rd week of April), range week 16 to week 25. A comparable number of influenza cases were detected compared to pre-COVID-19 years (2016-2019), although the number of specimens tested was higher in 2021 (2016, n=1644; 2017, n=1805, 2018, n=835; 2019, n=1718; 2020, n=1546; 2021, n=1941).

Table 4. Number of influenza cases by subtype and lineage, and total number of specimens collected by province for the influenza-like illness surveillance programme at primary health care clinics, South Africa, Weeks 1 to 52, 2021 (N=171).

Province	A(H1N1) pdm09	A (H3N2)	A subtype inconclusive*	B/Victoria	B/Yamagata	B lineage inconclusive*	Total cases	Detection rate % (n/N)
KwaZulu-Natal	14	1	1	16	0	3	35	12 (35/304)
Mpumalanga	1	3	1	0	0	0	5	2 (5/246)
North West	46	5	1	13	0	0	65	8 (65/798)
Western Cape	33	17	2	13	0	1	66	11 (66/593)
Total	**94**	**26**	**5**	**42**	**0**	**4**	**171**	**9 (171/1941)**

Surveillance sites included primary health care clinics in 4 provinces: KwaZulu-Natal (Edendale Clinic), Mpumalanga (Agincourt Clinic), North West (Jouberton Clinic) and Western Cape (Eastridge Clinic and Mitchell's Plain Clinic). *Inconclusive: insufficient viral load in sample and therefore unable to characterise further (primary test PCR C_t value >35).

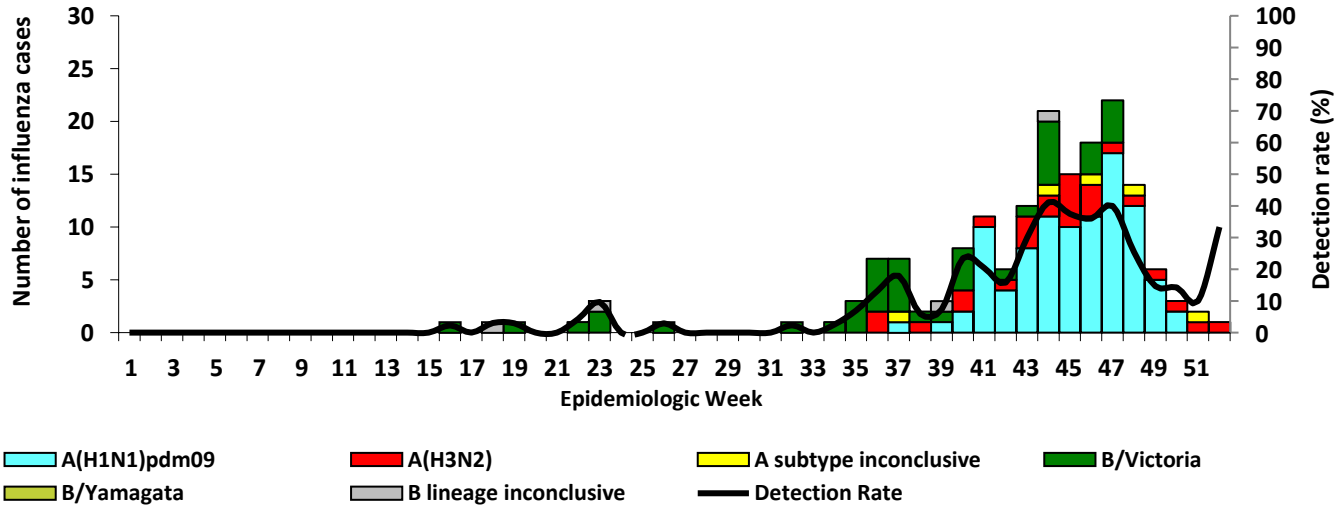

Figure 2. Number of influenza cases by subtypes/lineages and detection rate by epidemiologic week - Influenza-like illness (ILI) surveillance programme at primary health care clinics, South Africa, Weeks 1 to 52, 2021 (N=171).
Inconclusive: insufficient viral load in sample and therefore unable to characterise further.

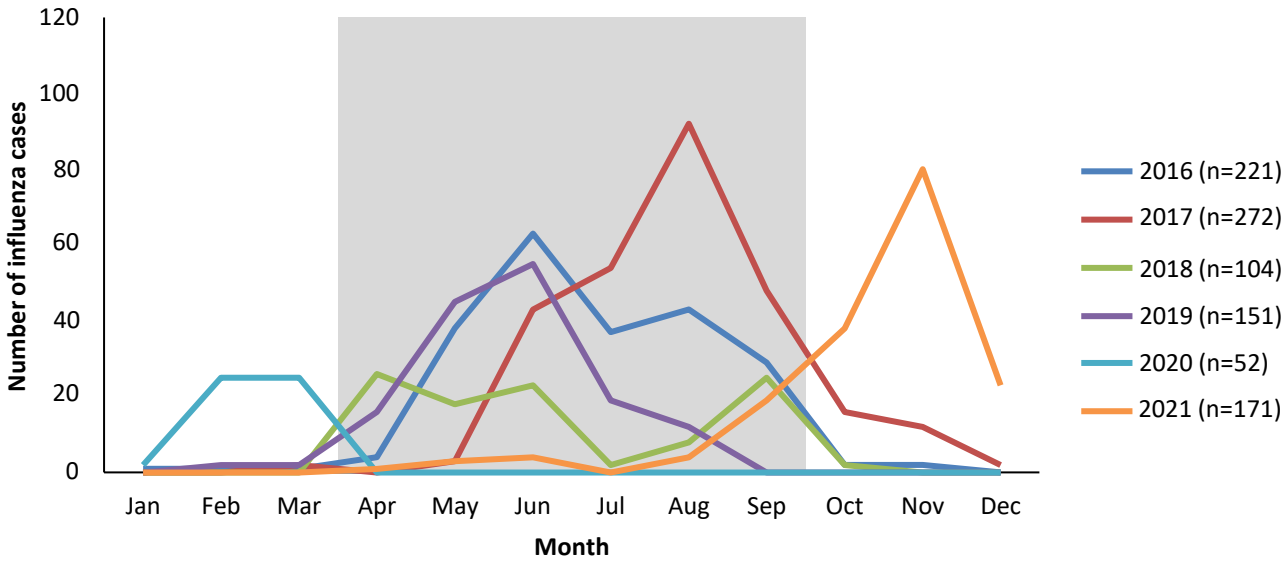

Figure 3. Number of influenza infections detected in the influenza-like illness surveillance programme at public health care clinics by month and year, South Africa, 2016-2021. Grey shading indicates typical range of South African influenza season. Number of samples tested: 2016, n=1644; 2017, n=1805, 2018, n=835; 2019, n=1718; 2020, n=1546; 2021, n=1941.

Influenza transmission thresholds are calculated using the Moving Epidemic Method (MEM), a sequential analysis using the R language (http://CRAN.R-project.org/web/package=mem) designed to calculate the duration, start and end of the annual influenza epidemic. MEM uses the 40th, 90th and 97.5th percentiles established from available years of historical data to calculate thresholds of activity. Thresholds of activity for influenza are defined as follows: below threshold, low activity, moderate activity, high activity and very high activity. Thresholds from influenza-like illness surveillance at primary healthcare clinics (outpatients) are used as an indicator of disease transmission in the community and thresholds from pneumonia surveillance (inpatients) are used as an indicator of impact of disease on health care provision.

Using the MEM, with a baseline determined from previous years (2012-2019), the estimated level of influenza disease transmission in the community reached a level of moderate activity between weeks 44 and 47 of 2021 in the ILI surveillance programme at public healthcare clinics (**Figure 4**).

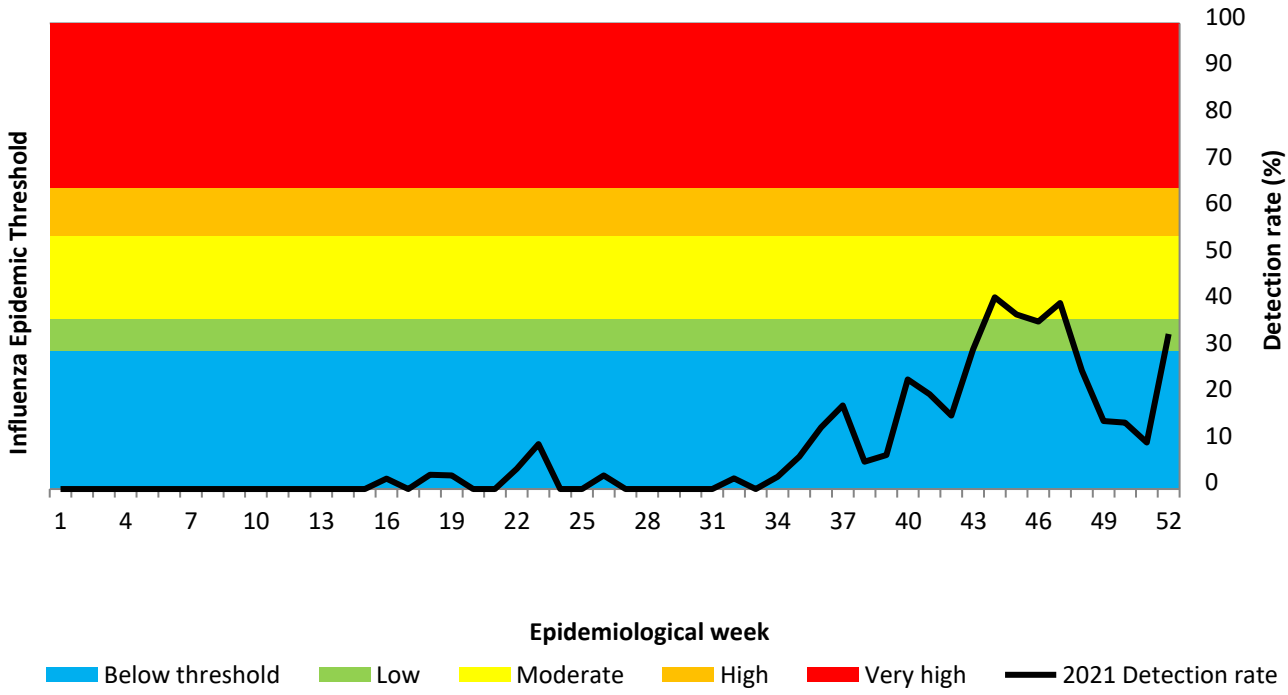

Figure 4. Influenza detection rate and epidemic thresholds*, influenza-like illness (ILI) surveillance at primary health care clinics, South Africa, 4 January 2021 – 2 January 2022 (Weeks 1-52). *Influenza transmission thresholds based on 2012-2019 data and calculated using the Moving Epidemic Method (MEM).

Pneumonia surveillance programme

Specimens from 6213 patients hospitalised with severe respiratory illness were received from the ten sentinel hospitals located in five provinces, and 208 (3%) influenza cases were detected. Among influenza-positive samples which could be further characterised, 55% (104/190) were A(H1N1)pdm09, 27% (52/190) were B/Victoria and 18% (34/190) were A(H3N2) (**Table 5**). Influenza B/Yamagata infection was not detected in the pneumonia surveillance programme in 2021. The influenza detection rate increased between weeks 38 and 49, with a peak detection rate of 17% (18/104) in week 47 (**Figure 5**). As in the ILI surveillance programme, the period of increasedinfluenza activity in the pneumonia surveillance programme occurred during the late spring season (**Figure 6**). A comparable number of influenza cases were detected in 2021 compared to pre-COVID-19 years (2016-2019), although the number of specimens tested was higher in 2021 (2016, n=3670; 2017, n=4335, 2018, n=4660; 2019,n=4406; 2020, n=4320; 2021, n=6213). Data obtained through pneumonia surveillance in hospitalised patients (2010-2019) was used to set MEM thresholds for impact of influenza on healthcare provision. The impact of the 2021 influenza disease was estimated to be low from week 37 through week 50, and below the threshold for therest of the year. (**Figure 7**).

Table 5. Number of influenza infections by subtype and lineage, and total number of specimens collected by province for the pneumonia surveillance programme, South Africa, 4 January 2021 – 2 January 2022 (Weeks 1-52).

Province	A(H1N1) pdm09	A(H3N2)	A subtype inconclusive*	B/Victoria	B/Yamagata	B lineage inconclusive *	Total cases	Detection rate % (n/N)
Gauteng	24	14	3	17	0	5	63	4 (63/1642)
KwaZulu-Natal	8	3	0	13	0	0	24	2 (24/984)
Mpumalanga	13	2	2	3	0	0	20	2 (20/848)
North West	18	1	3	4	0	2	28	3 (28/957)
Western Cape	41	14	3	15	0	0	73	9 (73/782)
Total	**104**	**34**	**11**	**52**	**0**	**7**	**208**	**3 (208/6213)**

Surveillance sites included hospitals in five provinces: Gauteng (Helen Joseph and Rahima Moosa Hospitals), KwaZulu-Natal (Edendale Hospital), Mpumalanga (Mapulaneng, Matikwana and Tintswalo Hospitals), North West (Klerksdorp-Tshepong Hospital Complex) and Western Cape (Red Cross Children's Hospital and Mitchell's Plain Hospital). *Inconclusive: insufficient viral load in sample and therefore unable to characterise further.

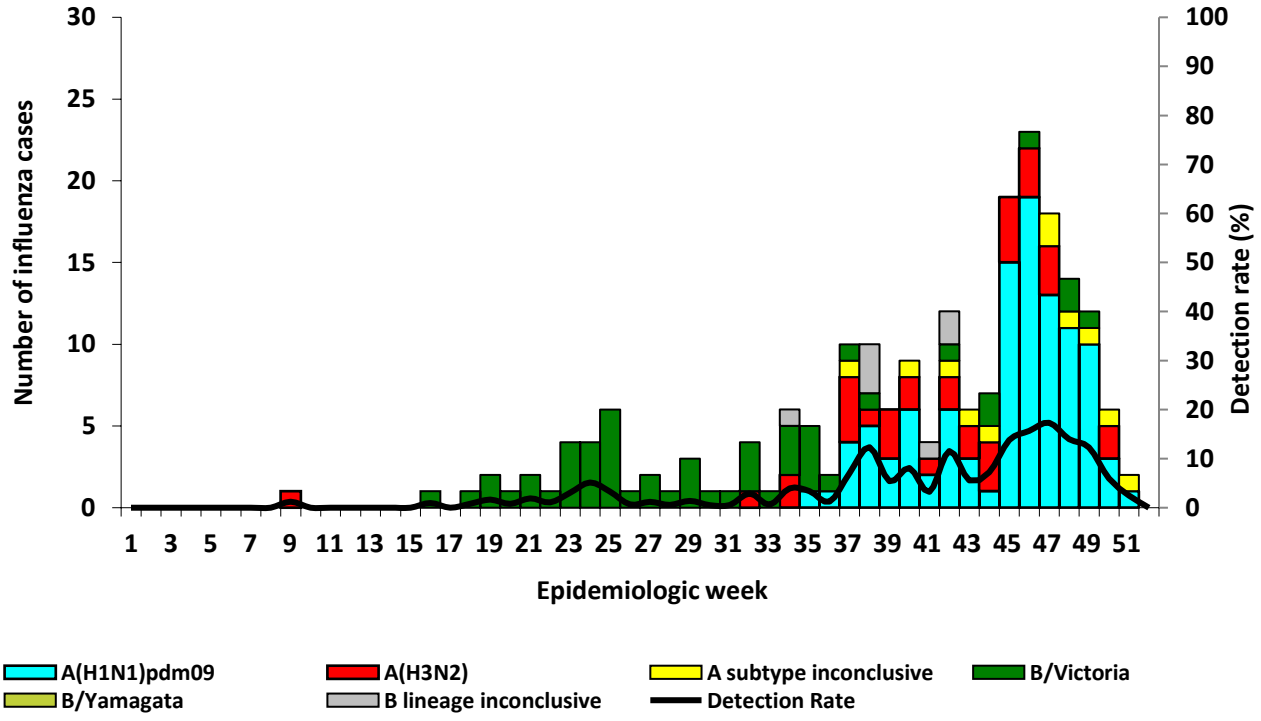

Figure 5. Number of influenza cases by subtypes/lineages and detection rate by epidemiologic week – National pneumonia surveillance, South Africa, Weeks 1 to 52, 2021 (N=208). Inconclusive: insufficient viral load in sample and therefore unable to characterise further.

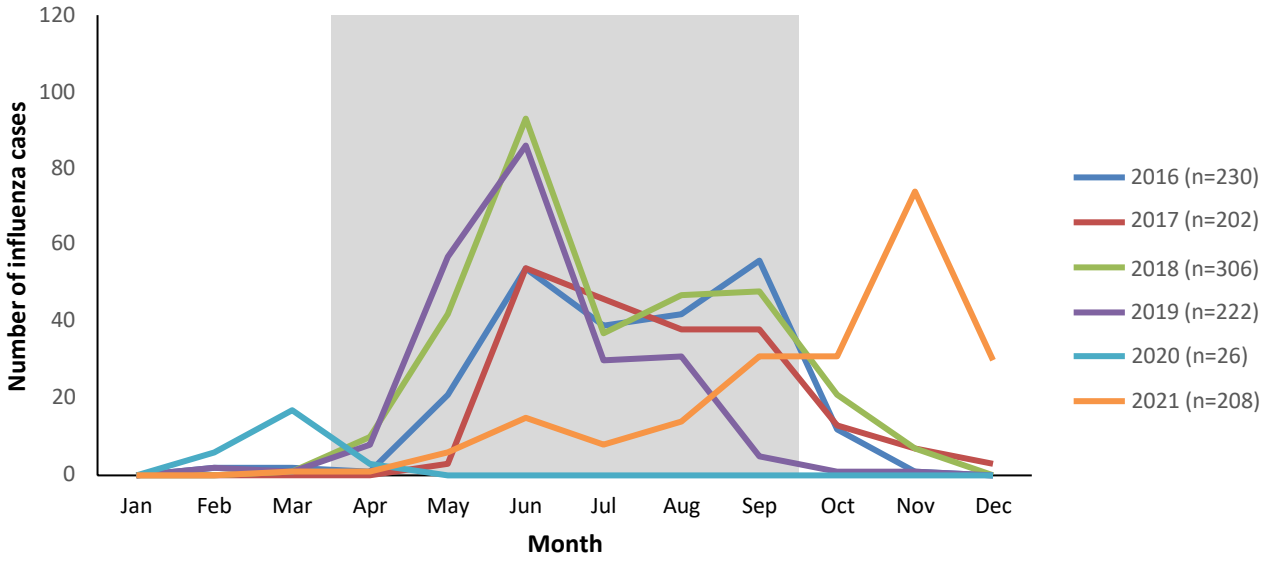

Figure 6. Number of influenza infections detected in the pneumonia surveillance programme, South Africa, 2016-2021. Grey shading indicates typical range of South African influenza season. Number of samples tested: 2016, n=3670; 2017, n=4335, 2018, n=4660; 2019, n=4406; 2020, n=4320; 2021, n=6213.

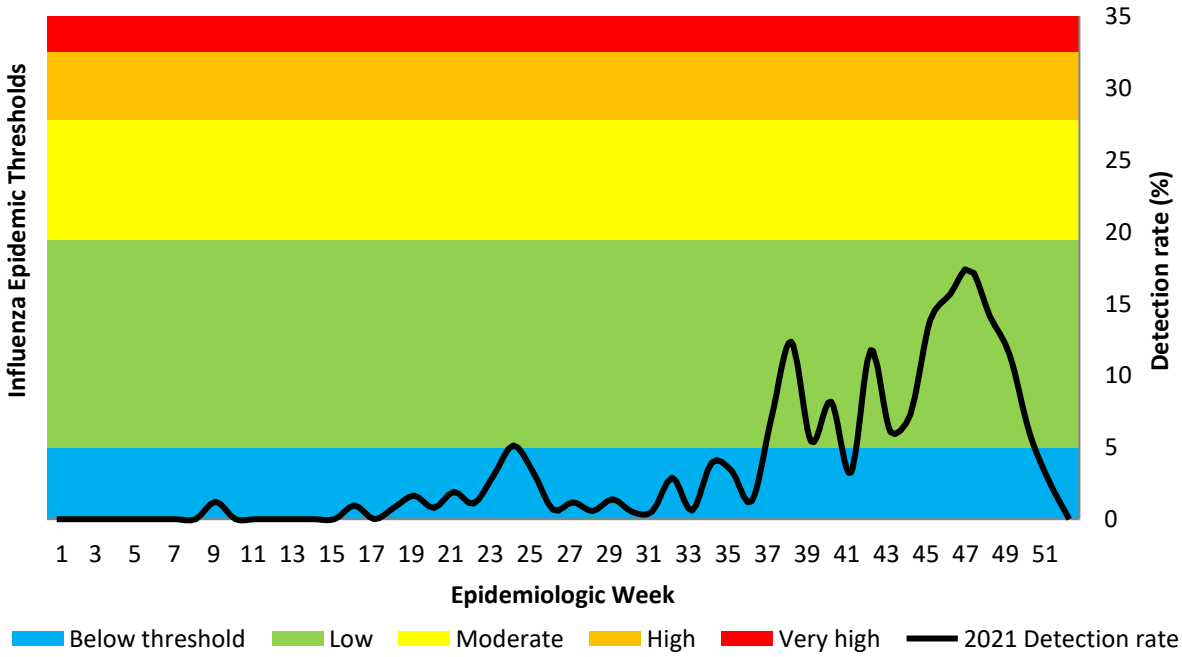

Figure 7. Influenza detection rate and epidemic thresholds*, National pneumonia surveillance programme, South Africa, 4 January 2021 – 2 January 2022 (Weeks 1-52). *Influenza transmission thresholds based on 2010-2019 data and calculated using the Moving Epidemic Method (MEM).

Influenza virus isolation

During 2021, influenza virus isolation was attempted on clinical specimens (n=232) testing positive for influenza on rRT-PCR with a high viral load (C_t value ≤30). Madin-Darby Canine Kidney (MDCK) cells were used for virus isolations with an overall isolation rate of 87% (202/232) (**Table 6**). The isolation success rate was highest for A(H1N1)pdm09 viruses (92%). In total, 92 A(H1N1)pdm09, 68 B/Victoria and 42 A(H3N2) viruses were isolated. Influenza virus isolation in embryonated hens' eggs remains challenging and was not attempted due to high SARS-CoV-2 workloads in the laboratory.

Table 6: Summary of influenza virus isolations in Madin-Darby Canine Kidney (MDCK) cell cultures, South Africa, 2021

Program	Specimens cultured	Successful cultures	Number of cultures/ attempted (%)		
			A(H1N1)pdm09	A(H3N2)	B/Victoria
Viral Watch	6	3	0	0	3/6 (50)
Influenza-like illness surveillance	106	96	51/53 (96)	15/19 (79)	30/34 (88)
Pneumonia surveillance	120	103	41/47 (87)	27/30 (90)	35/43 (81)
Total	**232**	**202**	**92/100 (92)**	**42/49 (86)**	**68/83 (82)**

Antigenic characterisation of influenza virus isolates

The haemagglutination inhibition (HAI) assay results for antigenic characterization of influenza A(H1N1)pdm09, A(H3N2) and B/Victoria are summarised in **Table 7**. Turkey red blood cells were used as indicator cells in the HA and HAI assays. All the HAI assays were completed using the 2019 VIDRL WHO CC kit or IRR 2020-2021 WHO influenza reagent kit for identification of influenza isolates (CDC International Reagent Resource).

A total of 133 virus cultures was characterised antigenically, including 50 A(H1N1)pdm09, 20 A(H3N2) and 63 B/Victoria cultures (**Table 7**). 88% (44/50) of A(H1N1)pdm09 viruses had normal A/Brisbane/02/2018-like reactivity and 70% (14/20) of A(H3N2) had normal A/Kansas/14/2017. For the B/Victoria viruses, 93% (26/28) were classified as normal reactors for the B/Colorado/6/2017-like (2019 kit) assay, and 100% (35/35) as normal reactors for the B/Washington/02/2019-like (2021 kit) assay. An additional 33 cultures from 2021 are currently pending HAI results.

Table 7: Summary of haemagglutination inhibition (HAI) assay results, South Africa, 2021.

Programme	Number of cultures with HAI titers	A(H1N1)pdm09		A(H3N2)		B/Victoria		B/Victoria	
		A/Brisbane/02/2018-like		A/Kansas/14/2017		B/Colorado/6/2017-like (2019 kit)		B/Washington/02/2019-like (2021 kit)	
		Normal reactors	Low reactors	Normal reactors	Low reactors	Normal reactors	Low reactors	Normal reactors	Low reactors
Viral Watch	3	0	0	0	0	3	0	0	0
Influenza-like illness	65	25	5	3	5	4	0	23	0
Pneumonia surveillance	65	19	1	11	1	19	2	12	0
Total n/N (% per virus)	**133**	**44/50 (88)**	**6/50 (12)**	**14/20 (70)**	**6/20 (30)**	**26/28 (93)**	**2/28 (7)**	**35/35 (100)**	**0/35 (0)**

Influenza specimens shared with WHO Collaborating Centres

Influenza virus cultures and original specimens from 174 individuals were shared in July and December 2021 with the WHO Collaborating Centres for Influenza Surveillance and Research (WHO-CC) in Australia, United Kingdom and United States for antigenic and genetic characterisation (**Table 8**). Among specimens shared, 34% (59/174) were A(H1N1) pdm09, 14% (25/174) were A(H3N2) and 52% (90/174) were B/Victoria.

Table 8: Summary of influenza virus specimens collected in South Africa and shared with WHO-CCs for Influenza Surveillance and Research, 2021.

WHO-CC	A(H1N1)pdm09	A(H3N2)	B/Victoria	Total
Australia	28	12	21	61
United Kingdom	31	13	36	80
United States	0	0	33	33
Total	**59**	**25**	**90**	**174**

Genetic characterisation of influenza viruses

Viruses included for genetic characterisation were sequenced at the WHO-CCs for Influenza Surveillance and Research in Australia and United Kingdom; A(H1N1)pdm09 (n=24), A(H3N2) (n=11), and B/Victoria (n=80). Additional sequences deposited by the Vaccine and Infectious Disease Analytics-University of Witwatersrand (WITS-VIDA); A(H1N1)pdm09 (n=10), A(H3N2) (n=6) were also included. All the sequences analysed were obtained from GISAID on the 10 February 2022. Genetic characterisation of influenza A(H1N1)pdm09, A(H3N2), and B/Victoria was carried out by sequencing and phylogenetic analysis (using the MAFFT alignment editor and IQTREE v1.6.12 software with ultrafast bootstraps) of the haemagglutinin (HA) genes. Groups and sub-groups were identified by specific amino acid mutations relative to a designated reference strain as described by the WHO Vaccine Consultation Meeting team (https://www.who.int/influenza/vaccines/virus/recommendations/201909_recommendation.pdf?ua=1).

Influenza A(H1N1)pdm09

Genetic analysis of the HA gene of 34 South African influenza A(H1N1)pdm09 viruses collected in 2021 indicated that all belong to clade 6B.1A (**Figure 8**). The South African 2021 strains further clustered into two genetic subgroups namely 6B.1A.5a.1 (characterised by R130K, D204A, H416N, E523S amino acid mutations) and 6B.1A.5a.2 (characterised by L8M, K147N, N173K, K226I and K226M amino acid mutations). The 2020 viruses (N=61) also belonged to the 6B.1A clade, however, their genetic subgroups possessed some amino acid substitutions which were not found in the 2021 strains **(Figure 8).**

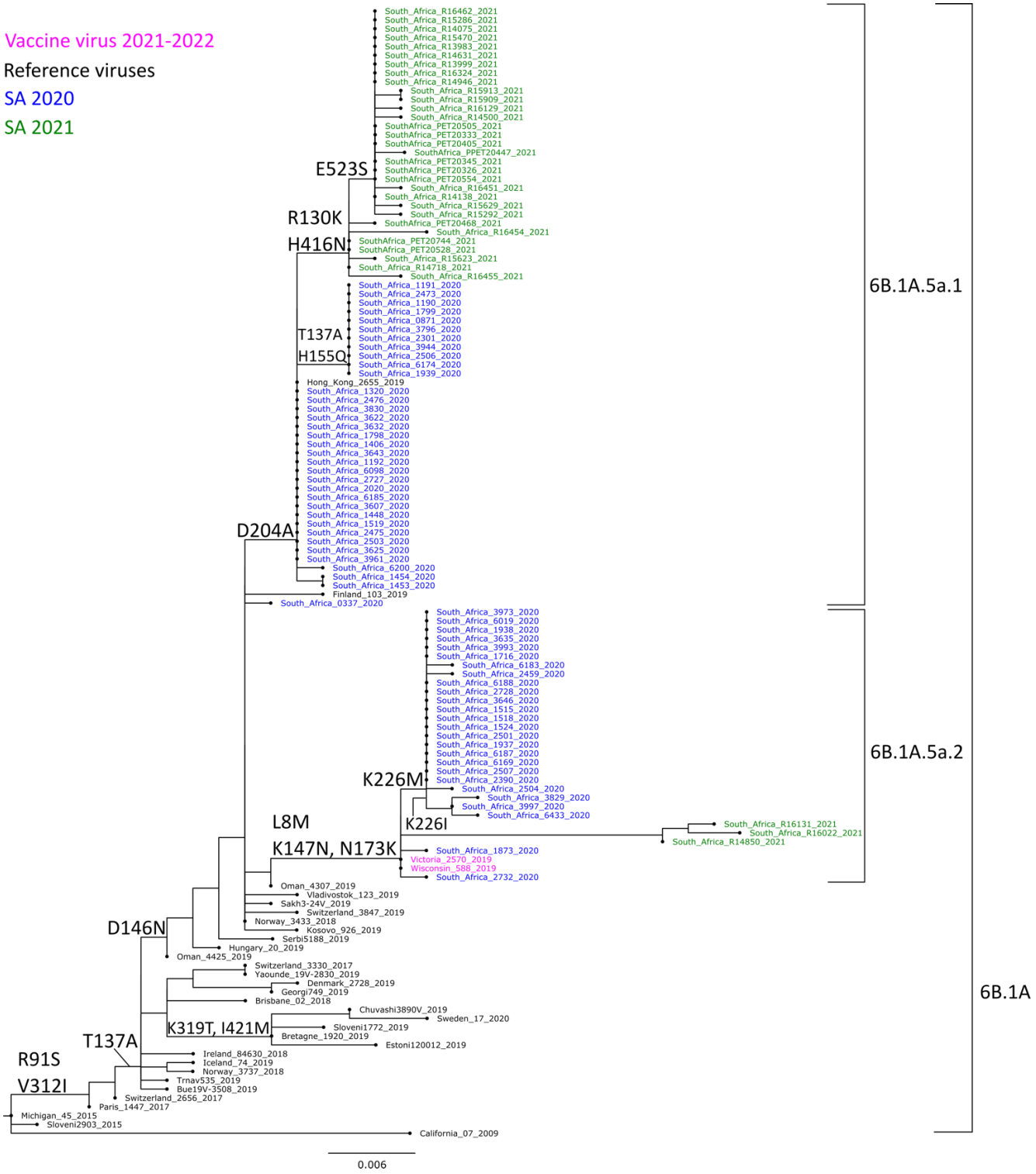

Figure 8. Maximum likelihood phylogenetic tree (ML tree, FLU + Gamma Model, No. of Bootstrap replications n=2000, constructed with IQTREE) of the haemagglutinin gene of influenza A(H1N1)pdm09 viruses. The 2021-2022 southern hemisphere vaccine strains are indicated in pink, South African 2020 viruses in blue (n = 61), South African 2021 viruses in green (n = 34) and reference strains in black. A/California/07/2009 (H1N1) was used as the root.

Influenza A(H3N2)

Genetic analysis of the HA gene of 2021 South African influenza A(H3N2) viruses (n=17) indicated that they belonged to the 3C.2a1b subgroup within the 3C.2a clade, as did the 2020 South African strains (n=3) (**Figure 9**). However, further genotyping of the 2021 strains indicated their diversity as they belonged to three different genetic subgroups with each subgroup characterised by different amino acid substitutions in the HA; 3C.2a1b.1a (T147N), 3C.2a1b.1b (K187N, K327R) and 3C.2a1b.2a.2 (Y175N, L180Q).

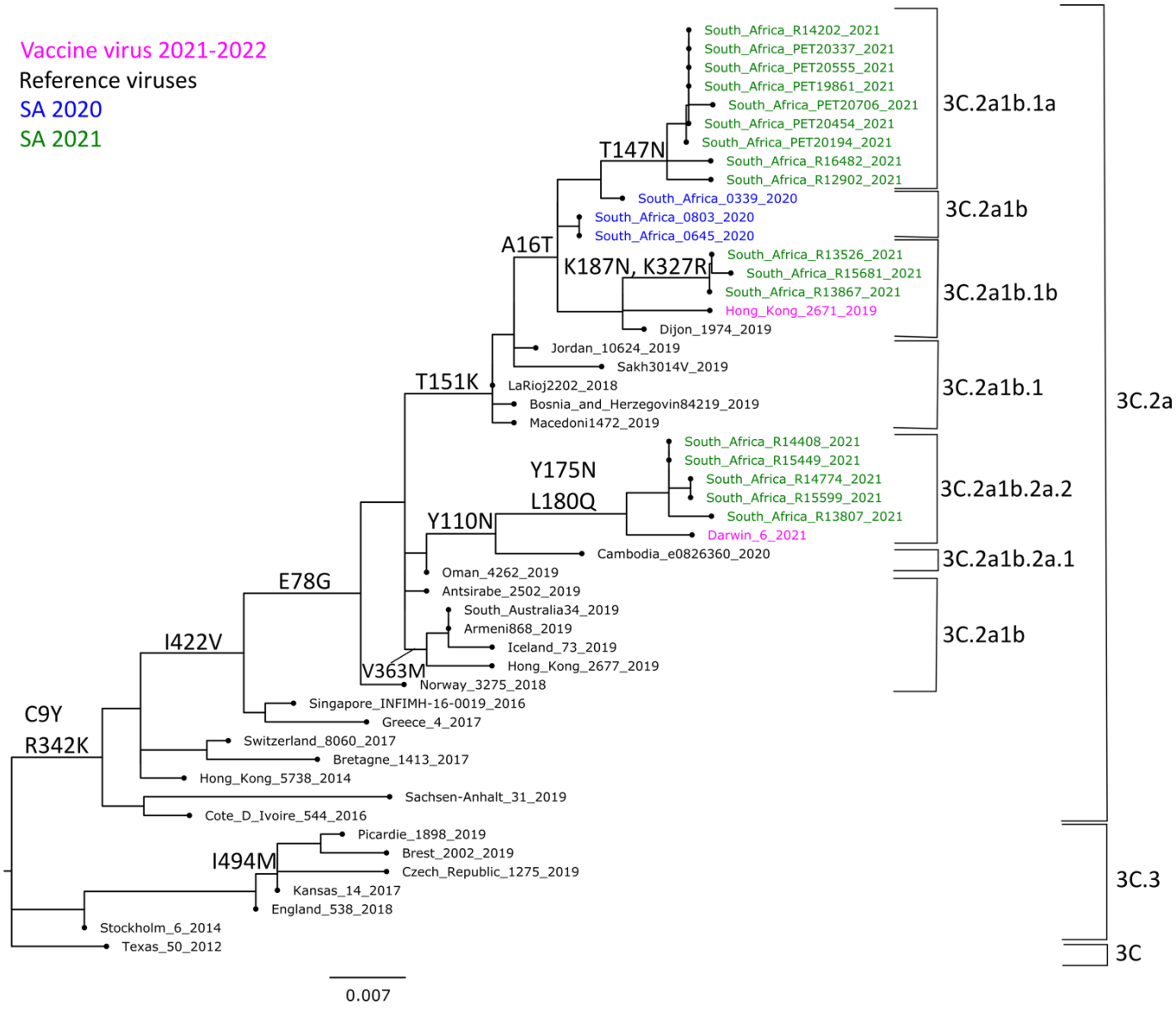

Figure 9. Maximum likelihood phylogenetic tree (ML tree, FLU + Gamma Model, No. of Bootstrap replications n=2000, constructed with IQTREE) of the haemagglutinin gene of influenza A(H3N2) viruses. The 2021-2022 southern hemisphere vaccine strains are indicated in pink, South African 2020 viruses in blue (n = 3), South African 2021 viruses in green (n = 17) and reference strains in black. A/Texas/50/2012 (H3N2) was used as the root.

Influenza B

Genetic analysis of 80 influenza B/Victoria viruses from 2021 showed that all belonged to clade V1A.3 and fell within the genetic subgroup V1A.3a.2 **(Figure 10**). These viruses were closely related to other global strains from Qatar (Qatar/47-VI-19-0066811/2019), USA (Texas/43/2019, Rhode Island/01/2019) and Croatia (Croatia/7789/2019). The 2021 South African strains possessed additional amino acids changes (N141S, E213G, E213K, A217V, N540D), which distinguished them from other strains within the same clade. Moreover, the 2020 South African strains (n=14) belonged to the same clade (V1A.3) but clustered in a different genetic subgroup with different amino acid substitutions**.**

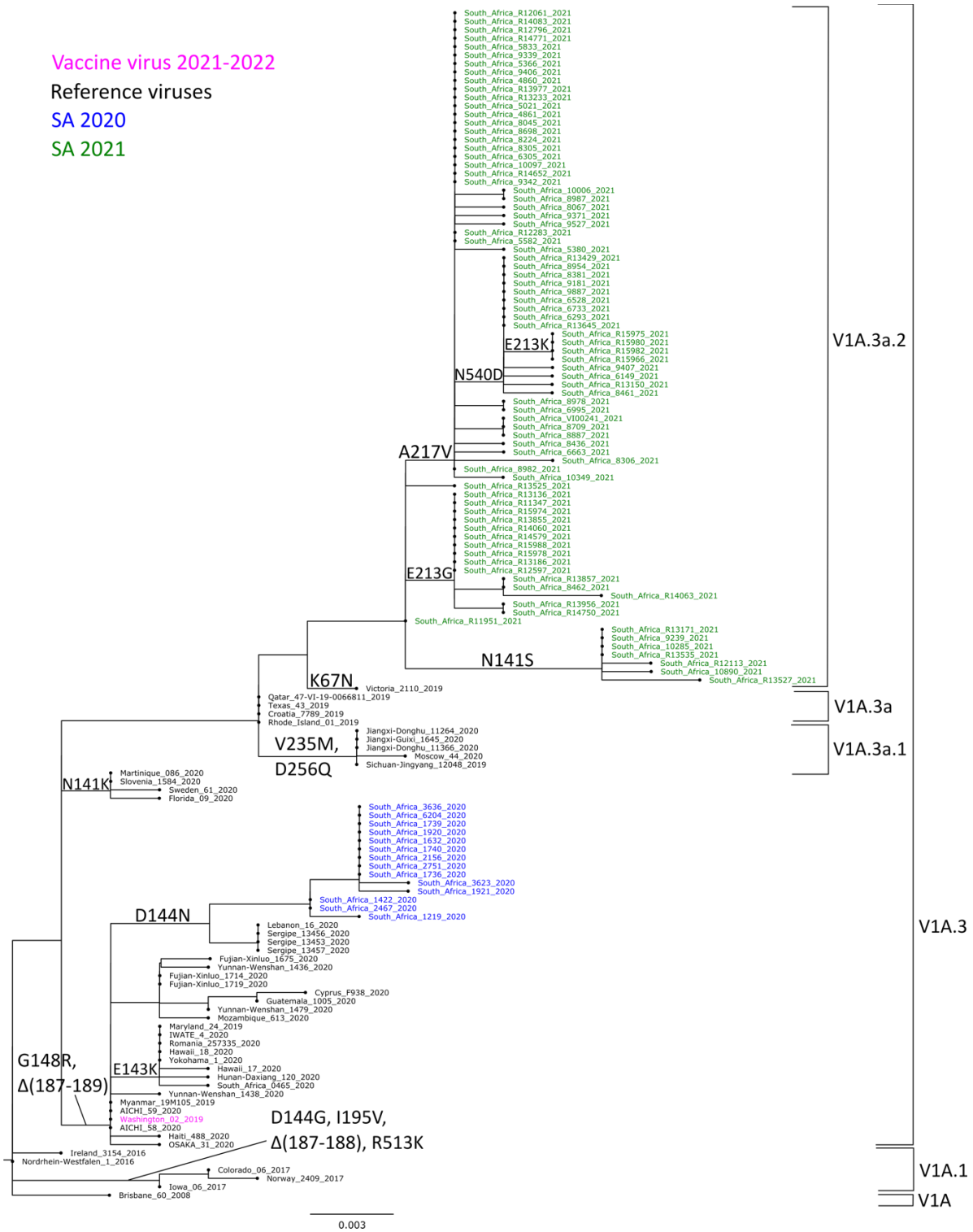

Figure 10. Maximum likelihood phylogenetic tree (ML tree, FLU + Gamma Model, No. of Bootstrap replications n=2000, constructed with IQTREE) of the haemagglutinin gene of influenza B/Victoria viruses. The 2021southern hemisphere vaccine strain B/Washington/02/2019 is indicated in pink, South African 2020 viruses in blue(n = 14), South African 2021 viruses in green (n = 80) and reference strains in black. B/Brisbane/60/2008 was usedas the root.

Conclusions and recommendations

During 2021, influenza activity was observed from week 9 through 52, with a period of increased activity occurring outside of the normal winter influenza season. Influenza circulation was due to seasonal influenza viruses and was dominated by A(H1N1)pdm09, followed by B/Victoria and A(H3N2). The atypical influenza circulation observed in 2021 is likely due to the immunity gap created as a result limited influenza circulation during the COVID-19 pandemic in 2020 and 2021[1], as well as easing of COVID-19 restrictions.

While the majority of influenza infections cause mild illness, influenza may cause severe disease and death.[2] Groups at an increased risk of severe complications of influenza include pregnant women, persons living with HIV, those with chronic illnesses or conditions such as diabetes, lung disease, tuberculosis, heart disease, renal disease and obesity, the elderly (65 years and older) and children under the age of two years.[3] These groups should be encouraged to receive the influenza vaccine[4] and seek medical help early.

To prevent contracting or spreading influenza, it is recommended that

- Close contact with ill people be avoided,
- Ill persons with respiratory symptoms stay at home,
- One's mouth and nose be covered when coughing or sneezing,
- Face masks be worn,
- Hands are regularly sanitized,
- Contact with one's mouth, eyes and nose be avoided,
- Communal spaces, equipment and utensils be regularly disinfected.

Clinicians are encouraged to consider influenza as a differential diagnosis when managing patients presenting with respiratory illness.

Weekly updates on influenza activity in South Africa are available on the NICD website.[5]

Acknowledgements

This report was compiled by the National Influenza Centre (NIC) housed within the Centre for Respiratory Diseases and Meningitis (CRDM) at the National Institute for Communicable Diseases (NICD).

Laboratory Team

Anele Mnguni, Ms
Anne von Gottberg, Prof
Alexandra Moerdyk, Ms
Amelia Buys, Ms
Boitshoko Mahlangu, Mr
Cardia Fourie, Ms
Cayla Reddy, Ms
Daniel Amoako, Dr
Dikeledi Kekana, Ms
Emmanuel Phalane, Mr

Fahima Moosa, Ms
Gerald Motsabi, Mr
Jinal N. Bhiman, Dr
Josie Everatt, Ms
Kedibone Ndlangisa, Dr
Linda de Gouveia, Ms
Lorens Maake, PhD
Mignon du Plessis, Dr
Maimuna Carrim, Ms
Naume Tebeila, Ms
Nicole Wolter, Dr
Nokuthula Linda, Ms
Noluthando Duma, Ms
Noxolo Ntuli, Ms
Nthabeleng Makakole, Ms
Qiniso Mkhize, Mr
Sibusisiwe Zulu, Ms
Siyabonga Mazibuko, Ms
Teresa Mashaba, Ms
Thabo Mohale, Mr
Thulisile Dlamini, Ms
Thulisile Nkabinde, Ms
Valencia Petje, Ms
Wesley Dlamini, Mr

Epidemiology Team

Cheryl Cohen, Prof (Head CRDM)
Jackie Kleynhans, Mrs
Jocelyn Moyes, Dr
Mvuyo Makhasi, Mr
Nicola Chiwandire, Ms
Sibongile Walaza, Dr
Thulisa Mkhencele, Ms

Contributors:

We thank all who have contributed to this report particularly participants, coordinators, medical officers, surveillance officers and data capturers from the pneumonia, ILI and Viral Watch surveillance programmes and personnel from the Centre for Vaccines and Immunology, cell culture laboratory and from the Centre for Respiratory Diseases and Meningitis.

The WHO Collaborating Centre for Influenza Surveillance and Research in Australia (Victorian Infectious Diseases Reference Laboratory), United Kingdom (The Francis Crick Institute) and United States (Centers for Disease Control and Prevention) for sharing virological data generated using 2021 influenza season viruses/ isolates submitted by the NIC South Africa.

Influenza surveillance is funded by the National Institute for Communicable Diseases, South Africa. In addition, the pneumonia surveillance programme has received supplemental funding through a co-operative agreement with the United States Centers for Disease Control and Prevention and through Wellcome Trust (grant number 221003/Z/20/Z) in collaboration with the Foreign, Commonwealth and Development Office.

The following public health facilities and laboratories participated in the pneumonia and ILI surveillance programmess:
Agincourt Health Care Centrec, Agincourt, Mpumalanga Province
Edendale Hospital, KwaZulu-Natal Province
Edendale Gateway Clinic, KwaZulu-Natal Province
Helen Joseph and Rahima Moosa Mother and Child Hospitals, Gauteng Province
Jouberton Clinic, North West Province
Klerksdorp and Tshepong Hospital Complex, North West Province
Mapulaneng and Matikwana Hospitals, Mpumalanga Province
Mitchell's Plain Hospital, Western Cape Province
Tintswalo Hospital, Mpumalanga Province
The Red Cross Childrens' War Memorial Hospital, Western Cape Province

References

1. Tempia S, Walaza S, Bhiman JN, et al. Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa, January to October 2020. *Euro Surveill* **2021**; 26:1–10. Available at: http://dx.doi.org/10.2807/1560-7917.ES.2021.26.29.2001600.

2. Tempia S, Walaza S, Moyes J, et al. Risk factors for influenza-associated severe acute respiratory illness hospitalization in South Africa, 2012-2015. *Open Forum Infect Dis* **2017**; 4:2012–2015.

3. National Institute for Communicable Diseases. Influenza NICD recommendations for the diagnosis, management, prevention and public health response. Available at: https://www.nicd.ac.za/wp-content/uploads/2021/07/Influenza-guidelines_-April-2021-final.pdf. Accessed 7 March 2022.

4. National Institute for Communicable Diseases. The COVID-19 vaccine and flu vaccine. Available at: https://www.nicd.ac.za/the-covid-19-vaccine-and-the-flu-vaccine/. Accessed 7 March 2022.

5. National Institute for Communicable Diseases. Weekly Respiratory Pathogens Surveillance Report. Available at: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports/weekly-respiratory-pathogens-surveillance-report-week/. Accessed 7 March 2022.