Influenza Surveillance in Ireland – Weekly Report

Influenza Week 9 2019 (25th February – 3rd March 2019)









CI Intensive Care Society of Ireland

Summary

All indicators of influenza activity decreased significantly during week 9 2019 (week ending 3rd March 2019) compared to previous weeks. Influenza-like illness (ILI) rates have continued to decrease and are now below baseline levels. Influenza A(H1N1)pdm09 and A(H3N2) are now co-circulating. However influenza A(H1N1)pdm09 has been the dominant circulating virus in the 2018/2019 season overall.

- <u>Influenza-like illness (ILI):</u> The sentinel GP influenza-like illness (ILI) consultation rate was 13.9 per 100,000 population in week 9 2019. This is a decrease compared to the updated rate of 25.8 per 100,000 reported during week 8 2019.
 - ILI rates are now below the Irish baseline threshold (17.5 per 100,000 population).
 - o ILI age specific rates are below baseline levels in all age groups.
- National Virus Reference Laboratory (NVRL):
 - Influenza detections decreased during week 9 2019, with 70 (17%) influenza positive specimens reported by the NVRL from sentinel and non-sentinel sources: 35 influenza A(H3N2), 30 A(H1N1)pdm09, and 5 influenza A(not subtyped).
 - o Influenza A(H1N1)pdm09 and A(H3N2) are now co-circulating. However influenza A(H1N1)pdm09 has been the dominant circulating virus in the 2018/2019 season overall.
 - The NVRL has carried out molecular and antigenic characterisation on 39 influenza A(H1N1)pdm09 specimens to date this season. Results show that the current vaccine is a good match for the circulating influenza A(H1N1)pdm09 viruses. Twelve influenza A(H3N2) specimens and three influenza B specimens were also characterised and most belonged to the vaccine virus clades.
 - Respiratory syncytial virus (RSV) detections continued to decrease during week 9 2019 and RSV is now at low levels.
 - Human metapneumovirus, adenovirus, parainfluenza virus and picornavirus (which includes both rhinovirus and enterovirus) continue to be detected.
- <u>Hospitalisations:</u> One hundred and sixty nine confirmed influenza hospitalised cases were notified to HPSC during week 9 2019, bringing the season total to 2,509. The majority of hospitalisations were associated with influenza A. Where information on subtype was available, most of the hospitalised cases were due to influenza A(H1N1)pdm09.
- <u>Critical care admissions:</u> one hundred and sixteen confirmed influenza cases were admitted to critical care units and reported to HPSC during the 2018/2019 season to date.
- Mortality: Fifty four deaths in influenza cases have been notified to HPSC in the 2018/2019 season to date.
 The median age of those who died was 70.5 years. Excess all-cause mortality was reported in week 4 2019.
- <u>Outbreaks:</u> Six acute respiratory infection (ARI)/influenza general outbreaks were notified to HPSC during week 9 2019, bringing the season total to 77 ARI/influenza outbreaks.
- <u>International</u>: Influenza activity continues to be widespread throughout Europe and in other countries in the temperate zone of the northern hemisphere.

1. GP sentinel surveillance system - Clinical Data

- During week 9 2019, 39 influenza-like illness (ILI) cases were reported by sentinel GPs, corresponding to an ILI consultation rate of 13.9 per 100,000 population. This was a decrease compared to the updated rate of 25.8 per 100,000 population reported during week 8 2019 (figure 1).
- The ILI rate for week 9 2019 was below the Irish baseline ILI threshold (17.5/100,000 population) for the first time since week 52 2018 (figure 1).
- ILI age specific rates were below baseline levels in all age groups (figure 2).
- HPSC, in consultation with the European Centre for Disease Prevention and Control (ECDC) has revised the Irish baseline ILI threshold for the 2018/2019 influenza season to 17.5 per 100,000 population; this threshold indicates the likelihood that influenza is circulating in the community. The Moving Epidemic Method (MEM) has been adopted by ECDC to calculate thresholds for GP ILI consultations in a standardised approach across Europe.1
- The baseline ILI threshold (17.5/100,000 population), medium (62.3/100,000 population) and high (122.2/100,000 population) intensity ILI thresholds are shown in figure 1.

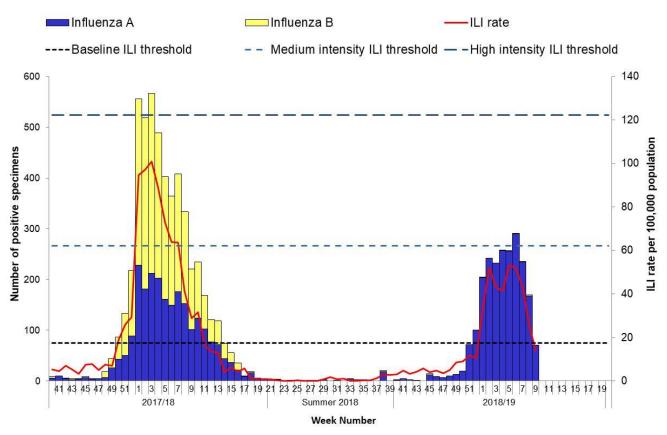


Figure 1: ILI sentinel GP consultation rates per 100,000 population, baseline ILI threshold, medium and high intensity ILI thresholds and number of positive influenza A and B specimens tested by the NVRL, by influenza week and season. Source: ICGP and NVRL

For further information on the Moving Epidemic Method (MEM) to calculate ILI thresholds: http://www.ncbi.nlm.nih.gov/pubmed/22897919

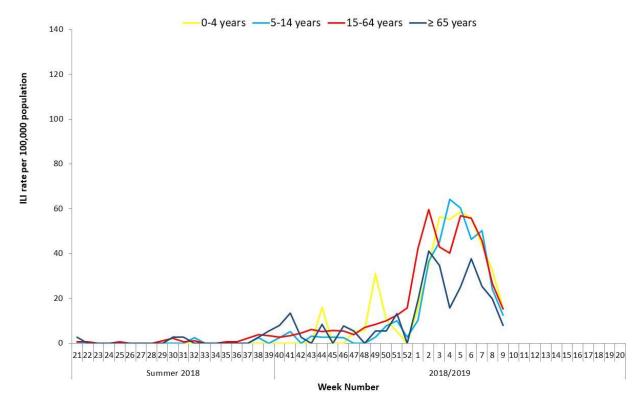


Figure 2: Age specific sentinel GP ILI consultation rate per 100,000 population by week during the summer of 2018 and the 2018/2019 influenza season to date. *Source: ICGP*.

2. Influenza and Other Respiratory Virus Detections - NVRL

The data reported in this section for the 2018/2019 influenza season refer to sentinel and non-sentinel respiratory specimens routinely tested for influenza, respiratory syncytial virus (RSV), adenovirus, parainfluenza viruses types 1, 2, 3 & 4 (PIV-1, -2, -3 & -4) and human metapneumovirus (hMPV) by the National Virus Reference Laboratory (NVRL) (figures 3, 4 & 5 and tables 1 & 2).

- Influenza detections decreased during week 9 2019, with 70 (17% of samples tested) influenza positive specimens reported by the NVRL from sentinel and non-sentinel sources, compared to an updated figure of 170 (24% of samples tested) detections for week 8 2019.
- Of the positives detected during week 9 2019, 35 (50%) were influenza A(H3N2), 30 (43%) were influenza A(H1N1)pdm09 and 5 (7%) were influenza A(not subtyped).
- Data from the NVRL for week 9 2019 and the 2018/2019 season to date are detailed in tables 1 and 2.
- Influenza A(H1N1)pdm09 and A(H3N2) are now co-circulating. However influenza A(H1N1)pdm09 has been the dominant circulating virus in the 2018/2019 season overall. Low numbers of influenza B detections are also being reported (figures 3 & 4).
- Respiratory syncytial virus (RSV) detections continued to decrease during week 9 2019 and RSV is now at low levels (table 2 & figure 5).
- Co-infections of all seasonal respiratory viruses were reported during week 9 2019. Thirteen percent of influenza cases detected from non-sentinel sources were co-infected with another respiratory virus.
- Human metapneumovirus, adenovirus, parainfluenza virus and picornavirus (which includes both rhinovirus and enterovirus) continue to be detected (table 2).
- The overall proportion of non-sentinel specimens positive for respiratory viruses was 28% during week 9.

Virus Characterisation

The recommended composition of trivalent influenza vaccines for the 2018/2019 influenza season in the northern hemisphere includes: an A/Michigan/50/2015 (H1N1)pdm09-like virus; an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage). For quadrivalent vaccines, a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) is recommended. Trivalent vaccines are currently the mostly widely used influenza vaccines in Europe. http://www.who.int/influenza/vaccines/virus/recommendations/en/

The NVRL carried out molecular and antigenic characterisation of a selection of influenza positive specimens between week 40 2018 and week 2 2019. Influenza viruses were sequenced and compared to a bank of recommended reference sequences provided by ECDC for the 2018/2019 season.

Influenza A(H1N1)pdm09

The hemagglutinin genes of all influenza A(H1N1)pdm09 viruses characterised (n=39) since week 40 2018 were all found to be group 6B.1 viruses, represented by A/Michigan/45/2015. This is the dominant global influenza A(H1N1)pdm09 variant and is included in the current 2018/2019 northern hemisphere trivalent and quadrivalent vaccines. All viruses carry the characteristic amino acid mutations for this group and have evolved rapidly this season forming several distinct clusters within the 6B.1 clade. There is no evidence that these amino acid substitutions are associated with antigenic change. In fact, antigenic characterisation performed on 11 Irish specimens established that the influenza viruses cultured from patient samples were well recognised by the antiserum raised against the currently used vaccine virus, A/Michigan/45/2015. This demonstrates that, as reported in other European countries, the current vaccine remains a good match for the A(H1N1)pdm09 viruses circulating in Ireland.

Influenza A(H3N2)

Influenza A(H3N2) viruses have circulated in low levels throughout the season in Ireland. The vast majority of influenza A(H3N2) viruses characterised in Ireland in the 2018/2019 season to date fell in the current vaccine component clade 3C.2a1, represented by A/Singapore/INFIMH-16-0019/2016 (91.7%, n=11/12). All of these viruses were in the 3C.2a1b subgroup, represented by A/Alsace/1746/2018. The 3C.2a variants have circulated in Ireland and Europe since 2014 evolving further into 3C.2a1a and 3C.2a1b subclades in recent years. Additionally, one virus (8.3%) was characterised as a 3C.3a virus, represented by A/England/538/2018. This strain has been identified sporadically throughout Europe since 2013 and has continued to circulate in Ireland at low levels since this time.

Influenza B

Influenza B viruses have circulated at very low levels throughout Ireland and Europe during the 2018/2019 season to date (<1% detections in Ireland and <2% detections in Europe). In Ireland, just 5 influenza B viruses have been detected at the NVRL to date. Three of the influenza B viruses were suitable for further molecular characterisation, which identified 2 B-Victoria lineage and 1 B-Yamagata lineage viruses. Of the 2 B-Victoria lineage viruses detected, both fall into the B/Brisbane/60/2008 clade. One of these viruses contains the double deletion of AAs 162 and 163 (Δ 162-163) in the HA gene, represented by B/Colorado/06/2017 virus. This variant emerged in 2016 and is the strain included in the 2018/2019 Northern Hemisphere trivalent and quadrivalent vaccines. The B-Yamagata virus was identified as a clade 3 B/Phuket/3073/2013-like virus using antigenic characterisation. All circulating influenza B Yamagata viruses reported globally in the last 8 months have been clade 3 viruses and this virus is included in the 2018/2019 northern hemisphere quadrivalent vaccine.

Further genetic and antigenic testing is ongoing at the NVRL.

See ECDC influenza surveillance reports for further information.

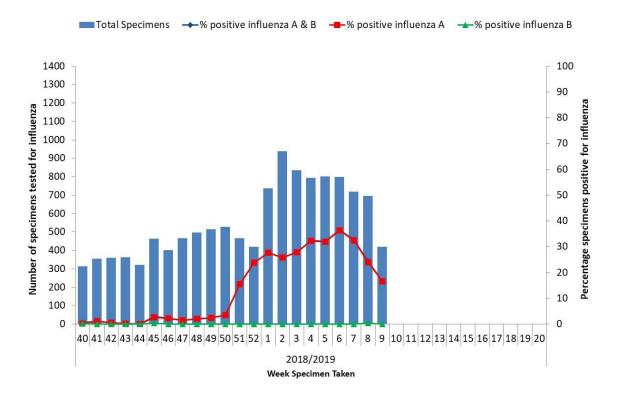


Figure 3: Number of specimens (from sentinel and non-sentinel sources combined) tested by the NVRL for influenza and percentage influenza positive by week for the 2018/2019 influenza season. *Source: NVRL*.

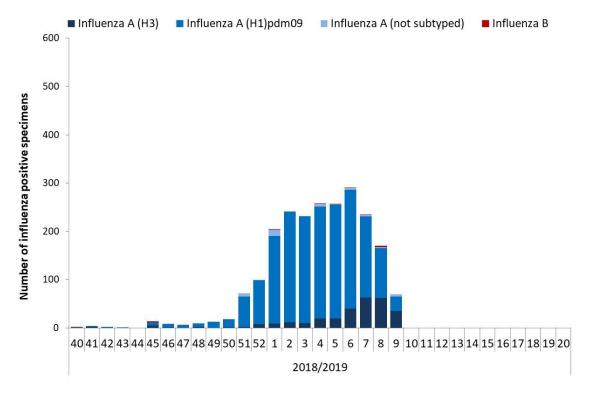


Figure 4: Number of positive influenza specimens (from sentinel and non-sentinel sources combined) by influenza type/subtype tested by the NVRL, by week for the 2018/2019 influenza season. *Source: NVRL*.

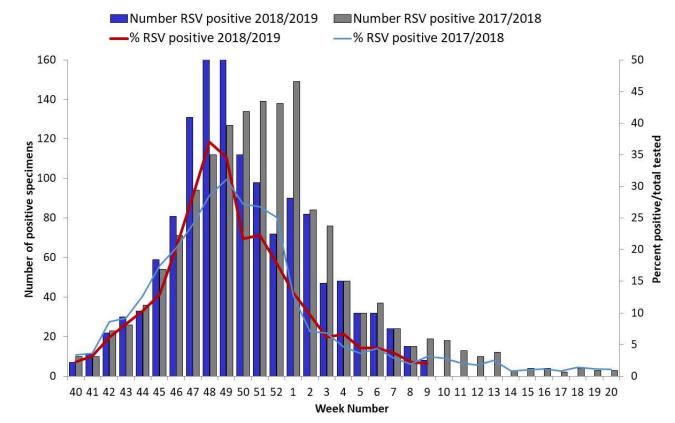


Figure 5: Number and percentage of non-sentinel RSV positive specimens detected by the NVRL during the 2018/2019 season, compared to the 2017/2018 season. *Source: NVRL.*

Table 1: Number of sentinel and non-sentinel respiratory specimens tested by the NVRL and positive influenza results, for week 9 2019 and the 2018/2019 season to date. Source: NVRL

Week	Specimen type	Total tested	Number influenza positive	% Influenza positive					
					A (H1)pdm09	A (H3)	A (not subtyped)	Total influenza A	Influenza B
9 2019	Sentinel	22	9	40.9	5	0	4	9	0
	Non-sentinel	399	61	15.3	25	35	1	61	0
	Total	421	70	16.6	30	35	5	70	0
2018/2019	Sentinel	739	343	46.4	290	45	6	341	2
	Non-sentinel	11480	1870	16.3	1571	247	43	1861	9
	Total	12219	2213	18.1	1861	292	49	2202	11

Table 2: Number of non-sentinel specimens tested by the NVRL for other respiratory viruses and positive results, for week 9 2019 and the 2018/2019 season to date.

Source: NVRL

Week	Specimen type	Total tested	RSV	% RSV	Adenovirus	% Adenovirus	PIV-1	% PIV-1	PIV-2	% PIV-2	PIV-3	% PIV-3	PIV-4	% PIV-4	hMPV	% hMPV
9 2019	Sentinel	22	0	0.0	1	4.5	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0
	Non-sentinel	399	8	2.0	18	4.5	0	0.0	1	0.3	12	3.0	0	0.0	11	2.8
	Total	421	8	1.9	19	4.5	0	0.0	1	0.2	13	3.1	0	0.0	11	2.6
2018/2019	Sentinel	739	31	4.2	10	1.4	1	0.1	0	0.0	7	0.9	2	0.3	30	4.1
	Non-sentinel	11480	1386	12.1	275	2.4	2	0.0	30	0.3	138	1.2	166	1.4	559	4.9
	Total	12219	1417	11.6	285	2.3	3	0.0	30	0.2	145	1.2	168	1.4	589	4.8

[†] Please note that non-sentinel specimens relate to specimens referred to the NVRL (other than sentinel specimens) and may include more than one specimen from each case.

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3. Regional Influenza Activity by HSE-Area

Influenza activity is based on sentinel GP ILI consultation rates, laboratory data and outbreaks.

The geographical spread of influenza/ILI during week 9 2019 is shown in figure 6. Localised influenza activity was reported in HSE-E, -NE, -MW, -SE and -W, sporadic activity was reported in HSE-M and -S and no activity was reported in HSE-NW (figure 6).

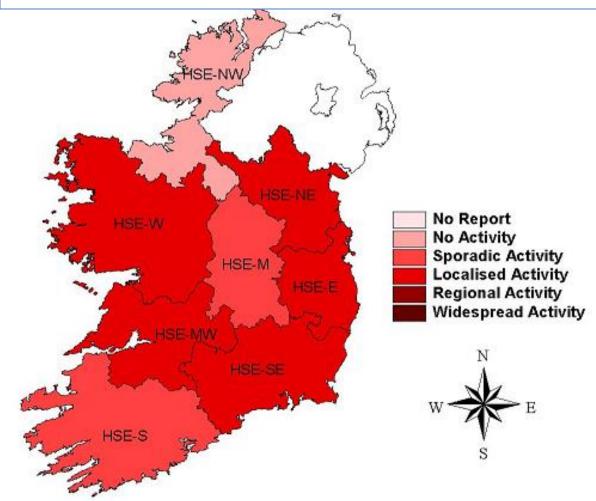


Figure 6: Map of provisional influenza activity by HSE-Area during week 9 2019

Sentinel hospitals

The Departments of Public Health have established at least one sentinel hospital in each HSE-Area, to report data on total, emergency and respiratory admissions on a weekly basis.

Respiratory admissions reported from the network of sentinel hospitals were at moderate levels, at 282, during week 9 2019. This was a decrease compared to week 8 2019 when 381 respiratory admissions were reported. It should be noted that one sentinel hospital did not report data in week 9 (figure 7).

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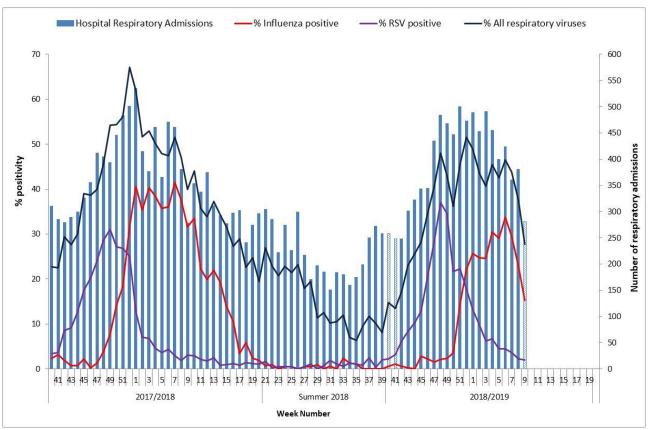


Figure 7: Number of respiratory admissions reported from the sentinel hospital network and % positivity for influenza, RSV and all seasonal respiratory viruses tested by the NVRL by week and season. Source: Departments of Public Health - Sentinel Hospitals & NVRL.

4. GP Out-Of-Hours services surveillance

The Department of Public Health in HSE-NE is collating national data on calls to nine of thirteen GP Out-of-Hours services in Ireland. Records with clinical symptoms reported as flu or influenza are extracted for analysis. This information may act as an early indicator of increased ILI activity. However, data are self-reported by callers and are not based on coded influenza diagnoses.

The proportion of influenza—related calls to GP Out-of-Hours services was 1.7% in week 9 2019. This was a decrease compared to the updated figure of 2.6% for week 8. Six services reported data for week 9 and there were 263 calls relating to self-reported influenza (figure 8).

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[‡] All seasonal respiratory viruses tested refer to non-sentinel respiratory specimens routinely tested by the NVRL including influenza, RSV, adenovirus, parainfluenza viruses and human metapneumovirus (hMPV). Weeks where data were missing or unavailable are represented by the hatched bar

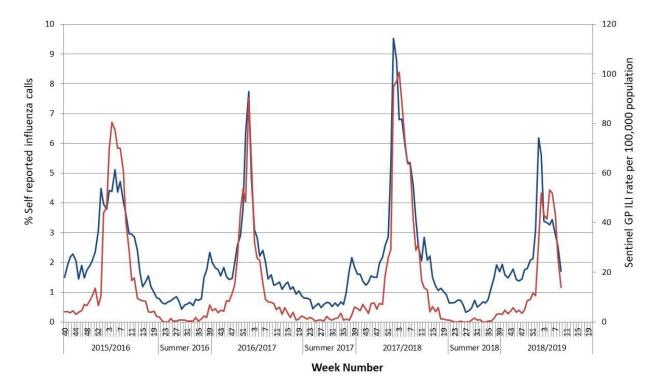


Figure 8: Self-reported influenza-related calls as a proportion of total calls to Out-of-Hours GP Co-ops and sentinel GP ILI consultation rate per 100,000 population by week and season. Source: GP Out-Of-Hours services in Ireland (collated by HSE-NE) & ICGP.

5. Influenza & RSV notifications

Influenza and RSV cases notifications are reported on Ireland's Computerised Infectious Disease Reporting System (CIDR), including all positive influenza/RSV specimens reported from all laboratories testing for influenza/RSV and reporting to CIDR.

Influenza and RSV notifications are reported in the <u>Weekly Infectious Disease Report for Ireland</u>. Influenza notifications decreased during week 9 2019, with 498 cases reported compared to 698 in week 8. During week 9 2019, 111 cases were due to influenza A(H1N1)pdm09, 57 were due to A(H3N2), 323 were due to influenza A (not subtyped), 5 were due to influenza B and the influenza type was not reported for 2 cases.

For the 2018/2019 influenza season to date, 6,454 confirmed influenza cases have been notified to HPSC: 2,013 were due to influenza A(H1N1)pdm09, 212 were due to A(H3N2), 4,182 were due to A (not subtyped), 38 were due to influenza B and the influenza type was not reported for 9.

Respiratory syncytial virus (RSV) notifications continued to decrease and were at low levels during week 9 2019, with 27 cases notified compared to 52 during week 8 2019.

6. Influenza hospitalisations

One hundred and sixty nine confirmed influenza hospitalised cases were notified to HPSC during week 9 2019. For the 2018/2019 influenza season to date, 2,509 confirmed influenza hospitalised cases (99% influenza A and 1% influenza B) have been notified to HPSC: 829 were due to A(H1N1)pdm09, 46 were due to A(H3N2), 1,612 were due to A (not subtyped)), 16 were due to influenza B and 6 were due to influenza-type not reported (figure 9).

Age specific rates for hospitalised influenza cases are reported in table 3, with the highest rates reported in those aged less than five years old (201/100,000 population).

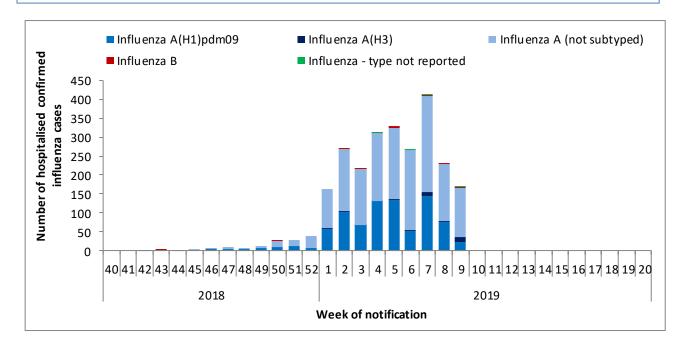


Figure 9. Number of confirmed influenza cases hospitalised by influenza type/subtype and by week of notification Source: Ireland's Computerised Infectious Disease Reporting System (CIDR).

7. Critical Care Surveillance

The Intensive Care Society of Ireland (ICSI) and the HSE Critical Care Programme are continuing with the enhanced surveillance system set up during the 2009 pandemic, on all critical care patients with confirmed influenza. HPSC processes and reports on this information on behalf of the regional Directors of Public Health/Medical Officers of Health.

One hundred and sixteen confirmed influenza cases were admitted to critical care units and reported to HPSC during the 2018/2019 influenza season to date. Fifty four were associated with influenza A(H1N1)pdm09, two with influenza A(H3N2), fifty nine with influenza A(not subtyped)) and one with influenza B. The age specific rates for admission to critical care are shown in table 3. The highest ICU admission rates were in children <1 year of age (6.4/100,000 population) and adults aged 65 years and older (5.6/100,000 population).

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Table 3: Age specific rates for confirmed influenza cases hospitalised and admitted to critical care during the 2018/2019 influenza season to date. Age specific rates are based on the 2016 CSO census.

		Hospitalised	Admitted to ICU			
Age (years)	Number	Age specific rate per 100,000 population	Number	Age specific rate per 100,000 population		
<1	131	210.4	4	6.4		
1-4	537	199.4	8	3		
5-14	337	49.9	3	0.4		
15-24	72	12.5	1	0.2		
25-34	148	22.4	7	1.1		
35-44	169	22.6	15	2		
45-54	202	32.3	22	3.5		
55-64	242	47.5	20	3.9		
<u>></u> 65	671	105.2	36	5.6		
Total	2509	52.7	116	2.4		

8. Mortality Surveillance

Influenza-associated deaths include all deaths where influenza is reported as the primary/main cause of death by the physician or if influenza is listed anywhere on the death certificate as the cause of death. HPSC receives daily mortality data from the General Register Office (GRO) on all deaths from all causes registered in Ireland. These data have been used to monitor excess all-cause and influenza and pneumonia deaths as part of the influenza surveillance system and the <u>European Mortality Monitoring Project</u>. These data are provisional due to the time delay in deaths' registration in Ireland.

- Fifty four deaths in notified influenza cases were reported to HPSC in the 2018/2019 influenza season to date. Most of the cases who died were aged 65 years or older and the median age at death was 70.5 years.
- All-cause excess mortality was reported in Ireland during week 4 2019 after correcting GRO data for reporting delays with the standardised EuroMOMO algorithm. It is important to note that these data are provisional due to the time delay in deaths' registration in Ireland.
- Increased all-cause mortality has been reported in Europe in recent weeks. The excess mortality has
 mostly been among those aged 65 years and above, but also in the 15-64 years age group and was
 mainly identified in southern and central European countries http://www.euromomo.eu/.

9. Outbreak Surveillance§

- Six respiratory outbreaks were notified to HPSC during week 9 2019.
- Five were due to influenza: three were in community hospitals/long-stay units in HSE E and two were in HSE-SE, one was in a community hospital/long stay unit and one in a nursing home.
- One acute respiratory infection (ARI) outbreak was reported in a residential institution in HSE S.
- For the 2018/2019 influenza season to date, 77 influenza/ARI general outbreaks have been notified; fifty two were due to influenza, eight were due to RSV, three were due to coronavirus, three were due to human metapneumovirus, two were due to rhinovirus/enterovirus and the pathogen was not reported for the remaining nine outbreaks. Table 4 summarises respiratory outbreaks notified on CIDR during the 2018/2019 season to date.

[§] Excludes family outbreaks
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Table 4: Summary of respiratory outbreaks by HSE area and disease during 2018/2019 Source: CIDR

HSE area	Influenza	Respiratory syncytial virus infection	Acute respiratory infection	Total
HSE-E	24	2	1	27
HSE-M	2	0	2	4
HSE-MW	2	0	0	2
HSE-NE	3	1	1	5
HSE-NW	4	4	0	8
HSE-SE	10	0	2	12
HSE-S	6	0	9	15
HSE-W	1	1	2	4
Total	52	8	17	77

10. International Summary

- Influenza activity was widespread in the European Region during week 8 2019. Influenza type A virus
 detections dominated with slightly more A(H1N1)pdm09 than A(H3N2) viruses. Very few influenza B
 viruses were detected.
- The influenza A(H1N1)pdm09 viruses that have been characterised to date are antigenically similar to the 2018–2019 northern hemisphere influenza vaccine virus. Fewer influenza A(H3N2) viruses have been antigenically characterised.
- In general, current influenza vaccines tend to work better against influenza A(H1N1)pdm09 and influenza B viruses than against influenza A(H3N2) viruses. Preliminary vaccine effectiveness estimates continue to support the use of vaccines. Early data suggest the vaccines are effective, but estimates vary depending on the population studied and the proportions of circulating influenza A virus subtypes. See data from six European studies, Canada, Finland, Hong Kong, Sweden, and the United States.
- Circulating viruses remain susceptible to neuraminidase inhibitors supporting early initiation of treatment and prophylactic use according to national guidelines.
- In the temperate zone of the northern hemisphere influenza activity continued to increase.
- National Influenza Centres (NICs) and other national influenza laboratories from 115 countries, areas or territories reported data to FluNet for the time period from 4th to 17th February 2019. The WHO GISRS laboratories tested more than 220,347 specimens during that time period; 74,302 were positive for influenza viruses, of which 72,225 (99%) were typed as influenza A and 1,077 (1%) as influenza B. Of the sub-typed influenza A viruses, 19,600 (65%) were influenza A(H1N1)pdm09 and 10,447 (35%) were influenza A(H3N2). Of the characterised B viruses, 82 (26%) belonged to the B-Yamagata lineage and 231 (74%) to the B-Victoria lineage.
- See <u>ECDC</u> and <u>WHO</u> influenza surveillance reports for further information.

Further information is available on the following websites:

Northern Ireland http://www.fluawareni.info/
Europe – ECDC http://ecdc.europa.eu/

Public Health England http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectiousDiseases/InfectionsAZ/SeasonalInfluenza/

United States CDC http://www.cdc.gov/flu/weekly/fluactivitysurv.htm
Public Health Agency of Canada http://www.phac-aspc.gc.ca/fluwatch/index-eng.php

- Information on Middle Eastern Respiratory Syndrome Coronavirus (MERS), including the latest ECDC rapid risk assessment is available on the <u>ECDC website</u>. Further information and guidance documents are also available on the <u>HPSC</u> and <u>WHO</u> websites.
- Further information on avian influenza is available on the ECDC website.

11. WHO recommendations on the composition of influenza virus vaccines

On February 22nd, 2018, the WHO vaccine strain selection committee recommended that trivalent vaccines for use in the 2018/2019 northern hemisphere influenza season contain the following:

- an A/Michigan/50/2015 (H1N1)pdm09-like virus
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). http://www.who.int/influenza/vaccines/virus/recommendations/2018 19 north/en/

On the 21st of February 2019, WHO recommended that the quadrivalent influenza vaccines for use in the 2019/2020 northern hemisphere influenza season include:

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A(H3N2) virus to be announced on 21 March 2019*;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage);
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).
- * In light of recent changes in the proportions of genetically and antigenically diverse A(H3N2) viruses, the recommendation for the A(H3N2) component has been postponed.

https://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/

Further information on influenza in Ireland is available at www.hpsc.ie

Acknowledgements

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