



## CLINICAL UPDATES

## Influenza



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The World Health Organisation estimates that approximately one billion people are infected and up to 500 000 people die from influenza each year.<sup>1</sup> The greatest burden of illness usually occurs among children, while the highest burden of severe disease (in terms of hospitalisation and death) occurs in those with underlying medical conditions, infants and young children, and elderly people.<sup>2</sup> Current circulating influenza strains in humans include influenza A(H1N1)pdm09, influenza A(H3N2), and both influenza B viruses (B/Victoria and B/Yamagata).<sup>3 4</sup> This article provides non-specialists with information on how to diagnose, manage, and prevent flu.

### What is influenza virus?

There are four types of influenza viruses: influenza A, B, C, and D,<sup>3-6</sup> but only influenza A and B viruses cause clinically important human disease and seasonal epidemics (table 1).<sup>1</sup> Influenza A viruses cause the most severe clinical disease and are the commonest cause of seasonal epidemics and pandemics in human populations.<sup>1</sup>

### What are the symptoms of influenza?

Influenza is characterised by sudden onset of fever, myalgia, headache, malaise, dry cough, sore throat, and nasal congestion (fig 1).<sup>13-15</sup> Gastrointestinal symptoms including nausea, vomiting and diarrhoea are also common.<sup>16</sup> The incubation period of influenza (time from infection to development of symptoms) is 1 to 4 days.<sup>17</sup> Viral shedding, when the virus is infectious, usually occurs from one day before the onset of symptoms, to 5-7 days after.<sup>18-20</sup>

Influenza can cause severe illness or death, particularly in high risk populations (box 1).<sup>23</sup> Mortality is higher among individuals with complicated influenza (illness necessitating hospital

admission, or an exacerbation of an underlying chronic illness) across all age groups, but is highest in infants aged 6 months or younger.<sup>2</sup>

### How do influenza epidemics and pandemics occur?

Minor changes that occur in virus proteins between influenza seasons (known as antigenic drift) result in annual epidemics, with winter peaks in temperate regions (November-April in the northern hemisphere, and May-October in the southern hemisphere, see fig 2).<sup>3</sup> In tropical and subtropical regions the seasonality of influenza is less well defined (fig 2).<sup>24 25</sup>

In contrast, pandemics (severe global epidemics) of influenza occur when a new influenza A subtype emerges abruptly because of a major shift in the proteins on the virus surface (antigenic shift), often because of combination with viruses circulating in animals.<sup>26</sup> As most people have no immunity to the new subtype, infection spreads quickly (table 2).

### How is influenza diagnosed?

Most influenza is diagnosed clinically in the community at times when the virus is known to be circulating. Patients admitted to hospital may have respiratory samples taken for testing by polymerase chain reaction (PCR), rapid antigen test, or immunofluorescence assay. With respiratory outbreaks in a closed setting (such as care homes, schools, hospitals) nasal swabs may be taken from the first few symptomatic individuals to identify the responsible organism.

**What you need to know**

- Influenza is an acute viral infection of the respiratory tract that spreads easily from person to person
- Influenza is usually self limiting in healthy individuals, with recovery in 3-7 days
- Elderly people, children under 6 months old, pregnant women, and people with chronic conditions or immunosuppression are at increased risk of complications
- Offer influenza vaccination to people at risk of complications and increased influenza exposure, as well as to young children, who are efficient infection spreaders
- People in high risk groups may benefit from antiviral therapy, hospitalisation, or intensive care

**Box 1: Who should be prescribed antiviral treatment for influenza?\****Individuals at risk of influenza related complications*

- Adults >65 years old
- Individuals with underlying chronic health conditions (chronic heart, lung, kidney, liver, neurological, and metabolic diseases, such as diabetes)
- Individuals with reduced immunity (such as after chemotherapy, asplenia, prolonged steroid treatment, splenic dysfunction, or HIV infection)
- Pregnant women, including up to two weeks post-partum
- Any other individual whom the clinician feels is at increased risk of developing complications from influenza
- Morbidly obese individuals (body mass index >40)

*Individuals admitted to hospital with suspected or confirmed influenza*

\*Based on guidance from National Institute for Health and Care Excellence (NICE)<sup>21,22</sup>

**What treatments are available for influenza?**

Influenza is usually self limiting in healthy individuals. Treatment of uncomplicated disease in healthy individuals is supportive and includes antipyretics, adequate fluid intake, rest, and staying off work or school until 24 hours after resolution of fever to limit spread to others.<sup>21</sup>

Most randomised trials of antiviral drugs have been conducted among otherwise healthy individuals and have shown modest reductions in symptom duration (0.7 days).<sup>27</sup> Fewer studies have been conducted among individuals at risk of complicated influenza. Data from observational studies and trials suggests that antiviral treatment may reduce adverse outcomes.<sup>28-30</sup> For example, the meta-analysis from 2015 reported fewer lower respiratory tract complications requiring antibiotics after oseltamivir treatment compared with placebo (risk difference -3.8%) and fewer hospital admissions (risk difference -1.1%).<sup>30</sup> NICE,<sup>21</sup> Public Health England,<sup>12</sup> UK Chief Medical Officers,<sup>31</sup> and the WHO<sup>32</sup> recommend treatment of suspected and confirmed influenza for individuals at risk of complicated influenza (box 1). General practitioners considering prescription of antivirals should discuss with patients likely benefits, as well as possible harms including nausea (number treated to cause nausea in one patient=28)<sup>27</sup> and vomiting (number treated to cause vomiting in one patient=22).<sup>27</sup>

Individuals with complicated influenza may be helped by antiviral treatment.<sup>21,22</sup> Treatment is most effective if started within 48 hours of symptom onset, and it should not be delayed while awaiting results of investigations.<sup>12,28</sup> Neuraminidase inhibitors oseltamivir and zanamivir inhibit viral release from infected cells and reduce the rate of viral replication. Meta-analysis of individual participant data found that, compared with late treatment, early treatment (within 48 hours of symptom onset) of hospitalised individuals with complicated influenza reduced the odds of mortality by 52%.<sup>28</sup> Some individuals may require antibiotic therapy to treat secondary bacterial infections.

**How can influenza be prevented?****Vaccination**

Vaccination is the most effective means of preventing influenza and its complications. Immunity developed in one influenza season may not provide protection in future years mainly because of changes in circulating strains, antigenic drift, and waning immunity. Influenza vaccines are updated annually to include the viral strains that are predicted to circulate in winter.<sup>3,4</sup>

Box 2 lists the UK recommendations for vaccination.<sup>23</sup> Vaccination schedules may vary internationally, and so it is important to check local policies. In healthy adults, trivalent inactivated vaccines have an overall vaccine efficacy of 60%.<sup>33,34</sup> Newer quadrivalent vaccines are being increasingly adopted due to the broader protection provided by the inclusion of an additional influenza B virus.<sup>35-38</sup>

Since 2013, the UK influenza vaccination programme has been extended to children aged 2-4 years, with planned phased introduction to children of school ages,<sup>23</sup> as it reduces morbidity by directly protecting children and provides indirect protection to vulnerable groups (such as grandparents) by reducing transmission in the community.<sup>39,40</sup> Attenuated live nasal spray formulation is recommended in children aged 2-<17 years based on its superior efficacy and greater immunity against mismatched strains compared with inactivated vaccines.<sup>41-43</sup>

Studies have found that inactivated influenza vaccines cannot cause influenza disease and are safe in pregnancy.<sup>44-47</sup>

Common side effects of vaccination include local injection site reactions and cold-like symptoms. Fever, malaise, and myalgia are less common.<sup>33</sup> Contraindications include confirmed severe allergic reaction (anaphylaxis) to a previous influenza vaccine or to any component of the vaccine.<sup>23</sup> Live attenuated influenza vaccine (LAIV) should not be given to children or adolescents with severe immunodeficiency or to those taking salicylate treatments because of the risk of Reye's syndrome.<sup>23</sup> LAIV is also not recommended for pregnant women or adults with immunosuppression.<sup>23</sup>

**Box 2: Who is offered influenza vaccination in the UK?<sup>23</sup>***People at risk of influenza related complications\**

- Adults over 65 years old
- Individuals with underlying chronic health conditions (for example, chronic heart, lung, kidney, liver, neurological, and metabolic diseases, such as diabetes)
- Individuals with reduced immunity (such as after chemotherapy, asplenia or splenic dysfunction, or HIV infection)
- Pregnant women
- Morbidly obese individuals (body mass index >40)

*People at risk of influenza exposure or transmitting influenza to vulnerable groups*

- Health and social care workers
- Individuals who live with or care for vulnerable people

*People living in settings where rapid spread is likely after introduction of infection, potentially resulting in high morbidity and mortality*

- Individuals living in long-stay care facilities

*Efficient influenza spreaders*

- Children aged 2-<17 years

\*Children <6 months old are not eligible to receive influenza vaccines and should be protected against influenza through vaccination of their mother during pregnancy.

**Antiviral chemoprophylaxis**

Influenza may be prevented or rendered less severe by post-exposure prophylaxis (PEP) with antivirals (oseltamivir and zanamivir).<sup>27-48</sup> NICE<sup>21</sup> and Public Health England<sup>12</sup> recommend that, when influenza is circulating, antivirals are offered to those who are:

- In at-risk groups (box 2) *and*
- Who have had close contact with people with confirmed or suspected influenza (that is, living in the same household or residential setting) *and*
- Able to start prophylaxis within 48 hours (oseltamivir) or 36 hours (zanamivir) of contact *and*
- Have not received vaccination in the current influenza season, or who have been vaccinated <14 days since contact or where there is significant mismatch between vaccine and circulating strains, or during an outbreak in a closed setting regardless of vaccination history.

**Infection control and isolation**

Although published evidence for effectiveness is limited, hand and cough hygiene are likely to be important interventions to reduce influenza spread in the community, as well as in closed settings (table 3).<sup>49</sup>

During an outbreak, consider isolation of residents of closed settings for the duration of the infectious period (five days after symptom onset) to limit spread to others. Cohorting of patients (that is, in separate hospital bays or on separate floors of a residential home) may be necessary. Residential homes may need to be closed to new admissions until the outbreak is controlled. Care must be taken when discharging a patient from a ward with a known influenza outbreak to a care home, or vice versa.

**New developments in prevention and treatment of influenza**

Vaccine candidates have recently been developed that can elicit antibodies against multiple influenza strains, and thus could overcome the need for annual influenza vaccines.<sup>55-57</sup> Several antiviral drugs are currently in development for influenza

treatment, including favipiravir,<sup>58</sup> nitazoxanide,<sup>59-60</sup> and arbidol.<sup>61-62</sup>

Contributors: SG and PM conceived of the review. SG is the guarantor of the manuscript. SG, PM, and AH undertook the literature review, and were supported by Dr Bethan Roberts, foundation year 2 trainee in health protection, Cheshire and Merseyside Health Protection Team, Public Health England North West. SG, PM, and AH contributed to writing drafts of the manuscript. PM designed and wrote code for the interactive application. All authors have seen and approved the final manuscript version.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Provenance and peer review: Not commissioned; externally peer reviewed.

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### Sources and selection criteria

We searched PubMed and the Cochrane Library databases (search terms "influenza," "flu," "influenza-like illness"). We obtained information on the epidemiology of influenza from annual reports produced by authoritative bodies and organisations such as Public Health England (PHE), Centers for Communicable Disease Prevention and Control (CDC), and the World Health Organization (WHO). We reviewed up-to-date influenza guidelines and reviews, including those published by PHE, Cochrane Reviews, and the National Institute for Health and Care Excellence (NICE).

### Education into practice

- What steps have you taken to improve the uptake of influenza vaccination among staff and eligible patients under your care?
- Have you reviewed your organisation's infection control policy for responding to an outbreak of influenza-like illness?
- Have you reviewed antivirals prescribed (treatment or prophylaxis) for eligible patients with influenza and their close contacts?

### Further educational resources

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### How patients were involved in the production of this article

No patients were involved in the production of this article

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## Tables

Table 1 | Influenza viruses

Influenza type	Classification	Reservoir	At risk groups
A	<ul style="list-style-type: none"> <li>Classified into subtypes on the basis of haemagglutinin (H) and neuraminidase (N) antigens on the surface of the viral envelope</li> <li>To date, 18 haemagglutinin subtypes and 11 neuraminidase subtypes have been identified</li> <li>Only three haemagglutinin types (H1, H2, and H3) are recognised to cause epidemic disease in humans</li> <li>Nomenclature includes the virus type and subtype, natural host species, geographical origin, year of isolation, and strain number (such as H1N1/A/duck/Alberta/35/76)<sup>7</sup></li> </ul>	The primary reservoir is aquatic birds, but viruses also circulate among many other species, such as pigs, horses, and sea mammals <sup>8</sup>	Infects people of all ages, but disproportionately causes severe disease in older adults and individuals with underlying chronic health problems
B	Divided into lineages on the basis of the haemagglutinin glycoprotein	Mainly infects humans	Children are affected by influenza B infection at a disproportionately higher rate among the general population <sup>9 10</sup>
C	Unlike influenza A or B, which have two glycoproteins (HA and NA), influenza C has only one glycoprotein (HEF)	Mainly infects humans	Affects individuals of all ages, but tends to cause mild illness <sup>11</sup>
D	Little known about it, but is thought to be related to influenza C viruses	Mainly infects pigs and cattle	Not known to cause human disease <sup>5</sup>

Table 2| Antigenic drift versus antigenic shift: implications for epidemics and pandemics

Antigenic drift	Antigenic shift
Accumulation of mutations in genes that code for antibody binding sites on viruses leading to emergence of new strains	A sudden major change in the virus antigenicity
Only one virus strain (accumulation of point mutations)	From one or more virus strains (from genome reassortment)
Occurs frequently	Occurs occasionally
Usually responsible for seasonal influenza epidemics and affects effectiveness of influenza vaccine	Gives rise to pandemics, which occur irregularly and unpredictably due to a lack of immunity to the new strain in the human population
Occurs in influenza virus A, B, and C	Only occurs in influenza virus A

Table 3| Responding to influenza cases and clusters or outbreaks by setting

Interventions	Community setting		Care home setting	Acute clinical setting
	At-risk patients	Low risk patients		
Isolation of patients <sup>49 50</sup>	Avoid contact with other at-risk people and exclude from work, school, or childcare until asymptomatic	Avoid contact with at-risk people and exclude from work, school, or childcare until asymptomatic	Yes*	Yes
Use of PPE including surgical masks <sup>51 52</sup>	Not recommended	Not recommended	Yes	Yes
Implementation of rigorous infection control procedures (hand hygiene; cough etiquette; environmental cleaning and waste disposal) <sup>49 51 53</sup>	Provide advice on hand hygiene and correct cough etiquette	Provide advice on hand hygiene and correct cough etiquette	Yes	Yes
Symptomatic management <sup>21</sup>	Yes	Yes	Yes	Yes
Antiviral therapy for patients with influenza <sup>12 54</sup>	Recommended	Not recommended	Recommended†	Recommended†
Regular review to assess for clinical deterioration <sup>12</sup>	Yes‡	Not recommended	Yes‡	Yes

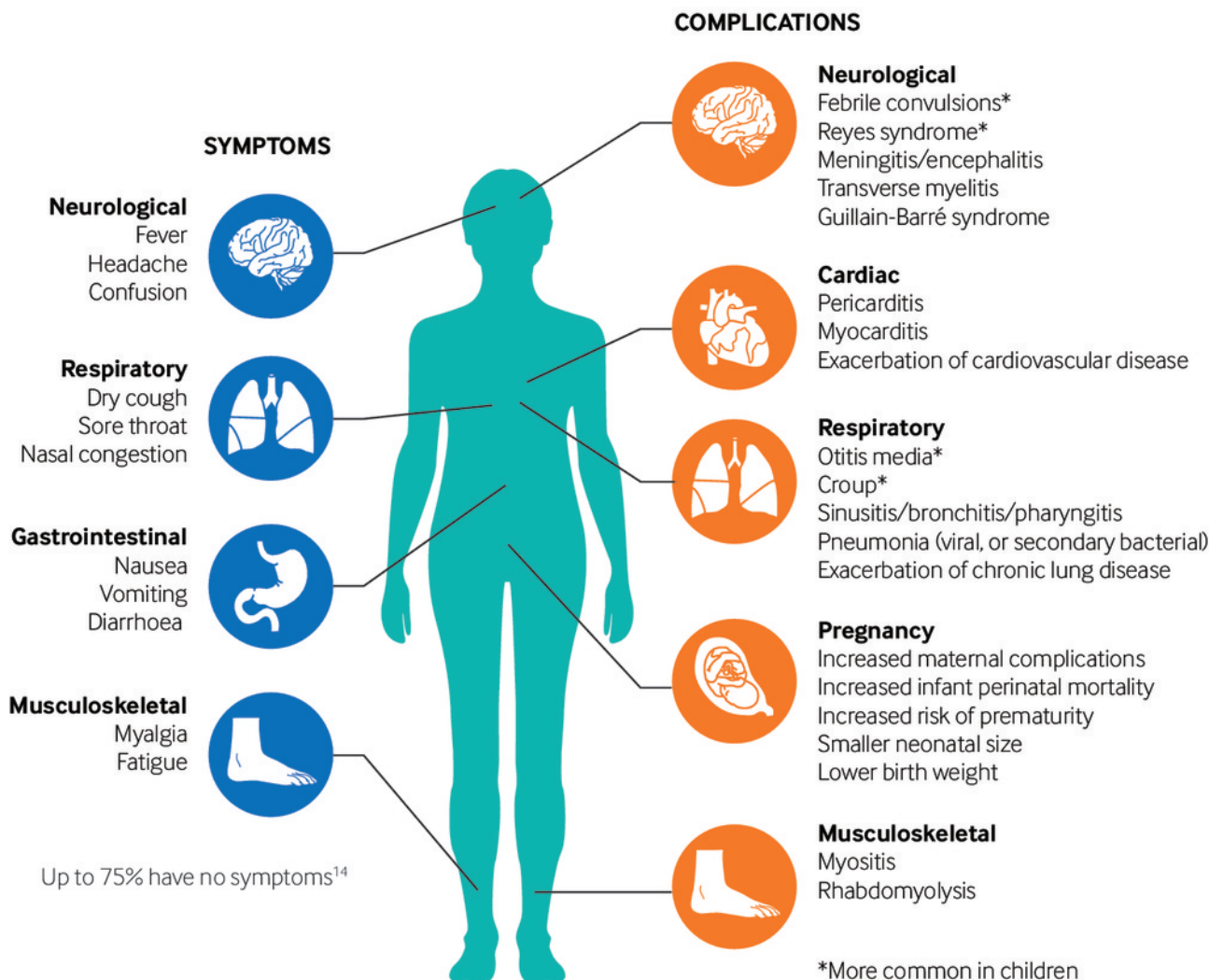
\*If not possible or practical, consider cohorting of patients as soon as possible.

†Consider post-exposure prophylaxis for other at-risk patients and residents in hospitals and care home settings.

‡Have low threshold for referring to secondary care.

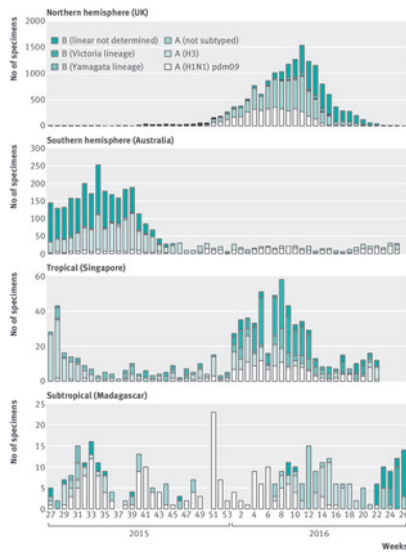


# Figures



**Fig 1** Symptoms and complications of influenza. Complicated influenza is defined as an infection that requires hospital admission<sup>12</sup>

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**Fig 2** Circulating influenza viruses reported to WHO through global laboratory surveillance systems for selected countries: 2015-16. Data from WHO FluNet Interactive [https://pmapc.shinyapps.io/Influenza\\_isolates/](https://pmapc.shinyapps.io/Influenza_isolates/)