



Public Health
England

Seasonal influenza

Guidance for adult critical care units

November 2019

The Faculty of
Intensive Care Medicine

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society**
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Public Health England

Wellington House

133-155 Waterloo Road

London SE1 8UG

Tel: 020 7654 8000

www.gov.uk/phe

Twitter: [@PHE_uk](https://twitter.com/PHE_uk)

Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Acute Respiratory Infections Unit, TARGET, National Infection Service

Contact: jake.dunning@phe.gov.uk



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Contributors

Dr Jake Dunning, Consultant in Infectious Diseases, TARGET, National Infection Service, PHE; Honorary Consultant in Infectious Diseases, Royal Free London NHS Foundation Trust

Dr Gavin Dabrera, Consultant in Public Health, TARGET, National Infection Service, PHE

Dr Richard Pebody, Consultant in Public Health, Immunisations and Countermeasures, National Infection Service, PHE

Dr Meera Chand, Consultant in Microbiology, TARGET, National Infection Service, PHE; and Consultant in Microbiology, Guy's and St Thomas' NHS Foundation Trust

Dr Matthew Donati, Consultant Medical Virologist/Head of Virology, National Infection Service, PHE Bristol Public Health Laboratory

Dr Elizabeth Johnson, Head, Mycology Reference Laboratory, National Infection Service, PHE

Prof Stephen Brett, Consultant in Intensive Care Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust; ICS representative

Dr Bob Winter, formerly National Clinical Director for Emergency Preparedness and Critical Care, NHS England

Surgeon Commander Stuart Dickson RN, Consultant in Acute Medicine, Infectious Diseases & Intensive Care Medicine, University Hospitals Plymouth NHS Trust; FICM Representative

Dr Anna Batchelor, Consultant in Anaesthetics and Intensive Care Medicine, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust; RCoA Representative

Prof Peter Wilson, Consultant Microbiologist, Department of Microbiology & Virology, University College Hospital, University College London Hospitals NHS Foundation Trust

Charlotte Flynn, Public Health Registrar, National Infection Service, PHE

Contents

About Public Health England	2
Contributors	2
Foreword	6
Introduction	7
Seasonal influenza activity	7
Morbidity and mortality	7
Complicated illness	8
Risk groups for complicated illness	8
Importance of the prompt recognition of influenza	8
Diagnosis of influenza	10
Clinical suspicion of influenza virus infection	10
Diagnostic sampling	11
Laboratory testing for influenza virus	12
Role of repeat sampling in establishing the diagnosis	13
Role of repeat or “follow-up” sampling in patients with confirmed influenza	13
Antiviral resistance testing	14
Antiviral treatment	15
Evidence supporting the use of antivirals	15
Principles of antiviral treatment	16
Antiviral treatment considerations in Critical Care	16
Duration of antiviral treatment	16
Routes of administration and dosing considerations	17
Use of intravenous zanamivir aqueous solution (intravenous zanamivir)	18
Antiviral resistance	19
Other treatment considerations	21
Bacterial complications	21
Fungal complications	22
Respiratory virus complications	23
Adjunctive therapies including corticosteroids	23
Infection prevention and control	25
General principles and requirements	25
Patient placement	25
Cleaning considerations	26
Personal protective equipment (PPE)	26
Devices and equipment	27
Duration of IPC precautions	27
Staff considerations	28
Deceased patients	28
Appendix	29
Putting on and removing personal protective equipment	29

Useful resources	31
References	32

Foreword

Seasonal influenza virus infections are an important cause of severe acute respiratory illness. While most influenza virus infections are self-limiting and do not result in hospitalisation, complications and deaths can be seen in any age group, including patients with no underlying risk factors for severe illness. Admissions to critical care units are to be expected, particularly in winter months, and critical care teams should be prepared to care for patients with complicated influenza.

The guidance has been developed by Public Health England (PHE) in association with the Intensive Care Society (ICS), the Faculty of Intensive Care Medicine (FICM), the Royal College of Anaesthetists (RCOA) and NHS England and NHS Improvement. The guidance provides advice and recommendations for healthcare professionals who provide critical care to adults with seasonal influenza. Areas covered include sampling and laboratory diagnosis, antiviral therapy, bacterial complications, and infection prevention and control measures.

Recommendations consider the available evidence and expert opinions. Links to related PHE guidance are provided within the document. The guidance will be reviewed periodically and updated when necessary; users are advised to check the PHE website to ensure that current guidance is being followed.

The guidance should be read in conjunction with [PHE's influenza antiviral guidance](#), and [PHE guidance on infection prevention and control measures for acute respiratory infections](#).

Separate guidance is available for [avian influenza](#). In the event of a [novel influenza pandemic](#), specific guidance will be made available by PHE and the Department of Health.

Key updates in version 2.0 are:

- asplenia/splenic dysfunction and learning disabilities have been added to the list of risk groups for complicated influenza illness
- expanded guidance on fungal co-infections, particularly invasive aspergillosis
- updated information on accessing intravenous zanamivir
- the recommended duration of oseltamivir treatment in immunosuppressed patients has been revised, in line with updated manufacturer's information

Introduction

Basic virology and transmission of influenza viruses

Seasonal influenza is caused by established, circulating influenza viruses, currently A(H3N2), A(H1N1)pdm09 and influenza B viruses. These RNA viruses evolve over time, facilitating immune escape and recurrent infections in both individuals and populations. Influenza virus is present in the respiratory secretions of infected persons; human-to human transmission occurs primarily by direct and indirect contact with large particle respiratory droplets (for example following coughing and sneezing), and possibly by short-range aerosolisation of small particle droplets.

Seasonal influenza activity

The relative dominance and impact of each seasonal influenza virus varies from season to season. Additionally, separate peaks of influenza virus activity, corresponding to virus type, can be seen within the same season. Following the 2009-10 influenza pandemic, A(H1N1)pdm09 (“swine flu”) became an established seasonal influenza virus, alongside A(H3N2) and influenza B viruses. The annual influenza season in the UK typically runs from mid- to late-autumn through to late spring; most activity occurs in winter, but sporadic cases can be seen throughout the year, including infections imported from other countries. PHE issues [national influenza surveillance reports](#) that describe the relative frequencies of the different circulating viruses, including weekly reports during each influenza season.

Morbidity and mortality

All seasonal influenza viruses can cause complicated illness. Morbidity and mortality rates vary between influenza seasons, and by the infecting influenza virus. Morbidity and mortality rates may also be higher in a year when the vaccine is not well matched to the circulating virus. In England, 2,924 confirmed influenza admissions to ICU/HDU and 273 deaths in ICU were reported by 140 NHS acute trusts during the 2018-2019 season; 39.8% of ICU/HDU cases were aged 45 to 64 years and 19.8% of cases were aged 15 to 44 years (1). Rates of ICU/HDU admission for confirmed influenza A(H3N2) infection tend to be highest in those aged 75 years and over; by contrast, for influenza A(H1N1) infection, ICU/HDU admissions tend to be highest in 45-64 year-olds. Influenza B virus infections also cause complicated influenza; in the 2017-2018 season, influenza B infections accounted for 48% of ICU/HDU influenza admissions in the UK, with all age groups affected to a similar degree.

Complicated illness

Most influenza virus infections result in a self-limiting, uncomplicated, acute illness of short duration (typically 2-5 days). Subclinical or asymptomatic infection is also recognised. Most complications affect the respiratory tract (for example viral pneumonia), but complicated illness can involve other systems (for example encephalopathy, myositis). Primary influenza pneumonia can be particularly challenging to treat and acute respiratory distress syndrome (ARDS) is a common complication in patients admitted to ICUs. Secondary bacterial complications, including pneumonia and septicaemia, may occur and can be difficult to distinguish from manifestations of primary viral illness. Atypical presentations may also be seen for example neurological manifestations without significant respiratory signs or symptoms, or absence of fever and minimal symptoms followed by rapid deterioration in immunocompromised patients.

Risk groups for complicated illness

Complicated seasonal influenza can occur in previously healthy individuals, especially when infection is caused by A(H1N1)pdm09 virus infection (2, 3). Additionally, there are well-recognised risk groups for complicated seasonal influenza (4) which are:

- chronic neurological disease (for example neuromuscular, neurocognitive and seizure disorders) and learning disabilities
- chronic hepatic disease (for example cirrhosis)
- chronic kidney disease (for example CKD requiring dialysis or transplantation)
- chronic pulmonary disease (for example COPD, asthma, cystic fibrosis)
- chronic cardiovascular disease (for example congestive cardiac failure; atherosclerotic disease)
- diabetes mellitus
- severe immunosuppression (see [antiviral guidance](#) for examples)
- asplenia/splenic dysfunction
- age over 65 years
- pregnancy (including up to 2 weeks post-partum)
- morbid obesity (BMI ≥ 40)

Importance of the prompt recognition of influenza

It is important to consider influenza in the differential diagnosis of a patient presenting with compatible symptoms, and to confirm influenza virus infection rapidly by requesting appropriate laboratory investigations. Equally important is the rapid commencement of empirical antiviral therapy before a virological diagnosis has been obtained, since delays in commencing antivirals have been shown to be associated with increased mortality (5, 6).

Patients with severe, complicated influenza often require admission to critical care units at the time of hospitalisation or soon after admission (3, 7). There may be reduced awareness of influenza at the beginning of a season and also in those assessing individuals who have travelled recently or who have unexplained severe acute respiratory infections out-of-season. Influenza may be missed as a potential diagnosis in immunocompromised individuals and in those with atypical or extra-pulmonary presentations. In addition to consequences for the infected individual, failure to consider influenza may increase the risk of nosocomial transmission and outbreaks within critical care units if appropriate infection prevention and control measures have not been implemented. Secondary or concurrent bacterial infection can result in increased morbidity or death (8, 9), especially if antibiotic treatment is delayed.

Diagnosis of influenza

Clinical suspicion of influenza virus infection

Influenza virus infection should be considered in the differential diagnosis for the following presentations:

- community acquired pneumonia
- hospital acquired pneumonia
- severe acute respiratory infection
- exacerbations of chronic lung disease for example asthma, COPD
- generalised sepsis
- encephalopathy, encephalitis, transverse myelitis, aseptic meningitis, and Guillain-Barré syndrome
- myocarditis
- rhabdomyolysis

Influenza virus infection is more likely to be a causative agent during winter months, but should be considered at other times of the year if there are known epidemiological risks, including travel-related exposure, history of exposure to a confirmed case, or if the case is part of a known outbreak.

Influenza virus and other viral and bacterial infections may occur concurrently and it is difficult to differentiate between viral, bacterial and mixed infections using clinical and radiological assessments (2, 3, 10). Although bacterial infections may follow influenza virus infection, detection of a bacterial infection (for example pneumococcal pneumonia) does not exclude the possibility of concurrent influenza.

Seasonal influenza vaccination is an important public health measure, but vaccination does not guarantee protection against influenza virus infection. An individual's vaccination history should not influence the differential diagnosis or the decision to test for influenza and commence empirical antiviral therapy.

Immunocompromised patients can present with initial symptoms that are of modest severity and frequency, which may delay recognition of influenza. Atypical presentations for example absence of fever, myalgia, or cough, appear to be common in transplant recipients (11, 12).

Diagnostic sampling

Appropriate diagnostic samples (see below) should be obtained as soon influenza is suspected.

If viral swabs are used, ensure that the correct swab type is selected; local laboratories can advise on appropriate sampling equipment.

Do not use standard bacterial (Amies) swabs for respiratory virus sampling.

Units should ensure that appropriate sampling equipment is readily available.

Sampling should be performed by staff trained in the procedure and infection prevention and control recommendations should be followed when obtaining samples.

Recommended sample types for a **non-intubated** patient are:

- upper respiratory tract (URT) secretions (for example viral nasopharyngeal swab; combined viral nose and throat swab; viral nasal swab alone if oropharynx is inaccessible; nasopharyngeal aspirate); AND
- lower respiratory tract (LRT) secretions if there is evidence of LRT involvement (for example sputum if productive cough; bronchoalveolar lavage (BAL) fluid if bronchoscopy is scheduled)

The recommended sample types for an **intubated** patient are:

- URT secretions, as above; AND
- LRT secretions (options: endotracheal tube aspirate; non-directed bronchial lavage (NBL) fluid; BAL fluid if bronchoscopy is indicated)

LRT samples are important in critical care patients with clinical and/or radiological evidence of lower respiratory tract disease; this is because URT samples can become negative over time while LRT samples remain positive (13, 14).

A negative URT specimen alone in a patient with evidence of lower respiratory tract involvement does not exclude influenza virus infection.

Patients with suspected CNS complications of influenza who require diagnostic lumbar puncture may have CSF submitted for detection of influenza virus in addition to other pathogens.

In addition to obtaining samples to detect influenza virus, separate samples should be submitted to the microbiology laboratory to identify bacterial infections and fungal infections. The types of microbiology samples collected (for example respiratory tract

secretions, BAL fluid, blood for culture, urine for pneumococcal antigen testing) should be determined by the clinical presentation and local testing protocols.

Laboratory testing for influenza virus

PCR-based detection is the most widely available and preferred method for detecting influenza virus, because of its high sensitivity and specificity.

Clinical diagnostic laboratories that offer PCR typically detect and report “influenza A” and “influenza B”; in addition, some laboratories may also be able to subtype influenza A viruses, that is, they identify specifically A(H1N1)pdm09 and/or A(H3N2).

Rapid local subtyping of seasonal influenza A viruses is unlikely to influence clinical decision-making in most cases but may be useful in seasons where the proportions of A(H1N1)pdm09 and A(H3N2) are similar nationally, to guide more accurately the choice of antiviral in severely immunosuppressed individuals.

If a laboratory offers detection of influenza A without subtyping, decisions about offering zanamivir as first line treatment for specific groups (see antiviral section, below) should be informed by influenza virus surveillance data in [PHE’s national influenza reports](#).

Some clinical diagnostic laboratories may also offer PCR detection of the most common influenza virus mutation associated with oseltamivir resistance in A(H1N1)pdm09 virus infection; a more extensive antiviral resistance testing service is offered by PHE (see antiviral resistance testing, below).

Rapid antigen tests can provide results in 15 minutes or less and can be performed at the bedside; however, they tend to have unacceptably low sensitivity for detecting influenza virus.

Second generation point of care (POC) tests for respiratory viruses, which use more sensitive nucleic acid amplification technology, have been adopted by some NHS trusts and used in different clinical areas; for hospitals considering implementing POC tests, [further information](#) is available from PHE.

Virus isolation (virus culture) is not offered by most clinical diagnostic laboratories; it is offered by PHE as a specialist reference test but has a limited role in informing routine clinical care, due to the time it takes to isolate virus.

Serological assays that detect specific anti-influenza antibodies are not useful in diagnosing acute influenza and are not offered routinely by clinical diagnostic laboratories (15).

Antiviral treatment should not be withheld pending laboratory confirmation of infection; an indication to test for influenza virus infection is also an indication to commence empirical treatment.

Influenza virus RNA is rarely detected in CSF by PCR testing; however, a negative CSF result may not exclude influenza as the cause of acute neurological signs and symptoms.

Role of repeat sampling in establishing the diagnosis

If initial diagnostic tests are negative, but clinical suspicion of influenza remains high, diagnostic sampling should be repeated; seek advice from local Virology/Microbiology/ID specialists if necessary and ensure that appropriate sites have been sampled (see diagnostic sampling, above).

Role of repeat or “follow-up” sampling in patients with confirmed influenza

It can be challenging to assess clinical improvement in specific patient groups, such as those who are immunosuppressed or unconscious/ventilated, because they may have atypical or minimal clinical signs and symptoms, or be unable to describe symptoms, or have multiple problems that could contribute to their clinical status.

There are no reliable data to support routine repeat sampling for influenza virus RNA detection, to assess response to treatment or to inform step-down of related infection prevention and control measures, but results from repeat sampling may be useful when considered alongside findings from clinical assessment [expert recommendation].

For patients with confirmed influenza who are receiving antivirals, repeat or “follow-up” sampling for detection of viral RNA by polymerase chain reaction (PCR) can be considered if the patient deteriorates or has a non-resolving illness despite at least 5 days of antivirals and may require an extended duration of antiviral treatment; antiviral resistance testing should be requested if the repeat sample is positive.

Comparing estimated viral loads (for example by comparing influenza virus PCR Ct values) in the initial and repeat sample(s) may be helpful in determining the antiviral effect [expert recommendation].

For patients who develop influenza illness whilst receiving prophylactic-dose antivirals, sampling should be performed at the onset of illness, or in the context of non-resolution of influenza illness or clinical deterioration [expert recommendation].

For patients with lower respiratory tract involvement, non-detection of influenza virus in a repeat upper respiratory tract sample following antiviral treatment does not exclude

the possibility of ongoing influenza virus replication in the lower respiratory tract; lower respiratory tract samples should be tested in addition to upper respiratory tract specimens, where possible (13, 14).

Positive results from repeat sampling should also be considered in relation to infection prevention and control measures (see relevant section, below).

If BAL or NBL is repeated, it is recommended that samples are submitted on each occasion for microbiological analyses (for example bacterial culture and sensitivity; fungal culture), in addition to virological analyses.

Antiviral resistance testing

Tests that detect the H275Y mutation, which is the mutation most commonly associated with oseltamivir resistance in A(H1N1)pdm09 infection, may be available locally; consult Microbiology/Virology for availability.

Tests for H275Y and other resistance mutations, including those that affect other types/subtypes of influenza virus, and also mutations that confer resistance to zanamivir, are performed by the [National Reference Laboratory at PHE](#); requests should be discussed with local Microbiology/Virology laboratories.

When resistance to oseltamivir is suspected and ongoing antiviral therapy is required, switch to zanamivir before the results of testing are known; in addition, submit further samples for influenza virus detection locally and, if positive, ensure the samples are sent (along with any earlier positive samples) for resistance testing.

Antiviral treatment

Evidence supporting the use of antivirals

The majority of randomised controlled trials of antivirals for influenza include otherwise healthy patients in the outpatient setting; therefore, findings from these studies, or from systematic reviews (16, 17) of these studies, are not directly translatable to the critical care setting.

Data from randomised controlled trials of antivirals in patients with complicated influenza are lacking, but there is an abundance of data from observational studies examining antiviral efficacy in complicated influenza requiring hospitalisation, including critical illness.

A meta-analysis of data from 78 observational studies involving 29,000 patients who were hospitalised with A(H1N1)pdm09 infection during the 2009–10 pandemic (5) found:

- among patients aged >16 years, antiviral treatment (using neuraminidase inhibitors) was associated with a 25% reduction in the likelihood of death compared with no antiviral treatment
- early antiviral treatment (ie within 48 hours of development of illness) halved the risk of death compared with no antiviral treatment
- the clinical benefit is greatest when treatment is commenced within 48h of illness onset, supporting recommendations not to delay treatment in hospitalised patients
- in adults requiring critical care, even delayed treatment was associated with a reduced likelihood of mortality, compared with no treatment

For hospitalised influenza patients, neuraminidase inhibitor treatment commenced at admission is associated with a reduced length of stay, compared with later or no initiation of antiviral treatment (18).

Based on available evidence, the use of neuraminidase inhibitors in treating adult patients with complicated influenza is recommended by PHE (19), the World Health Organization (WHO) (20), the European Centre for Disease Prevention and Control (ECDC) (21), US Centers for Disease Control and Prevention (CDC) (22), and is supported by a review conducted by the Academy of Medical Sciences (23).

Principles of antiviral treatment

The **PHE antiviral guidelines** are applicable to treating patients in critical care settings and should be followed.

Clinical suspicion of influenza, or a decision to test for influenza, is an indication to commence empirical antiviral in hospitalised patients at risk of complicated illness.

Statutory prescribing restrictions for antivirals do not apply in secondary care; if hospital clinicians believe that a person's symptoms are indicative that the person has influenza and would suffer complications if not treated, they are able to prescribe antiviral medicines at any time of the year.

Benefits of antiviral treatment decrease when treatment is delayed (5, 24), but illness that is >48h duration is not a contraindication to prescribing antivirals in hospitalised patients (an off-label use), including those admitted to critical care units.

Oseltamivir (Tamiflu™) and zanamivir powder for inhalation (Relenza™) are neuraminidase inhibitors licensed in the UK and recommended for the treatment of influenza; zanamivir aqueous solution is also available (see below).

Combination therapy with oseltamivir and zanamivir is not recommended, based on available study data (25, 26).

For severely immunosuppressed patients where the infecting influenza type/subtype is not known, and for the prescribing of empirical antivirals, the choice of first line agent is guided by **the dominant circulating influenza virus** (see **PHE antiviral guidelines**).

Antiviral treatment considerations in critical care

Duration of antiviral treatment

The optimal duration of antiviral treatment is unknown for patients with complicated influenza; duration of treatment should be considered on a case-by-case basis.

Persistent detection of influenza virus RNA and 'rebound' of previously undetectable viral RNA have been described in patients with severe influenza who received 5 or 7-day courses of oseltamivir (27).

Extending the duration of treatment to at least 10 days may be considered in patients requiring critical care for influenza [expert opinion].

In 2019, the manufacturer of oseltamivir updated its product information and now recommends a longer treatment course, 75mg PO twice daily for 10 days, for immunosuppressed patients.

However, prolonged antiviral treatment can be associated with the development of antiviral resistance to one or more antivirals, particularly in immunosuppressed patients; antiviral resistance monitoring is recommended when prolonged treatment is considered necessary.

Routes of administration and dosing considerations

Critically ill patients typically require a systemically active antiviral; inhaled zanamivir is absorbed minimally from the respiratory tract and therefore is not considered to be systemically active.

Standard treatment-dose oseltamivir administered orally or via a nasogastric tube appears to adequately absorbed overall, based on levels detected in blood in a critical care cohort (28); an increase in dosage is not recommended in patients with severe illness caused by influenza A virus infection, due to a lack of evidence that it is any more effective (28-31).

The impact of known gastrointestinal dysfunction (for example gastric stasis, malabsorption states, gastrointestinal haemorrhage) on the absorption of oseltamivir is unclear, based on available data, but it can be assumed that gastrointestinal dysfunction may reduce absorption (see section on zanamivir aqueous solution, below).

It is not known whether an increased dose of oseltamivir is superior to standard dose oseltamivir in the treatment of critically ill patients infected with influenza B virus.

Data on the effect of doubling the standard treatment-dose (double-dosing) of oseltamivir in influenza B infections are limited (31); however, based on experience of double-dosing in influenza A infections, the increased dose is unlikely to be harmful.

Renal dysfunction: there are specific dosing considerations for oseltamivir and intravenous zanamivir; see [PHE antiviral guidelines](#) for further details on oseltamivir and also refer to manufacturer's guidance for intravenous zanamivir (provided with the product).

Hepatic dysfunction: dose adjustment is not required for oseltamivir or inhaled zanamivir, but dose adjustment is required for intravenous zanamivir (refer to manufacturer's guidance).

Obesity: dose adjustment is not required for oseltamivir or inhaled zanamivir, but dose adjustment is required for intravenous zanamivir (refer to manufacturer's guidance).

Pregnancy: antivirals are recommended for pregnant women due to the adverse clinical outcomes that have been observed for influenza infection in this group, and recent studies suggest there is no evidence of harm in pregnant women treated with oseltamivir or zanamivir (32, 33); see [PHE antiviral guidelines](#) for further information.

Use of intravenous zanamivir aqueous solution (intravenous zanamivir)

In 2019 the manufacturer of zanamivir aqueous solution for intravenous administration (IV zanamivir) received marketing authorisation in Europe; as such, it is expected that IV zanamivir (Dectova®, GlaxoSmithKline plc) will be available to purchase towards the end of 2019.

Once IV zanamivir becomes available as a commercial product, the named-patient programme for the unlicensed product will be withdrawn; until that time, IV zanamivir should continue to be obtained from the manufacturer on a named patient basis (see appendix in [PHE antiviral guidelines](#) for further details on how to access zanamivir aqueous solution).

IV zanamivir administered at a dose of 600 mg was shown not to be superior to oral oseltamivir 75mg twice daily in a randomised controlled trial involving hospitalised patients >16 years of age with oseltamivir-sensitive influenza virus infection at recruitment; median times to clinical response were similar for oseltamivir and IV zanamivir and adverse events were similar across treatment groups (34).

Therefore, IV zanamivir administered intravenously has a role in treating patients with suspected or confirmed oseltamivir-resistant influenza virus infection, or who are at risk of developing of oseltamivir resistance (as described in [PHE antiviral guidance](#)), AND who require a systemically active antiviral; for example, patients with critical illness caused by influenza, particularly patients with multi-organ dysfunction.

IV zanamivir may also be considered in patients who require a systemically active antiviral and who are unable to tolerate or absorb oral oseltamivir.

Nebulisation of zanamivir aqueous solution is no longer recommended by PHE for any patient group, and the marketing authorisation of zanamivir aqueous solution in Europe is for IV administration only; if a patient requires zanamivir, but inhaled zanamivir via a Diskhaler is inappropriate (for example, the patient has critical illness and/or severe respiratory disease), IV zanamivir should be used.

Zanamivir powder for inhalation should NOT be nebulised by dissolving the capsules in water, since this practice has been linked to deaths in ICUs, believed to be due to blockage of ventilator tubes.

Antiviral resistance

Antiviral resistance is a potential explanation for clinical deterioration or failure to improve and should be considered alongside other potential explanations for example progressive inflammatory damage that may follow influenza virus infection, or worsening sepsis due to bacterial co-infections.

Antiviral resistance can lead to treatment failure (35).

Surveillance data suggest that the frequency of antiviral resistance is low in seasonal influenza viruses that have circulated in the UK since 2009, but antiviral resistance patterns can change over time (36, 37).

National antiviral resistance surveillance data are included in [PHE influenza reports](#).

Infections caused by antiviral resistant influenza viruses can occur in any patient, but the groups that are at increased risk of resistance and should be monitored appropriately are:

- severely immunosuppressed patients (see [PHE antiviral guidelines](#) for examples)
- patients who develop influenza illness whilst receiving, or shortly after receiving, antiviral prophylaxis
- influenza-positive contacts of known resistance cases
- patients who have changed antiviral therapy, particularly if there have been gaps between one course finishing and another course commencing
- patients who demonstrate clinical deterioration during antiviral therapy

Most antiviral resistance occurs in association with antiviral exposure (on-treatment resistance and prophylaxis-associated resistance), but an individual can be infected with a resistant virus following exposure.

Virus mutations conferring resistance to both oseltamivir and/or zanamivir can occur in influenza A(H1N1)pdm09, A(H3N2) and influenza B virus infections.

In influenza A(H1N1)pdm09 virus infections, mutations associated with oseltamivir resistance have been more common than mutations associated with zanamivir resistance.

If oseltamivir resistance is suspected and further treatment is required, then consider switching to zanamivir before the results of resistance testing are known.

If zanamivir resistance is suspected, do not switch to oseltamivir, as there is a significant likelihood that the virus will be resistant to oseltamivir as well; pending the results of urgent resistance testing, continue zanamivir and seek advice from local infection specialists.

Treatment interruption should be avoided (for example when awaiting results of follow-up testing), since it can be associated with the development of antiviral resistance.

Clinicians should consult [PHE antiviral guidelines](#), which are updated annually, for the latest advice on antiviral treatment in the context of suspected or confirmed resistance.

Other treatment considerations

Bacterial complications

Bacterial infections are recognised complications of influenza, regardless of the infecting influenza virus type/subtype.

Secondary and concurrent bacterial infections can be associated with an increased risk of ICU admission and increased mortality (8, 9).

The risk of bacterial infection may be influenced by a number of factors, including the influenza type/subtype, comorbidities, interventions received, and pre-existing colonisation by relevant bacterial species (38).

As an example, a Spanish study found that bacterial complications occurred in 17.5% of critical care patients infected with A(H1N1)pdm09 during the 2009-10 pandemic (39).

Bacterial complications may occur concurrently with influenza virus infections or may occur after influenza virus is no longer detectable.

It is difficult to differentiate between bacterial, viral and mixed lower respiratory tract infections based on clinical and radiological findings (3, 10, 40), and currently available microbiological tests fail to identify bacteria in a significant proportion of patients with community acquired pneumonia (41).

Streptococcus pneumoniae, *Staphylococcus aureus* and *Haemophilus influenzae* are common causes bacterial complications in patients with influenza, particularly lower respiratory tract infections (38).

Bacterial septicaemia and invasive bacterial infections (for example invasive group A *Streptococcus* infection (42); invasive *Neisseria meningitidis* infection (43, 44)) have been described in association with influenza virus infection, as have co-infections with antimicrobial-resistant bacteria such as methicillin resistant *Staphylococcus aureus* (3, 38).

The treatment of bacterial complications, suspected or confirmed, should be in accordance with local antibiotic prescribing guidelines for treating bacterial infections such as community-acquired pneumonia or hospital-acquired pneumonia.

Fungal complications

Invasive aspergillosis (IA) is increasingly recognised as a complication of influenza and several recent studies have identified an association between influenza and *Aspergillus* infection, in both immunocompetent and immunocompromised patients (45-47).

IA most commonly presents as pulmonary aspergillosis, but tracheobronchitis and disseminated disease affecting extra-pulmonary sites can also occur.

Invasive pulmonary aspergillosis was identified in 83 of 432 (19%) patients critically ill with influenza virus infection in Belgium and the Netherlands between 2009 and 2016; the incidence was 14% in immunocompetent patients, 32% in immunocompromised patients, and 5% in a control group of flu-negative severe community-acquired pneumonia patients (47).

In the same study, the diagnosis of IA occurred at a median of 3 days (IQR 0-7) after ICU admission; IA may occur at admission and throughout the ICU stay (47).

Delay in diagnosis and treatment leads to poor outcomes, so a high index of suspicion should be maintained for patients not responding as expected to routine interventions, especially patients with antibiotic-refractory fever, rising CRP and failure to respond to antiviral and antibiotic therapies.

There are no published, prospectively validated surveillance schedules/algorithms to assist clinicians in deciding how to monitor critically ill patients at risk of developing influenza associated IA.

It is suggested that respiratory specimens obtained by bronchoscopy should be sent for fungal microscopy and culture / PCR / galactomannan assays, in addition to bacteriological and virological testing; the same testing should be performed when there is new suspicion of IA or unexplained pneumonia or clinical deterioration and the patient requires repeat bronchoscopy.

If local availability of diagnostic tests is limited, samples should be referred to a specialist centre with prompt turn-around-times for mycological testing.

Galactomannan testing of BAL is the single most sensitive biomarker for pulmonary aspergillosis. Serum galactomannan testing is also indicated but is less sensitive and CSF may be positive in cases of cerebral progression. A negative galactomannan result does not exclude IA.

Beta-glucan testing of serum is a sensitive but non-specific test for invasive fungal infection. CSF samples should also be tested if cerebral progression is suspected.

Positive beta-glucan tests unrelated to fungal infection are more likely during the first few days on the ICU and in patients with sepsis or receiving blood products or immunoglobulin therapy.

High resolution CT imaging is unlikely to aid a specific diagnosis of fungal infection but may include the finding of multiple nodules and cavities or progressive patchy bilateral opacification.

Antifungal prescribing should be in accordance with local policies; if patients are receiving ECMO then specialist advice on dosing should be sought.

Commence empirical antifungal therapy whilst awaiting the results of relevant investigations if there is a strong clinical suspicion of invasive aspergillosis; review the need to continue antifungal treatment when results become available (seek specialist advice if necessary).

If an isolate is available, specific susceptibility testing is indicated, as azole resistance is being encountered more frequently even in azole-naïve patients (48); if fungal DNA is available there are molecular tests for the 2 most common resistance mutations in *Aspergillus fumigatus*.

There is currently no evidence to suggest that routine prophylaxis is indicated, and this could lead to the selection of more resistant strains.

In patients receiving immunosuppressants, the degree of immunosuppression should be reduced whenever possible in patients with IA; discuss with the relevant specialist.

Respiratory virus complications

Co-infections with respiratory viruses other than influenza can occur (for example human rhinovirus, respiratory syncytial virus, human metapneumovirus), particularly in severely immunosuppressed patients (38); seek advice on diagnosis and treatment from local infection specialists if necessary.

Adjunctive therapies including corticosteroids

Although conclusive data from high quality studies are lacking, the use of corticosteroids specifically as an adjunctive therapy for complicated influenza is not recommended by PHE, CDC or WHO.

A meta-analysis of observational studies showed that corticosteroid therapy was associated with increased mortality (odds ratio (OR) 3.06, 95% confidence interval (CI) 1.58 to 5.92) (49).

Three observational studies have also reported greater odds of hospital-acquired infection in patients treated with corticosteroids (49).

Corticosteroids should not be withheld if they are required for another indication (for example adrenal insufficiency), but clinicians should be aware of potential corticosteroid-associated complications in patients with influenza.

There are no other adjunctive pharmacological therapies of proven benefit; it is recommended that use of adjunctive therapies, including immunomodulators, is restricted to enrolment in a registered clinical trial.

Infection prevention and control

General principles and requirements

Influenza virus is transmitted by droplet, contact, and possibly airborne routes.

Single rooms appropriate for respiratory isolation are recommended because of potential airborne transmission of influenza virus.

Nosocomial transmission of influenza is known to occur, sometimes leading to outbreaks (50-52), and influenza virus infection can have serious consequences for critical care patients; the aim of IPC measures is to prevent transmission of influenza from an infected patient to other patients and members of staff.

Critical care units should have in place local infection prevention and control (IPC) policies relevant to seasonal influenza.

PHE has published IPC guidance for respiratory tract infections that is applicable to managing influenza in critical care settings, including advice on personal protective equipment (PPE).

Droplet and contact precautions are required at all times and additional airborne precautions are required for aerosol generating procedures (refer to the airborne precautions section of the **PHE IPC guidance** for examples); this applies to the care of patients with suspected and confirmed seasonal influenza.

Aerosol-generating procedures performed electively in a shared occupancy space (such as a bay or on the open ICU) may expose other patients to influenza virus and should be avoided.

Patient placement

Patients with suspected or confirmed influenza should be placed in single rooms that are appropriate for respiratory isolation (see **PHE IPC guidance**).

Alternative arrangements for when single rooms are not available, including the cohorting of patients, are described in the **PHE IPC guidance**.

The cohorting of influenza patients, including patients with infections caused by different influenza/influenza subtypes, should be a decision made by local infection prevention and control teams.

Positive pressure rooms should not be used as they may spread infectious virus to other areas.

Cleaning considerations

Assume that the patient's environment is contaminated with influenza virus; staff should avoid self-contamination and adopt good hand hygiene practice before entering and after leaving the patient area, and rooms should be cleaned at least once daily.

Surfaces touched frequently by patients should be cleaned at least 3 times a day, and immediately if visibly contaminated.

Additional cleaning of frequently-touched surfaces and horizontal surfaces is required following aerosol-generating procedures.

Terminal cleaning following discharge of the patient should be performed according to local policy.

Further advice is available in the [PHE IPC guidance](#).

Personal protective equipment (PPE)

PPE needs to be applied, worn and removed appropriately; see the appendix for illustrated guidance.

Staff and visitors within 2 metres of a patient with suspected or confirmed influenza should wear a plastic apron, disposable gloves and surgical face mask; eye protection is advisable if there is a risk of eye exposure to infectious sprays (for example patients with persistent cough or sneezing).

For aerosol generating procedures, the following must be used: FFP3 face mask or respirator; fluid repellent gown; disposable gloves; eye protection (for example goggles or full-face visor).

It is a legal requirement that anybody who might be required to wear an FFP3 respirator be fit tested in order to check that an adequate seal can be achieved with each specific model; it is also important that the user carries out a fit check each time an FFP3 respirator is worn.

Cohorted patients: it may be more practical to put on a surgical face mask on entry to the cohort area and keep it on for the duration of all care activities, or until the mask requires replacement (when it becomes moist or damaged); all staff working within a

cohort area should wear an FFP3 mask when an aerosol generating procedure is being performed.

Devices and equipment

Consideration should be given to aerosol generation by devices including invasive and non-invasive ventilators, high flow humidified oxygen systems and high frequency oscillatory ventilators; critical care departments are advised to check manufacturers' guidance on potential aerosol generation and measures taken to mitigate risk (including integrated measures and/or measures that need to be applied).

The addition of an expiratory port with a bacterial/viral filter (for example HEPA filter) can reduce aerosol emission but may not eliminate it.

Closed tracheal suctioning is preferred over open tracheal suctioning in patients with influenza who are receiving invasive ventilation, to avoid the generation of aerosols.

Closed tracheal suctioning is not an aerosol-generating procedure but interrupting an active circuit (for example by attaching a sputum trap) may lead to the emission of aerosols.

Medical equipment can become contaminated, in addition to contamination of the patient's environment; refer to [PHE IPC guidance](#) for further information on managing and cleaning equipment.

Duration of IPC precautions

Generally, the duration of isolation precautions for immunocompetent patients should be continued for 24 hours after resolution of fever and respiratory symptoms attributable to influenza.

For prolonged illness with complications such as pneumonia in immunocompetent patients, precautions should be applied until symptoms and signs of respiratory disease have resolved.

Severely immunosuppressed patients can continue to shed influenza virus, which may be infectious, for longer than immunocompetent patients and with minimal symptoms.

Clinicians should be mindful of the potential need for continued infection control measures for inpatients if repeat sampling for influenza virus PCR testing provides positive results

Staff considerations

Annual vaccination with seasonal influenza vaccine is recommended for all healthcare workers involved in direct patient contact,(53) intending to minimise the risk of influenza illness in members of staff, and reducing the risk of influenza being spread to patients and co-workers.

Healthcare facilities should have policies in place for the monitoring and management of staff with illness that could be caused by influenza.

PHE recommends that staff with influenza or influenza-like illness are excluded from work until symptoms have resolved completely.

PHE does not recommend routine pre-exposure prophylaxis with antivirals for healthy staff caring for patients with seasonal influenza; vaccination remains the preferred method of pre-exposure prophylaxis for healthcare workers.

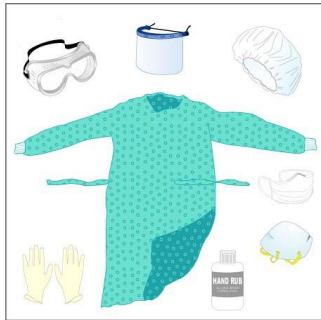
Deceased patients

If a deceased patient was known or suspected to have seasonal influenza virus infection at the time of death, the measures applicable are:

- staff handling or preparing the body (for example cleaning of the body, removal of devices, and placement of the body in a body bag) should wear a plastic apron, disposable gloves and surgical face mask; eye protection is advisable if there is a risk of eye exposure to infectious sprays
- if preparation of the body involves the potential generation of aerosols (for example open suctioning of blood or secretions), staff should wear a FFP3 face mask or respirator, fluid repellent gown, disposable gloves and eye protection (for example goggles or full-face visor); family members or other visitors should be excluded during potential aerosol generating procedures
- hand hygiene should be performed after removing PPE
- family members or other visitors who wish to view the body should wear a plastic apron and disposable gloves; if they have contact with the body and there is an associated risk of exposure to fluids or splashes, the addition of a surgical face mask and eye protection should be considered
- family members or other visitors should be supervised in removal of PPE and performing hand hygiene
- following removal of the body, terminal cleaning should be performed according to local policy

Appendix

Putting on and removing personal protective equipment



- 1** Identify hazards and manage risk.
 - Gather the necessary PPE.
 - Plan where to put on and take off PPE.
 - Do you have a buddy? Mirror?
 - Do you know how you will deal with waste?

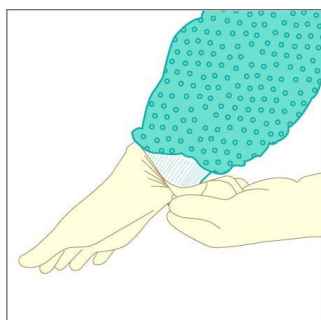
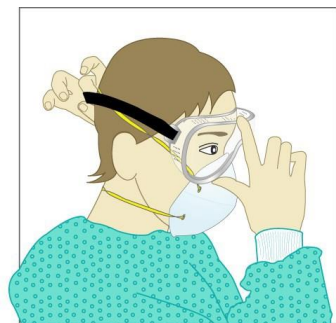


- 2** Put on a gown.



- 3** Put on particulate respirator or medical mask; perform user seal check if using a respirator.

- 4** Put on eye protection, e.g. face shield/goggles (consider anti-fog drops or fog-resistant goggles). Caps are optional: if worn, put on after eye protection.



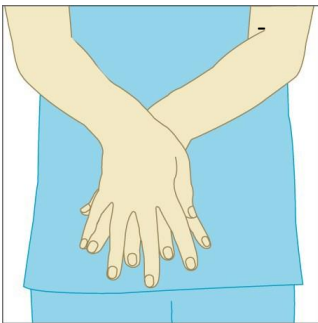
- 5** Put on gloves (over cuff).

Taking off PPE



Avoid contamination of self, others and the environment.
Remove the most heavily contaminated items first.

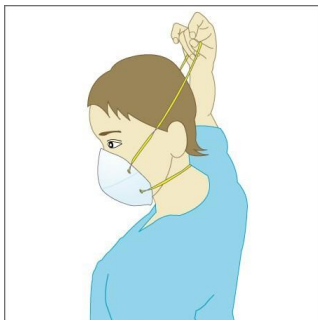
Remove gloves and gown:
peel off gown and gloves and roll inside, out;
dispose of gloves and gown safely.



Perform hand hygiene.



Remove cap (if worn).
Remove goggles from behind.
Put goggles in a separate container for reprocessing.



Remove respirator from behind.



Perform hand hygiene.

Useful resources

Seasonal influenza: guidance, data and analysis (PHE)

<https://www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis>

PHE guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza

<https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents>

Infection control precautions to minimise transmission of acute respiratory tract infections in healthcare settings (PHE)

<https://www.gov.uk/government/publications/respiratory-tract-infections-infection-control>

Weekly national flu reports (PHE)

<https://www.gov.uk/government/statistics/weekly-national-flu-reports>

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