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REVIEW ARTICLE

Pandemic (H1N1) 2009 influenza

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The clinical picture in severe cases of pandemic (H1N1) 2009 influenza is markedly different from the disease pattern seen during epidemics of seasonal influenza, in that many of those affected were previously healthy young people. Current predictions estimate that, during a pandemic wave, 12–30% of the population will develop clinical influenza (compared with 5–15% for seasonal influenza) with 4% of those patients requiring hospital admissions and one in five requiring critical care. This review covers the background, clinical presentation, diagnosis, and treatment. The role of immunization and antiviral drugs is discussed. Experience from the first wave of pandemic (H1N1) 2009 influenza suggests that a number of infected patients become critically ill and require intensive care admission. These patients rapidly develop severe progressive respiratory failure which is often associated with failure of other organs, or marked worsening of underlying airways disease. The critical care management of these patients and the implications for resources is reviewed. Guidance from a range of bodies has been produced in a relatively short period of time in response to pandemic (H1N1) 2009 influenza. Disease severity has the potential to change, especially if there is virus mutation. Clinicians must be prepared for the unexpected and continue to share their experiences to maximize patient outcomes.

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There have been three influenza pandemics in the last century. In comparison with the seasonal influenza outbreaks seen every winter, influenza pandemics usually occur every few decades. The 1918 pandemic was estimated to have killed more than 40 million people in less than 1 yr. In late March and early April 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico, with subsequent cases observed in many other countries, including the USA.[11 89] The clinical picture in severe cases of pandemic (H1N1) 2009 is markedly different from the disease pattern seen during epidemics of seasonal influenza, in that many of those affected are previously healthy young people. On June 11, 2009, the World Health Organization (WHO) raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission on at least two continents.[95]

Recent data from numerous outbreak sites indicate that the pandemic (H1N1) 2009 virus is currently the dominant influenza strain in most parts of the world.[92] By October 2009, 191 countries and territories had reported more than 375 000 laboratory confirmed cases of pandemic (H1N1) 2009 with more than 4500 deaths.[88] As of October 29, 2009, there had been 137 deaths related to pandemic (H1N1) 2009 in the UK since June 2009.[55] In response to WHO raising the pandemic alert level to phase 6, priorities shifted from containment and treatment to mitigation in order to minimize viral spread by using population-based measures.[88] In order to achieve this and avoid subsequent morbidity and mortality, effective preventative measures are needed by individuals, communities, and health-care workers (HCWs).

In health-care settings, priority should be given to the appropriate use of antiviral drugs and an effective immunization policy. A combination of triage, patient cohorting, adherence to infection control policies, and effective use of personal protective equipment (PPE), will also help reduce mortality and morbidity at different stages of the infection. Advice for the public includes guidelines issued by the Health Protection Agency (HPA) for the management of H1N1 in the health-care setting, schools, and business facilities.[43 44]

Pandemic (H1N1) 2009 influenza virus

Influenza A viruses are classified according to the structure of its two surface antigens: haemagglutinin and

neuraminidase. There are 16 H (haemagglutinin) and nine N (neuraminidase) types of antigens. H1N1 viruses are the most common, although H3N2 viruses have also been reported. Pigs, which can be infected by both avian and human strains, are considered 'mixing vessels' for the creation of novel strains of reassortant influenza A viruses.[4]

The pandemic (H1N1) influenza A virus is a novel reassortant virus comprising two swine strains, one human strain, and one avian strain of influenza. Influenza A viruses undergo minor changes known as antigenic drifts (which are associated with localized outbreaks), and major reassortment changes known as antigenic shifts. Antigenic shifts are associated with influenza A epidemics and pandemics.

Pandemic (H1N1) 2009: transmission

On the basis of early estimates from Mexico, pandemic (H1N1) 2009 appears to have higher transmissibility than seasonal influenza but lower clinical severity than the 1918 influenza pandemic.[39] It is thought that the route of transmission of pandemic (H1N1) 2009 is comparable with other influenza viruses. It is essentially human-to-human involving exposure to infected large particle respiratory droplets or contaminated surfaces. All bodily fluids and secretions of confirmed cases should be considered infectious. Immunocompromised persons may shed the virus for longer periods.

Pandemic (H1N1) 2009: presentation and clinical features

The Department of Health (DOH) has issued guidance on recognition of H1N1 infection. In both children and adults, the presentation of H1N1 infection resembles many winter viruses.[23]

Patients usually present with symptoms within a week of exposure and are infectious for about 8 days after onset of symptoms.[16] Hospitalized patients typically present with fever (95%), cough (88%), shortness of breath (60%), fatigue (43%), runny nose (38%), sore throat (31%), headache (34%), and myalgia (36%).[47] A proportion of affected patients have presented with gastrointestinal symptoms such as diarrhoea and vomiting. A small subset of patients have presented solely with gastrointestinal or neurological symptoms without fever or cough.[23 47]

Complications of H1N1 appear similar to seasonal influenza and include myocarditis, bacterial co-infections,[23] and neurological complications such as encephalitis.

In the critically ill patients, a spectrum of clinical features are associated with H1N1 infection.[83] These include:

- rapidly progressive lower respiratory tract disease, respiratory failure, and acute respiratory distress syndrome (ARDS) with refractory hypoxaemia;
- worsening of pre-existing co-morbidities in patients with chronic obstructive pulmonary disease, congestive heart failure, chronic renal failure, end-stage liver disease, poorly controlled diabetes, or immunocompromised patients;
- secondary bacterial infections, septic shock, and multi-organ dysfunction.

A study of 272 patients infected with H1N1 hospitalized in the USA found that 73% of the patients had a single co-morbidity on admission, of which asthma was most common (28%), followed by obesity (29%) and diabetes (15%). Of these hospitalized patients, 25% were admitted to the intensive care unit (ICU).[47] This is similar to the rate of intensive care admission of hospitalized patients (27%) in an Australian study.[17]

Laboratory findings include lymphopenia and elevated creatinine kinase (CK). A Mexican study found 62% and 63% of hospital admissions, respectively, with these abnormalities.[58] Higher CK levels have been reported in those who died.[31] An American post-mortem study of patients with H1N1 infection found co-infection with *Streptococcus pneumonia*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus mitis*, or *Haemophilus influenza* in 29%.[6]

Pandemic (H1N1) 2009: radiological findings

The chest radiograph pattern in patients with pandemic H1N1 ranges from multi-focal infiltrates to localized consolidation and nodular alveolar opacities.[62]

A study of hospitalized patients in Melbourne reported normal chest radiographs in 50% of patients, multi-focal changes in 27%, unifocal changes in 18%, and pleural effusions in 4% of the patients. Multi-focal changes were associated with worse hospital outcomes and were more likely to require ICU admission.[17] An American study found that 40% of hospitalized patients with pandemic H1N1 influenza had chest radiographs consistent with pneumonia on admission and 73% of patients admitted to intensive care had radiographic evidence of pneumonia.[47]

Case definitions

For reporting purposes, WHO uses the following case definitions of influenza illnesses.

- *Influenza-like illness*: fever and sore throat, cough, or both in the absence of another known cause.
- *Probable case*: influenza-like illness with positive test for influenza A but negative for H1 and H3 by real-time reverse transcriptase–polymerase chain reaction test (rRT–PCR).
- *Confirmed case*: influenza-like illness with confirmed H1N1 influenza infection based on rRT–PCR or viral culture.

Pandemic (H1N1) 2009: diagnostic tests

Tests available for pandemic (H1N1) 2009 include the rapid influenza diagnostic test (RIDT), rRT–PCR, viral culture, and direct immunofluorescence assay (DFA).

Diagnostic testing for influenza should be considered in hospitalized patients, or patients in whom a diagnosis of influenza will influence management regarding clinical care, infection control, and management of contacts.

Interpretation of test results

The RIDT test is easy to perform and results can be obtained swiftly (Table 1). However, RIDT and DFA tests have lower sensitivities than rRT–PCR tests or viral culture and cannot distinguish between pandemic (H1N1) 2009 and seasonal H1N1 or H3N2 influenza A viruses.[10] A negative RIDT or DFA result does not exclude influenza virus infection and should not be the sole determinant of a decision regarding treatment.[8] Further influenza-specific testing should be considered. Antiviral therapy and infection control measures should be undertaken regardless of whether there is a high clinical suspicion of influenza infection. Confirmation of pandemic (H1N1) 2009 virus infection can only be made with rRT–PCR or viral culture.[8] Real-time RT–PCR should be used for selected patients and circumstances, for example, in hospitalized and immunocompromised patients with suspected influenza where rapid testing is negative and for determination of influenza A virus subtype in suspected or confirmed cases of influenza A virus infection.

Isolation of pandemic (H1N1) 2009 virus by a positive viral culture is diagnostic of infection; however, the results may be too slow to guide clinical management. A negative viral culture does not exclude pandemic (H1N1) 2009.[9]

Specimens

The impact of specimen type on the laboratory diagnosis of pandemic (H1N1) 2009 virus infection is insufficiently understood.[83] Specimens should be collected on a swab with a synthetic tip on a plastic or aluminium shaft. Ideal specimens are nasopharyngeal swabs or nasal aspirate. Oropharyngeal and nasal swabs are also satisfactory if other samples are unavailable. For intubated patients, endotracheal aspirate should also be collected. Other acceptable specimens are sputum and bronchoalveolar lavage.[9]

The time from illness onset to specimen collection, the site and quality of the specimen swab, and the time elapsed between specimen collection and testing can all contribute to a lower sensitivity for tests to detect pandemic (H1N1) virus infection. Recent evidence supports viral replication and retrieval of the pandemic (H1N1) 2009 virus from lower respiratory tract samples (tracheal and bronchial aspirates) in patients with lower respiratory tract symptoms. These samples have higher diagnostic yields than samples from the upper respiratory tract.[83]

Rapid antigen tests in an Australian subgroup of 21 patients with severe (H1N1) 2009 infection (requiring mechanical ventilation) were noted to have had poor sensitivity to the virus.[36 74] Rapid antigen tests performed on nasal and throat swabs tested positive in only 25% of these patients. Similarly, influenza type-specific immunofluorescent antigen assays performed on bronchoscopic specimens were positive in only 25% of the patients. However, RT–PCR testing performed on specimens from both the upper and the lower respiratory tracts for all patients tested positive for the virus in 81% and 100% of patients, respectively.[36]

This highlights the need for careful interpretation of diagnostic testing for pandemic (H1N1) 2009 virus infection. The type of assay used and the origins of the sample tested may affect the accuracy of the diagnostic testing.[3]

Pandemic (H1N1) 2009: treatment overview

Antiviral neuraminidase inhibitor drugs oseltamivir (Tamiflu®) and zanamivir (Relenza®) are used in the treatment of pandemic (H1N1) 2009 influenza. Treatment recommendations will have to be modified as further information on the clinical spectrum of the illness and adverse events of antiviral utilization are available.

Table 1 Comparison of available influenza diagnostic tests.[10] Serologic testing on paired acute- (within 1 week of illness onset) and convalescent-phase (collected 2–3 weeks later) sera is limited to epidemiological and research studies, is not routinely available through clinical laboratories, and should not inform clinical decisions. *The amount of time needed from specimen collection until results are available. †Compared with rRT–PCR tests; rRT–PCR tests are compared with other testing modalities including other rRT–PCR assays. ‡RIDTs include tests that are CLIA waived (can be performed in an outpatient setting) and tests that are moderately complex (can be performed only in a laboratory). Clinical specimens approved for RIDTs vary by test, and may not include all respiratory specimens. ¶Performance of these assays relies heavily on laboratory expertise and requires a fluorescent microscope. §Requires additional testing on the viral isolate. ‖The performance of rRT–PCR assays specific for 2009 H1N1 influenza has not been established for bronchoalveolar lavage and tracheal aspirates. If testing these specimens for 2009 H1N1 influenza, consider testing in parallel with a nasopharyngeal, nasal, or oropharyngeal swabs or a nasal aspirate. #See discussion above on available rRT–PCR assays

Influenza diagnostic tests	Method	Availability	Typical processing time*	Sensitivity† for H1N1 2009 influenza (%)	Distinguishes H1N1 2009 influenza from other influenza A viruses?
RIDT‡	Antigen detection	Wide	0.5 h	10–70	No
Direct and indirect immunofluorescence assays (DFA and IFA)¶	Antigen detection	Wide	2–4 h	47–93	No
Viral isolation in tissue cell culture	Virus isolation	Limited	2–10 days	—	Yes§
Nucleic acid amplification tests (including rRT–PCR)‖	RNA detection	Limited#	48–96 h (6–8 h to perform test)	86–100	Yes

Monitoring by the Global Influenza Surveillance Network (GISN), supported by WHO Collaborating Centres had identified 35 oseltamivir-resistant pandemic H1N1 influenza viruses worldwide by October 16, 2009. They all exhibited H275Y mutation which causes resistance to oseltamivir, but not to zanamivir.[90] Antiviral sensitivities for seasonal influenza virus vary according to the subtype.

WHO has alerted clinicians to two situations carrying a high risk for emergence of viruses resistant to oseltamivir:

(i) Patients who had received post-exposure prophylaxis but still developed influenza.
(ii) Severely immune-suppressed patients who have received oseltamivir for a prolonged period but still show viral replication have a higher risk of oseltamivir resistance.[81]

Who should be treated?

In general, the WHO does not recommend the use of antiviral drugs for prophylaxis. An alternative to post-exposure prophylaxis is early treatment based on signs and symptoms. There is no direct comparative evidence of the role of neuraminidase inhibitors in the current H1N1 pandemic but some observational data for hospitalized patients with pandemic H1N1 2009 suggests that there may be a reduction in morbidity and mortality.[47] For a healthy patient with mild to moderate uncomplicated illness, no treatment is required. For a high-risk patient or a patient with severe or progressive clinical illness, oseltamivir or zanamivir is recommended, ideally within 48 h of onset. In those patients who initially present with severe illness or whose condition begins to deteriorate, treatment should be commenced promptly without waiting for confirmation of the laboratory tests.

The HPA recently has produced detailed prescribing guidelines for antiviral drugs.[45] This includes advice on prescribing for high-risk groups which include infants, children, adults with chronic health conditions, patients with renal impairment, or on renal replacement therapy and pregnant women. Older patients (>65 yr) appear less susceptible to infection by pandemic H1N1 influenza virus, but are assumed to be at higher risk of more severe or complicated illness if infected.[81] The Royal College of General Practitioners (RCGP) have an assessment and treatment algorithm for pandemic (H1N1) 2009 influenza.[63]

Pandemic (H1N1) 2009 influenza

Vaccination

Vaccination is one of the most effective ways of reducing morbidity and mortality. Pandemic influenza vaccines are not expected to provide protection against other influenza viruses. The vaccine becomes effective approximately 14 days after vaccination. Patients infected 1–3 days before or after immunization can still get the disease. Depending on the adequacy of the virus match, vaccination can prevent 50–80% of influenza illness in healthy adults and children.[49] HCWs have a seasonal influenza vaccination rate of <40%. These rates should be improved because seasonal influenza vaccination not only provides protection against the predominant circulating influenza strain, but also reduces the risk of an HCW being co-infected with different influenza strains, potentially causing genetic reassortment which could lead to the emergence of a new more virulent strain.[40]

Some pandemic vaccines contain an adjuvant to reduce the amount of virus antigen to be used. Adjuvants can greatly increase the potency of vaccines and therefore increase the number of people who can be vaccinated with a given supply.

Glaxo Smith Kline (GSK) H1N1 vaccine (Pandemrix®) has been authorized for use for the pandemic (H1N1) 2009 by the European Commission after endorsement on September 30, 2009, by the European Medicines Agency (EMEA).[19 35] This is an adjuvanted inactivated vaccine. Contraindications to its administration include a history of an anaphylactic reaction to its components or egg-containing products.

In England, the DOH have issued specific guidelines regarding pandemic (H1N1) 2009 vaccination.[29] Certain groups have been given priority for vaccination. These include individuals in the current seasonal flu vaccine at-risk groups, all pregnant women (subject to licensing conditions), household contacts of immunocompromised individuals, and frontline HCWs.[30]

As of November 19, 2009, WHO had been notified of vaccination information from 16 of the 40 countries conducting national H1N1 pandemic vaccine campaigns.[93] On the basis of this information, WHO has estimated that around 65 million people have been vaccinated.

Commonly reported side-effects of the vaccination include swelling, erythema, and pain at the injection site which usually resolve spontaneously shortly after vaccination. Less frequently, fever, headache, fatigue, and myalgia occurring shortly after vaccine administration have also been reported. These symptoms usually resolve within 48 h. A variety of allergic reactions have also been observed, the frequency of which is within the expected range.

So far no differences in the safety profile of severe adverse events using non-adjuvanted inactivated vaccines, adjuvanted inactivated vaccines, and live attenuated vaccines have been detected.[93] As of November 19, 2009, fewer than 10 suspected cases of Guillain–Barre syndrome in vaccinated people have been reported to WHO. These cases are being investigated to determine whether these are randomly occurring events or if they might be associated with vaccination. All these cases have recovered. WHO has received no reports of fatal outcomes among suspected or confirmed cases of Guillain–Barre syndrome detected since vaccination campaigns began.[93]

Pandemic (H1N1) 2009 influenza and pregnancy

Treatment and prophylaxis

Pregnant women are not known to be at increased risk of becoming infected with H1N1 2009 influenza. However,

due to the changes in their immune systems, they are at greater risk of developing complications should they acquire the illness.[24 71] Therefore, they should be prioritized for antiviral treatment or prophylaxis, if influenza infection is suspected or confirmed.

Pregnant women with influenza-like illness should be treated as soon as possible with antiviral medications, and WHO recommends treatment with oseltamivir. Treatment should be started as soon as possible after onset of symptoms.[13] The greatest benefit of treatment is derived when it is initiated within 48 h of symptom onset. Fever during pregnancy should be treated with acetaminophen due to the risk to the fetus. Hyperthermia in early pregnancy has been associated with neural tube defects and other congenital anomalies. Fever during labour is a risk factor for neonatal seizures, newborn encephalopathy, cerebral palsy, and death.[53 60]

Zanamivir may be preferable for post-exposure prophylaxis for suspected or confirmed influenza, because inhaled medication reduces the amount of systemic absorption and fetal exposure. However, caution is advised in women at risk of respiratory problems as it can cause bronchospasm. An alternative to post-exposure prophylaxis is early treatment based on signs and symptoms.

Pandemic (H1N1) 2009: hospital management of the pregnant patient

The Royal College of Obstetrics and Gynaecology (RCOG) have issued guidelines about management of the pandemic H1N1 patient.[65] Pregnant women with confirmed/suspected swine flu who require hospital admission should be isolated whenever possible. They should be cared for in a single room with barrier nursing (gloves, plastic aprons, surgical face masks, attention to hand washing and hygiene, etc.). At delivery, the use of surgical masks and eye protection in addition to plastic aprons is recommended as there is splash risk with Caesarean sections and instrumental deliveries. However, the use of Entonox is not considered an aerosol-generating procedure.[24]

If the numbers of admissions with H1N1 infection were to overwhelm the availability of single rooms, infected patients would need to be cohorted. If a parturient due to have an elective Caesarean section or induction of labour reports flu-like symptoms, then unless there is a pressing obstetric reason to proceed with induction or Caesarean section, balanced consideration should be given to delaying the procedure for 5 days. This would give the woman time to recover from her acute illness and will help reduce the risk to staff and other women in the hospital from contracting the virus.[65] Post-natally, breastfeeding should be encouraged. Infants who are not breastfed may be more susceptible to viral infection. Occasionally, it may be necessary to care for mother and baby separately (e.g. if the baby needs admission to the special care baby unit or if the mother has an active infection and fever).[14]

Pandemic (H1N1) 2009: pregnancy and intensive care

Pregnant women are over-represented in the group of patients admitted to hospital requiring intensive care. Observations from the USA,[47] Canada,[50] and Australasia[74] showed that pregnant women formed between 7% and 9% of admissions to ICUs.

Criteria for identifying pregnant women who may benefit from intensive care would include:[24]

- severe dyspnoea and hypoxaemia with Pa_{O_2} <8 kPa, despite maximal oxygen administration. Supplemental oxygen requirement and dyspnoea are strongly predictive of ICU care and death;
- influenza-related pneumonia. Pneumonia on admission is strongly predictive of significant complications after admission (including ICU multi-organ support and death);
- progressive hypercapnia;
- refractory hypotension (some evidence suggests that excessive fluid resuscitation may contribute to respiratory compromise);
- septic shock;
- severe acidosis (pH <7.26);
- GCS <10 or deteriorating conscious level.

If the parturient with pandemic (H1N1) 2009 develops severe complications and shows signs of hypoxia requiring ITU admission, the anaesthetic, respiratory, and haematology team should be involved early. Platelets and coagulation should be monitored as disseminated intravascular coagulation has been reported. Other complications include venous thromboembolism, pulmonary embolism, and cognitive impairment post-viraemia.[52] It is vital that obstetric complications such as pre-eclampsia or pulmonary embolism presenting with abdominal pain or respiratory symptoms are not missed.

Delivery of the baby has to be considered if maternal indications necessitate it, that is, to aid in the supportive management of the mother (e.g. to help with her oxygenation and ventilation). Where a decision is made to deliver the fetus prematurely for maternal or fetal reasons, consideration should be given to the current practice of maternal administration of corticosteroids to promote fetal lung maturity. The practice of multiple, repeated doses of corticosteroids is not recommended. All clinical decisions have to be made in conjunction with the mother, but if she is too unwell, her partner or closest relatives should be involved. Although the clinical decisions are made mainly in the interest of the mother, the baby's welfare also needs to be taken into consideration.[64]

Pandemic (H1N1) 2009 management of the hospitalized patient

Current predictions estimate that, during a pandemic wave, 12–30% of the population will develop clinical flu

(compared with 5–15% for seasonal flu) with 4% of those requiring hospital admissions, with one in five requiring critical care.[28 66] Hospitals have been advised to anticipate a four-fold increase in emergency admissions. Such demand on hospitals will require significant adaptations in how services are delivered.

Guidelines have been issued to all hospital departments, aiming to provide the greatest good to the most patients. The guidelines have been developed from those produced by the WHO and DOH over the last few years in anticipation of such a pandemic.[20 91]

The general principles include increased support within the community, including specialist teams offering telephone advice to those working in primary care. Outpatient clinic capacity may be reduced by 90% with patients receiving triage cards for new and follow-up appointments in order that those with life-limiting illnesses continue to be seen regularly but those without have their appointments delayed during the pandemic phase. Despite such interventions, hospital capacity may still only meet 20–25% of predicted demand. There should be common understanding and equity of measures across medical specialities in order to maintain public understanding and acceptance of such measures that may, inevitably, have adverse morbidity and mortality outcomes.

Flexibility of staffing in some areas will be necessary as staffing levels will, potentially, become compromised by up to 50% due to personal illness, child care, and restrictions in transport to and from work.

The majority of patients will present to Emergency Departments or Medical Admissions Units (MAU). From arrival, patients should be cohorted into the influenza and non-influenza groups in order to minimize cross-infection. Trusts are likely to use the MAU as the influenza cohort area with medical care being led by the Acute Medical, General Internal Medicine, Infectious Diseases, and Respiratory teams.

Pandemic (H1N1) 2009: exceptional demands on health-care resources

The DOH has issued clinical guidelines including a triage tool (Table 2) to be used in the event of exceptional demands on health-care resources.[26] This tool has been designed to ensure consistency in clinical management and to aid staff working in areas that they are unaccustomed.

Diagnosis should be made on clinical grounds alone. Those suffering from severe infection, and requiring hospital admission, may present with respiratory failure, cardiovascular failure, septic shock, or encephalopathy. Those at high risk of the more severe manifestations of the illness are patients with chronic diseases, immunosuppression, medically treated asthma, pregnancy, and those more than 65 yr or under 5 yr.[27] Inpatients at high risk of severe illness from pandemic (H1N1) 2009 infection should be segregated into a non-influenza area.

Table 2 DOH clinical triage tool

Criteria label	Adults will be considered for admission at the nearest general hospital if they present with any of the following
A	Severe respiratory distress Severe breathlessness, e.g. unable to complete sentences in one breath Use of accessory muscles, supra-clavicular recession, tracheal tug, or feeling of suffocation
B	Increased ventilatory frequency measured over at least 30 s More than 30 bpm
C	Oxygen saturation $\leq$92% on pulse oximetry, breathing air, or on oxygen Absence of cyanosis is a poor discriminator for severe illness
D	Respiratory exhaustion New abnormal breathing pattern, e.g. alternating fast and slow rate or long pauses between breaths
E	Evidence of severe clinical dehydration or clinical shock Systolic arterial pressure $<$90 mm Hg, diastolic arterial pressure $<$60 mm Hg, or both Sternal capillary refill time $>$2 s, reduced skin turgor
F	Altered conscious level New confusion, striking agitation, or seizures
G	Causing other clinical concern to the clinical team or specialist doctor, e.g. a rapidly progressive or an unusually prolonged illness

Patients who meet the admission criteria at triage should be admitted to a cohorted short stay area for 4 h and undergo supportive treatment for hypoxia and dehydration, whilst receiving oseltamivir (75 mg twice daily for 5 days for adults) and one of co-amoxiclav, doxycycline, or clarithromycin depending on the patient's allergy status. Oseltamivir should be commenced within 24–48 h of onset of symptoms but may be of benefit in those with severe illness within 7 days of onset.[45] Four hours later, those who respond may be discharged with home care advice, a 5 day course of oseltamivir, and their chosen antibiotic. Patients who have not improved should be observed for a further 4 h and then reassessed. If they continue to fail to meet discharge criteria, then they should be admitted, ideally to the influenza cohort ward. Patients admitted to the ward should only be those suffering from severe and complicated flu-like symptoms and the triage system should be enforced carefully at such times of overwhelming demand. A further clinical pathway[22] has been produced to guide inpatient management, following the principles of the assessment and management of the critically ill septic patient, including consideration of differential diagnoses. Criteria for referral to critical care services are then suggested.

Pandemic (H1N1) 2009: intensive care

Although there has been global preparation for a pandemic, the nature and severity of the disease could not be predicted before the outbreak. The majority of people worldwide infected with the pandemic (H1N1) 2009 virus

have experienced uncomplicated influenza-like illness, with full recovery within a week, even without medical treatment.

Experience from the first wave of pandemic (H1N1) 2009 suggests that a number of infected patients become critically ill and require intensive care admission. These patients rapidly develop severe progressive respiratory failure which is often associated with failure of other organs, or marked worsening of underlying airways disease. Primary viral pneumonia is the most common finding in these severe cases and a frequent cause of death. Secondary bacterial infections have been found in ~30% of fatal cases.[87] Respiratory failure and refractory shock have been the most common causes of death in this group.

In these severe cases, patients generally began to deteriorate around 3–5 days after symptom onset. Deterioration was rapid, with many patients progressing to respiratory failure within 24 h, necessitating admission to an ICU. The majority of these patients required immediate respiratory support with mechanical ventilation. However, some patients did not respond well to conventional ventilatory support, further complicating their management.[82]

The Royal College of Anaesthetists (RCOA), in collaboration with the HPA and the Intensive Care Society (ICS), have issued guidelines to direct clinical management of the patient with pandemic (H1N1) 2009.[62] A checklist for critical care admission is also available.[61]

H1N1 2009 intensive care: second wave

Data from the initial outbreak in Mexico suggest 6.5% of those admitted to hospital with pandemic (H1N1) 2009 became critically ill.[31] Other reports predict higher proportions (10–25%) may require critical care.[62] The absence of data has been problematic for intensive care clinicians when preparing for the unique needs of patients critically ill with pandemic (H1N1) 2009. Although recent pandemics can be referred to, the treatment options including the use of antibiotics, antivirals, vasopressors, and mechanical ventilation are more sophisticated when compared with the Spanish influenza pandemic of 1918.[80] Data from Mexico, Northern America, and the Southern Hemisphere go some way to helping critical care units prepare for the predicted second wave, although it is difficult to infer benefits of certain therapeutic manoeuvres due to differences between the groups that did and did not receive treatment[80] (Table 3).

H1N1 2009 intensive care: patient characteristics and presentation

Two recent reports from Mexico and Canada indicate critical illness resulting from pandemic (H1N1) 2009 occurred mainly in young fit adults.[31 50] Other risk factors aside from those associated with seasonal influenza include pregnancy[48] and obesity.[50 54] The Canadian study found

Table 3 General comparison of the clinical characteristics of the critically ill with H1N1 in the three geographical H1N1 outbreak regions. *Pregnancy and obesity. **Percentage of general population obese

Countries	**Mexico[31]**	**Canada[50]**	**Australia/NZ[74]**
Scope	6 hospitals	38 adult/paediatric ICUs	All ICUs in Australia and NZ
Study design	Retrospective observational	Prospective observational	Inception cohort
No. of cases	58 confirmed probable or suspected cases	168 confirmed and probable cases	722 confirmed cases
Rate of critical illness (% of those admitted to hospital)	6.5%	19%	No information
Co-morbidity*	49%	30.4%	27.9%
Obesity	36% (30%)**	33.3% (24%)**	28.6% (5.3%)**
Pregnancy	1%	13%	9.1%
Invasive ventilation	82%	81%	64.6%
Average days of ventilation	12	12	8
HFOV	1.7%	11.9%	No information
ECMO	0	4.2%	2.1%
Vasopressors	58.6%	32.7%	35.3%
Renal support	No information	7.1%	5.3%
Mortality	41.4% at 60 days	14.3% at 28 days; 17.3% at 90 days	14.3% at 99 days

a higher proportion of women required intensive care along with those of Canadian aboriginal origin. An Australian and New Zealand data set replicated the findings of increased incidence in indigenous populations,[74] while a small case series from the UK noted a high proportion of ethnic minorities admitted to intensive care.[56]

H1N1 2009 intensive care: symptoms

The most common presenting symptoms of patients admitted to intensive care with pandemic (H1N1) 2009 include fever in 97%, cough in 93%, shortness of breath in 87%, fatigue in 46%, vomiting in 25%, and diarrhoea in 24%.[47] Symptoms and signs that have been associated with more severe disease include dyspnoea, fever for >3 days, abdominal pain, persistent vomiting, hypotension, bloody sputum, and altered mental state.[12] The three studies from Mexico, Canada, and the Southern Hemisphere describe patients requiring critical care presenting with rapidly progressing respiratory failure and refractory hypoxia. The time from hospital admission to ICU admission was short with a median of 1 day.[31 50 74]

H1N1 2009 intensive care: respiratory management

Guidance from the HPA, the RCOA, and the ICS is in line with published international reports. They point out that many of those admitted to intensive care have rapidly progressing, profound respiratory failure. Their data suggest that viral pneumonitis has the most common cause seen in the UK patients and haemorrhagic pneumonitis in Northern America.[62] In addition to direct viral pneumonia, pneumonia caused by co-infection with bacteria can also contribute to a severe, rapidly progressive illness. Bacteria frequently reported include *Streptococcus* and *S. aureus*, including methicillin-resistant strains in some cases. These bacterial co-infections are more frequent than initially recognized. Clinicians therefore need to also consider empirical antimicrobial therapy for community-acquired pneumonia.[82]

The ANZAC study reported 48.8% of those admitted to ICU had ARDS or viral pneumonitis and 20.3% bacterial pneumonia.[74] Early mechanical intubation is recommended, and there is some suggestion that using non-invasive ventilation (NIV) as an interim measure may worsen outcome.[62] Hypoxia may be seen in two settings: patients may have compliant lungs, with the use of high PEEP and high-frequency oscillatory ventilation (HFOV) causing alveolar over distension, worsening oxygenation, and haemodynamic compromise. Other patients have poor lung compliance, and high PEEP and airway pressure release ventilation and HFOV may help.[62]

Much of the data describe a resistant hypoxia with rescue therapies frequently being used. The use of neuromuscular block, inhaled nitric oxide, and prone positioning has been described with uncertain outcome benefits.[80] HFOV has been useful in refractory hypoxia, although the standard HFOV circuits without a viral filter may be an infection hazard.[62]

H1N1 2009 intensive care: extracorporeal membrane oxygenation

Fifteen ICUs in Australia and New Zealand were able to offer extracorporeal membrane oxygenation (ECMO) for the sickest patients with pandemic (H1N1) 2009. This group had a mortality of 21%; however, not all patients who died from H1N1-related illness were offered ECMO. This compares with a mortality of 30–48% for other causes of ARDS receiving ECMO.[75] Although there may be a benefit for those with H1N1-related severe respiratory failure, it is impossible to compare the ECMO group with those receiving conventional ventilation as patients in the ECMO group were not randomized.[80] Recent data suggest that patients who might be considered for ECMO may often survive without it.[57] In many countries including the UK, ECMO is not widely available. Whichever mode of ventilation is used, it is clear that mechanical ventilation may be prolonged. An average of 12 days has been quoted in some studies.[31 50]

H1N1 2009 intensive care: cardiovascular management

Moderate hypotension is often seen which is responsive to fluid therapy and vasopressors. Caution should be exercised with volume expansion as overhydration may worsen outcome.[62] 13.7% of the Canadian patients required vasopressors, compared with 58.6% in Mexico and nine out of the 10 patients in a Michigan case series.[31 50 74] The need for vasopressor therapy was often associated with the requirement for high sedative doses to assist ventilation.

H1N1 2009 intensive care: renal management

Renal impairment is common and 10–50% of patients may require renal replacement therapy. After the initial resuscitation phase, achievement of a negative fluid balance by diuretics or haemofiltration has been shown to improve oxygenation.[62]

H1N1 2009 intensive care: pulmonary embolism

Pulmonary emboli were not noted in patients hospitalized with pandemic (H1N1) 2009 infection in Mexico.[58] A clinical study did not identify any increased risk for pulmonary embolism with seasonal influenza virus infection.[77] However, clinicians caring for patients with pandemic (H1N1) 2009 influenza virus infection should be aware of the potential for critically ill patients to develop pulmonary emboli which can cause severe complications, including fatal outcomes. A group from Michigan looked at a series of 10 patients with confirmed H1N1 influenza

admitted to ICU. Nine of the 10 patients were obese (BMI $\geq$30) and included seven who were morbidly obese (BMI $\geq$40). Five of these patients developed pulmonary emboli.[7]

A more recent study involved a retrospective analysis of imaging results from 66 patients with pandemic (H1N1) 2009.[1] Patients were divided into two groups, 14 who required mechanical ventilation in intensive care and 52 who did not. The first available chest radiographs were abnormal in all 14 patients in the first group and showed extensive bilateral air-space disease, but only in 27% (14 of 52) in the other group. CT scans in 10 of the ventilated patients showed pulmonary emboli in nine of these patients. Two other patients had deep venous thrombosis in the leg veins on indirect CT venography, confirmed on ultrasound.

H1N1 2009 intensive care: corticosteroids

Previous studies have indicated an increased possibility of secondary infections and neuromuscular disorders in patients with ARDS who have received corticosteroids.[46 70] During an outbreak of severe acute respiratory syndrome (SARS) in Hong Kong, steroids were extensively used. This was associated with an increased incidence of methicillin-resistant *S. aureus* (MRSA). It was 3.53% during the pre-SARS period, 25.30% during the SARS period, and 2.21% during the post-SARS period. The rate of ventilator-associated pneumonia due to MRSA during this outbreak was increased to 47%.[96]

Patients with H1N1 who were admitted to an ICU or died were more likely to have received corticosteroids (52%) compared with hospitalized patients who were not admitted to an ICU and survived (31%).[47] Prolonged use of high-dose corticosteroids in patients with pandemic H1N1 may also increase the susceptibility of the patients to opportunistic infections.[83] Corticosteroids may also increase the viral shedding time.[62] Hence, the use of corticosteroids in patients with pandemic (H1N1) 2009 should be restricted to patients with adrenal suppression or specific indications such as treatment of bronchospasm or asthma.

Pandemic (H1N1) 2009: intensive care and triage

It is understood that clinicians have an obligation to provide all reasonable requirements for health care with the resources available. The number of critical care beds required in a pandemic has been estimated using several models. The assumption is that peak demand for critical care beds will significantly exceed capacity.[32] There is a risk that an increase in the virulence of the virus will mean a huge increase in demand for critical care.[33] DOH guidance clearly acknowledges that previous emergency planning advice to achieve a 100% increase beyond normal critical care bed capacity is not likely to meet demand.[37] It is estimated that at the peak of the pandemic, the requirement for mechanical ventilation may exceed available beds 10-fold.[25] When resources are limited, it is ethically reasonable to aim for the maximum benefit for the most people.[2] Applying this principle, critical care services should be used preferentially for patients most likely to benefit. Despite understanding the necessity for triage criteria when resources are scarce to allocate access to critical care, HCWs find the idea morally challenging and legally ambiguous. Withdrawing care from an established critical care patient with uncertain outcome for the benefit of other individuals, so-called 'reverse triage' is particularly testing. Triage may be socially, ethically, and politically difficult to countenance for the population and politicians.

Critical care professionals routinely have to assess very sick patients and decide on withholding critical care admission or treatments and withdrawal of life-sustaining treatments, where it is in the patient's best interest. When faced with intense demand, basic assessment tools to aid this process in a fair manner could offer assistance and reassurance to both professionals and the public. Inclusion criteria for potential survivors should facilitate appropriate and rapid referral. Similarly, exclusion criteria which identify patients unlikely to gain benefit from critical care treatment would assist delivery of appropriate treatment in primary and secondary care settings. Deciding which patients should be in inclusion or exclusion categories should be based on objective evidence to prevent arbitrary admissions and prolonged treatment of patients unlikely to survive.[51]

However, there are no universally agreed procedures to triage and prioritize admission to critical care. The UK pandemic flu surge plan uses a staged triage scheme.[73] This is based on the Canadian expert panel's plan to triage admissions into and out of critical care units. Their plan uses the Sequential Organ Failure Assessment (SOFA) score;[79] combined with a list of inclusion and exclusion criteria for admission to the critical care unit as a triage tool to augment clinical judgement.[15] The scoring is simple, easily reproducible, and based on physiological parameters. It has been validated in a number of different critical illnesses and has good correlation with predicted and observed outcome.[5 38 78] The use of a protocol like this may improve appropriate use of resources and help modify the stress of *ad hoc* clinical resource allocation. The protocol inclusion criteria are based on the need for single organ support (most benefit for respiratory failure) or a SOFA score of 7 or above. The exclusion criteria include a SOFA score of 11 or above (predicted mortality 90%) and severe or advanced disease states that usually preclude admission to an ICU.[68 69 72] The appropriateness of critical care referral is judged on the initial SOFA score. On occasions when the score and clinical

assessment appear conflicting, additional review by an experienced clinician is recommended. The minimum requirement for survival requires reassessment of SOFA scores at 48 and 120 h to determine response to treatment. Those not improving at this point are felt likely to have a poor outcome. A SOFA score of 11 or above at any point after 48 h can also be used as a cut-off and critical care withdrawal considered, so that resources can be redirected to other patients who may have a better response. Concurrent global assessment of the patient by an experienced intensive care clinician should occur; withdrawal based solely on the score achieved is not advocated. Most clinicians would aim to avoid triage by increasing capacity by accepting a decrease in quality of care and an increase in rate of critical care transfers.

Triage decisions should be tiered, adaptable, and implemented across the health economy regionally/nationally and not just institutional. Triage decisions should be supported by public health agencies and have legal indemnity. The decision to triage should be made by two experienced clinicians and carefully documented. Although there may be no ethical difference between withholding and withdrawing treatment, it may be easier not to start a treatment, particularly high-intensity treatments such as renal replacement therapy.

Pandemic (H1N1) 2009 cardiopulmonary resuscitation

During cardiopulmonary resuscitation (CPR), there is the potential for rescuers to be exposed to H1N1 via infectious body fluids and aerosol-generating procedures (e.g. tracheal intubation and ventilation). Resuscitation team members must be trained (including respirator-fit testing) to don and remove PPE safely to avoid self-contamination.[76] Staff looking after patients with a flu-like illness and confirmed cases of H1N1 2009 influenza should have rapid access to the appropriate PPE (e.g. consider keeping PPE on resuscitation trolleys). The minimum PPE requirements to perform CPR are a surgical facemask, plastic apron, and gloves. Listening and feeling for breathing by placing the ear and cheek close to the patient's mouth or mouth-to-mouth ventilation should be avoided. If an FFP3 respirator is not available, then rescuers should wear a surgical mask.[76]

Pandemic (H1N1) 2009: infection control in health-care facilities

Effective infection control is a vital aspect of the overall management of the (H1N1) 2009 pandemic. All those within direct contact or 1 m of the patient are at risk of contamination and transmission.[25] Care must be taken to avoid infected patients coming into contact with non-infected individuals wherever possible. At risk groups are susceptible to serious illness and must be protected wherever possible.

Every HCW can reduce infection spread by adhering to simple procedures. A number of aide memoires have been produced to aid adherence to policies.[86] At a time of increased demand on HCWs, measures must limit their exposure to the virus for the protection of their health and to maximize their effectiveness at work.[18] Vaccines have been offered to all frontline health and social care staff to protect themselves, their families, and patients. Planning and integration of infection control response measures have, generally, been undertaken before the arrival of the H1N1 influenza pandemic.[85] Measures to limit the spread of H1N1 should complement standard infection control procedures already in place.

Infection control guidance had been published in advance to enable health-care providers to formulate an integrated response to the threat of such a pandemic.[18 21 25 34 62 86] These documents offer guidelines on all aspects of infection control from patient triage and isolation to disposal of waste and occupational health considerations.[84] Organizational aspects should be addressed as early as possible. As droplets can spread over 1 m, patients should be nursed at least 1 m apart. Those with confirmed H1N1 should be cohorted together in an isolation unit for 7 days from onset of symptoms.

Pandemic (H1N1) 2009: standard precautions

Meticulous hand washing remains the cornerstone of effective infection control.[21] Effective decontamination of hands must happen after every patient contact or contact with items contaminated with respiratory secretions, even if gloves or other PPE are worn. Hands should be washed with soap and water for 20 s or more or rubbed with alcohol gel, paying close attention to technique to ensure all areas of the hands and forearms are clean. Areas commonly missed are the web spaces and fingertips. Effective hand washing has been shown to reduce the transmission of respiratory infections; however, limited research has been conducted on influenza.[34]

Pandemic (H1N1) 2009: airborne precautions

Patients and HCWs should always adhere to respiratory etiquette. Patients should be encouraged to limit their droplet spread by using and disposing of tissues. Aerosol-generating procedures should be undertaken in a closed single-patient room with adequate ventilation (more than 12 changes per hour) using the minimum number of staff members who should all wear the recommended PPE.[62] Visitors to such patients should be limited to those essential for the patients' well-being. Visitors should be instructed in appropriate hand hygiene techniques and the use of PPE.

For HCWs, tracheal intubation in an uncontrolled setting without PPE should be avoided. NIV is a potentially infectious aerosol-generating procedure and correct PPE should be worn when caring for those patients requiring such a treatment.[24] HFOV circuits can be equipped with viral filters. A scavenger system attached to the exhalation port can help reduce the risk of airborne transmission.

Pandemic (H1N1) 2009: transfers

Transfers of patients within and outside the hospital should be kept to a minimum. However, if essential, the patient should wear a surgical mask for the transfer and care should be taken to decontaminate surfaces where necessary. Strategies should ensure that information is communicated about suspected cases that are transferred to other departments, for example, radiology. If the transferred patient is ventilated, then care should be taken to maintain the integrity of the ventilator circuit.

Pandemic (H1N1) 2009: waste disposal

Lined waste bins with foot-operated lids should be used whenever possible. Waste must be disposed of in the correct manner, all matter potentially contaminated with virus should be disposed of as clinical waste. Efficient environmental cleaning, including the patients' personal equipment, must be undertaken using the recommended detergents.

Pandemic (H1N1) 2009: health-care workers

If an HCW becomes symptomatic with H1N1, then they should stay at home and seek advice from their occupational health departments. The RCGP recommends that symptomatic patients and HCW should stay off work for at least 7 days, regardless of whether they have taken antivirals or not.

Pandemic (H1N1) 2009: personnel protective equipment

During the H1N1 (2009) influenza pandemic, HCWs may be at increased risk of infection. During the SARS outbreak between 19% and 45% of HCWs caring for patients became infected.[94] There were some exceptions, including a Vietnamese hospital, where no HCWs were infected, despite a high national infection rate. This was attributed to the use of PPE.[41]

Pandemic (H1N1) 2009: general personnel protective measures

For most medical staff including those in general practice, surgical masks (which should be water repellent), gloves, and aprons will be sufficient. The aim is to prevent contact with all biological fluids. Aerosol-generating procedures such as intubation, suctioning, bronchoscopy, CPR, surgery, and post-mortem where high speed devices are used are considered infectious.[21] The majority of these interventions will be carried out in critical care. However, the WHO recommends eye protection for nasal swabs and respirators and eye protection for nasopharyngeal or throat swabs.[84] Gloves need to be worn for routine care of infected patients as for standard infection control. If supplies of gloves become depleted, they may be reserved for body fluid contact, invasive procedures, and contact with sterile sites.

The DOH has issued guidance on PPE and when it should be worn.[21] This guidance is summarized in Table 4.

Pandemic (H1N1) 2009: surgical masks and respirators

Facemasks are used to block large droplets. With regard to surgical masks, the DOH recommends they are changed if they become moist and to discard after single use. However, the guidelines go on to suggest that when working in a cohorted area or when attending to multiple patients as in an 'influenza clinic', the mask could be kept on for the duration.[21]

Respirators (usually N95 or higher filtering respirator) are required in certain situations as they are designed to snugly cover the nose and mouth and purify the inspired air by filtering it or providing an independent air supply. Respirators and masks should be individually fit tested to provide the best protection.[67] In the UK, the FFP3 model is recommended.

Table 4 Department of Health. Guidance on PPE. Standard infection control principles apply at all times. Where possible, aerosol-generating procedures (A-GPs) should be performed in closed single-patient areas with minimal staff present. (A-GPs include intubation, tracheal suction, tracheostomy care, chest physiotherapy, bronchoscopy, and CPR.) [†]Gloves and an apron should be worn during certain cleaning procedures (Section 5, *Pandemic Influenza Infection Control Guidance for Critical Care*, available on DH website). [‡]Gloves should be worn in accordance with standard infection control principles. If the glove supplies become limited or come under pressure, this recommendation may need to be relaxed. The glove use should be prioritized for contact with blood and body fluids, invasive procedures, and contact with sterile sites. [¶]Consider a gown in place of an apron if extensive soiling of clothing or contact of skin with blood or other body fluids is anticipated (e.g. during intubation or when caring for infants). [§]If non-fluid-repellent gowns are used, a plastic apron should be worn underneath. [‖]Surgical masks (fluid repellent) are recommended for use at all times in cohorted areas for practical purposes. If mask supplies become limited or come under pressure, then in cohorted areas their use should be limited to close contact with a symptomatic patient (within 1 m)

	Entry to cohorted area, no patient contact	Within 1 m of patient	Aerosol-generating procedure
Hand hygiene	√	√	√
Gloves	X[†]	√[‡]	√
Aprons	X[‡]	√	X
Gown	X	X[¶,§]	√[§]
Surgical mask	√[‖]	√	X
FFP3 respirator	X	X	√
Eye protection	X	Risk assessment	√

Pandemic (H1N1) 2009: PPE stockpiling

The amount and type of PPE required will vary according to the health-care setting. Predicting how much to stockpile has been difficult.

An exercise simulating pandemic conditions on a medical ward in the UK found the WHO estimates for PPE to be inaccurate. Far fewer respirators were used but more gloves and surgical masks than expected.[59]

A Japanese study has attempted to calculate the amount of PPE required. They estimated four sets for each HCW in high-risk areas, and two appropriate sets for HCWs in intermediate- and low-risk areas. All non-medical workers would need at least one surgical mask a day along with patients' visitors. They also recommended that masks were provided for infected patients. This would amount to two per day for inpatients and one per day for outpatients. They recommend maintaining stocks to cover an 8 week period.[42] What is clear is that large amounts of PPE would be required and stockpiles in primary and secondary care may be inadequate.

Conclusion

Guidance from a range of bodies has been produced in a relatively short period of time in response to pandemic influenza (H1N1) 2009. This can be attributed to careful planning for a predicted pandemic and extensive international data sharing. Although there is guidance and information for clinicians regarding the care of patients with H1N1 infection, the pandemic continues to unfold. Disease severity has the potential to change, especially if there is virus mutation. Clinicians must be prepared for the unexpected and continue to share their experiences to maximize patient outcomes.

Note added in proof

A recent Cochrane meta-analysis by Jefferson *et al*. found that neuraminidase inhibitors had no effect against influenza-like illness when used prophylactically and, when used for treatment, they reduced seasonal influenza symptoms by about a day. [Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009; **339**: b5106, doi: 10.1136/bmj.b5106 (Published 8 December 2009)].

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