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Pulmonary Embolism

Includes 1 Pharmacotherapeutic/Pharmacology Hour

Audience
This course is designed for nurses, physicians, and PAs involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

Course Objective
The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.

Learning Objectives
Upon completion of this course, you should be able to:

1. Define a thromboembolic event.
2. Explain pathogenesis, risk factors, and demographics of pulmonary embolism (PE).
3. Review the diagnostic workup of PE.
4. Compare the different types of PE treatments in both inpatient and outpatient settings.

Faculty
Dalia Saha, MD, is a board-certified internal medicine physician with more than 15 years of clinical experience. With experience in both academic and private healthcare settings, Dr. Saha has vast exposure to many aspects of patient care and clinical medicine. Always interested in the didactic component of health care, Dr. Saha works on the education committee for the American College of Physicians and is an instructor and teaching staff for medical students and residents in George Washington University and Johns Hopkins Medical Schools. Lauded by her colleagues for her dedication and work ethic in the field of medicine, she has been awarded the Top Doctor Award in Washington, DC.

Faculty Disclosure
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INTRODUCTION

How are pulmonary emboli categorized?

Pulmonary embolism (PE) is very common in both inpatient and outpatient settings [1; 2]. It should be one of the first considerations when a patient presents with acute-onset dyspnea, shortness of breath, and chest pain. Other common symptoms include cough, hemoptysis, diaphoresis, and feverishness.

A PE is an abrupt occlusion of the pulmonary artery and/or one of its branches. The occlusion may consist of blood clot/thrombus, air, fat, or malignancy/tumor originating in another part of the body, which dislodges and travels through the venous system to the right side of the heart and thence the pulmonary vasculature. In most cases, PE arises from deep vein thrombophlebitis in the lower legs or pelvis, following trauma, surgery, infection, or an acquired hypercoagulable state.

The natural history of PE is variable. PE may be single or multiple (pulmonary emboli), small and clinically silent, large or recurrent with progressive obliteration of the pulmonary vascular bed, causing cardiorespiratory failure. Symptomatic PE is commonly associated with significant morbidity and mortality risk; the challenge for clinical care providers is early recognition and prompt therapeutic intervention to relieve pulmonary artery obstruction and prevent additional pulmonary emboli, any one of which could prove fatal [1; 2]. With modern technology, which can detect small embolic events, the condition is identified much earlier, making possible effective treatment prior to complete hemodynamic collapse [1; 2; 3]. Assessment and prevention in outpatient settings have also led to improvements in mortality. Research indicates that small, subclinical pulmonary emboli probably occur with some frequency but are transient in nature and go unnoticed; however,when there is predisposition to venous stasis (e.g., inflammation, injury, heart failure, coagulopathy), single large or recurrent PE becomes a challenging clinical illness requiring prompt diagnosis and treatment.

Classification of PE typically categorizes the disease as hemodynamically stable or unstable. The most common type is hemodynamically stable, which can range from small, mildly symptomatic or asymptomatic PE (previously referred to as low-risk PE or small PE) to those who present with right ventricular dysfunction but who are hemodynamically stable (previously referred to as submassive or intermediate-risk PE) [3; 4]. While PE characterized by right ventricular dysfunction can be hemodynamically stable, more severe (unstable) disease is characterized by the presence of systemic arterial hypotension, which indicates at least half of the pulmonary vascular tree is affected [4; 5]. Hemodynamically unstable PE (previously referred to as massive or high-risk PE) will result in significant hypotension. Hemodynamic instability is defined as the presence of cardiac arrest requiring resuscitation, or obstructive shock or persistent hypotension not caused by other pathologies [36].

EPIDEMIOLOGY

The annual incidence of PE is difficult to pinpoint but is estimated to be about 60 to 70 cases per 100,000 population [6]. General autopsy studies from all-cause mortality have found PE, variable in number and age, to be present in 30% to 45% of cases [6; 7; 8; 9].

Behind only stroke and coronary artery disease, PE is one of the most common types of cardiovascular disease. It is more common in patients 60 to 70 years of age, with the highest incidence in patients 70 to 80 years of age. Although death following a diagnosis of PE is relatively common, as high as 30%, many of these patients have coexisting serious conditions, such as cancer, recent surgery, or sepsis. The direct mortality associated with undiagnosed/untreated PE during the course of diagnosis and treatment is about 5% to 8%. An estimated 10% of patients with acute PE die suddenly; approximately two-thirds of patients who die from PE do so within two hours of presentation. The mortality rate for those treated for hemodynamically unstable PE is about 20%, and those with cardiogenic shock have a mortality rate of 25% to 30%. Those with a hemodynamically stable PE have a mortality rate of 1% to 25%, depending on the degree of right ventricular dysfunction [2; 4; 5; 10].

PATHOPHYSIOLOGY

What is the most common underlying cause of PE?

Most commonly, a PE occurs when a deep vein thrombus detaches and migrates, or embolizes, into the pulmonary circulation. This can lead to blockage of the pulmonary vasculature, causing a ventilation-perfusion (VQ) mismatch and impairing gas exchange and circulation. PE is more common in the lower lung fields, compared with the upper ones, and both lungs are typically involved. Peripheral PE, as opposed to central PE, can lead to a pulmonary infarction coupled with alveolar hemorrhage. As further obstruction of the pulmonary artery occurs, there is an increase in dead space ventilation and elevation of pulmonary arterial pressure by increasing pulmonary vascular resistance. This further worsens VQ mismatch, with vascular occlusion of the arteries.

Various serum factors are released during a PE formation, including serotonin and thromboxane, which are produced from activated platelets [1; 2; 4]. This induces a cascade of hormonal triggers and related vasoconstriction. Pulmonary arterial pressure increases, which worsens right ventricular afterload and can lead to right ventricular failure and eventually left ventricular system failure. Further clinical progression will lead to a myocardial ischemia due to inadequate coronary circulatory flow, systemic hypotension, and eventual death [1; 4; 5].

DIAGNOSIS

What conditions are included in the differential diagnosis of PE?

A strict (confirmatory) diagnosis of PE would require direct anatomic evidence of pulmonary artery obstruction, which by modern imaging technique (e.g., computed tomography [CT] angiography) would involve invasive measures and exposure to radiation. As the size and distribution (severity) of PE are variable, the preferred strategy for selecting diagnostic testing relies on degree of clinical suspicion, clinical judgment, and assessment of pre-test probability. Selection of noninvasive testing to rule out the diagnosis, based on the assessed clinical probability of PE, has proved effective in reducing the use of CT imaging, thereby minimizing lung and breast-tissue exposure to irradiation [27]. The differential diagnosis includes heart failure, pneumothorax, pneumonia, sepsis, acute chest syndrome, chronic obstructive pulmonary disease (COPD) exacerbation, and anxiety or other psychotropic illnesses. A systematic review and meta-analysis found that a history of sudden dyspnea, syncope, thrombophlebitis, previous deep vein thrombosis, leg swelling, active cancer, or recent surgery was associated with an increased probability of PE [54]. An inability to increase alveolar oxygen pressure (PaO_2) greater than 8.0 kPa (60 mm Hg) despite high-flow oxygen should also raise suspicion for PE.

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A retrospective chart review found that, for non-English-speaking patients suspected of having sustained a PE, the positive diagnostic yield of pulmonary angiogram for those who requested an interpreter (7.37%) was nearly double that of those who did not request an interpreter (3.23%) [49].

DIAGNOSTIC WORKUP

Vital Signs

In initial evaluation, vital signs such as blood pressure, heart rate, and rapid estimation of oxygenation by pulse oximetry are critical to assessing severity of vascular compromise and the stability of the patient. Arterial blood gas (ABG) testing will confirm if a patient has hypoxemia and can be used to obtain the arterial-alveolar gradient to determine if there is a PE or other VQ mismatch [10; 11; 12; 13].

D-dimer Level

Assessment of D-dimer levels can be used for screening purposes and to rule out PE if the pretest probability is intermediate or low. D-dimer is a byproduct of intrinsic fibrinolysis. It is considered to be a highly sensitive test for the absence of PE and has a very high negative predictive value. A normal D-dimer level effectively rules out PE or deep vein thromboembolism. In the event that the d-dimer is elevated, further testing (e.g., computed tomography [CT] angiography, planar VQ scanning) can be performed [10; 14; 15; 16]. Because the test is not specific, an elevated finding is not diagnostic. The specificity of D-dimer decreases with age, and the use of age-adjusted cut-offs is recommended for patients older than 50 years of age. The formula is age (years) x 10 mcg/L for patients older than 50 years of age.

Cardiac Biomarkers

Cardiac biomarker testing may also be useful, particularly as it can identify other diagnoses (e.g., myocardial infarction) [10; 11; 17]. It may help identify signs of right ventricular strain and/or ischemia. An elevated brain natriuretic peptide (BNP) level may indicate right ventricular dysfunction, and higher levels correlate with greater severity of dysfunction.

Various cardiac troponins have also been assessed for diagnostic significance in patients with PE. While these measurements are not diagnostic, elevated troponin is significantly associated with higher mortality in patients with PE [18].

Imaging

Diagnostic imaging is indicated for patients in whom PE cannot be ruled out based on clinical assessment and noninvasive testing. For these patients, CT pulmonary angiography is usually an easily accessible diagnostic imaging modality. It is fast, accurate, and both specific and sensitive. It is also useful for identifying other lung pathology, such as pneumonia and effusions [15; 16]. However, it does require that the patient have good renal function due to the use of iodinated contrast, and it also entails lung and breast-tissue irradiation. Ventilation-perfusion single-photon-emission CT (VQ scan) is a low-radiation option to minimize radiation exposure in younger patients.

Chest x-ray is nonspecific but can help identify pleural effusions and diaphragmatic changes. The classic Westermark sign, which shows a clarified area (loss of vascular markings) distal to a large occluded vessel, and Hampton hump, a dome-shaped, pleural-based opacification, may be present on x-ray. These findings are strongly specific for PE (92% and 82%, respectively) but are not sensitive (14% and 22%, respectively). Chest x-ray can also assist in ruling out pneumonia as part of the differential.

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MODIFIED PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS (PIOPED-II) CRITERIA	
Probability of PE	**Criteria**
High probability	Two or more large mismatched segmental perfusion defects or the arithmetic equivalent of moderate and/or large defects
Normal perfusion or very low probability	No perfusion defects Nonsegmental perfusion defects without other perfusion defects in either lung Perfusion defects smaller than corresponding chest x-ray opacity One to three small subsegmental perfusion defects Two or more matched ventilation and perfusion defects with a regionally normal chest x-ray and some areas of normal perfusion elsewhere Solitary triple-matched defect in a single segment in the middle or upper lung zone Stripe sign Large pleural effusion without other perfusion defects in either lung
Low or intermediate probability	All other findings

Source: [19] *Table 1*

VQ scans visualize areas that are ventilated but not perfused (i.e., VQ mismatch). This testing requires more time, is less specific than CT angiography, and should be done with clinical correlation. However, it is the imaging modality of choice for patients with suspected PE and normal chest x-ray for whom CT angiography is contraindicated, including those with impaired kidney function and pregnant patients. Normal ventilation is 4 L air/minute, and normal perfusion is 5 L blood/minute; thus, a normal VQ ratio is 0.8. A high VQ ratio (>0.8) indicates that the patient's ventilation is exceeding perfusion, while a low VQ ratio indicates a VQ mismatch caused by poor ventilation. When blood is diverted away from the occluded section, overperfusion can occur in the normally ventilated regions. The modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED-II) criteria score the probability of PE based on VQ scan findings (***Table 1***).

Duplex ultrasonography for detection of lower extremity venous thrombi is a useful noninvasive test to assess risk and probability in a patient suspected of having PE. It has both high sensitivity and specificity for thrombus [14; 20; 21; 22]. However, a negative test result does not rule out PE, as the thrombus may have dislodged and embolized prior to the testing.

Electrocardiogram

Electrocardiographic signs of right ventricle strain, such as T wave inversions in V1–V4, QR pattern in V1, the S1Q3T3 pattern, and incomplete or complete right bundle-branch block, are useful but insensitive for the assessment of right ventricle dysfunction in acute PE. However, the presence of right ventricular strain on electrocardiogram has been shown to correlate with the extent of pulmonary vascular obstruction and outcomes of acute PE [10; 11; 12; 14; 17; 24].

Echocardiogram

Echocardiography can demonstrate if there was a clot in the right atrium or ventricle and can also be used to show if there are signs of right ventricular dilatation and hypokinesis [12]. When performed, echocardiography has been shown to reduce other testing and lead to more aggressive early therapy [12; 22].

Pulmonary Arteriography

Pulmonary arteriography is a rare test typically performed only on patients with suspected PE for whom CT and chest x-ray are not feasible. It may also be used with cardiac catheterization to assess patients who have chronic thromboembolic pulmonary hypertension to determine if they are good candidates for pulmonary endarterectomy.

GENETIC TESTING

Factor V Leiden (FVL) and prothrombin (PT) genetic variants are associated with an increased risk of future venous thrombosis or PE. Genetic tests for FVL and PT variants are widely available and commonly used. One current use of these tests is to inform decisions regarding anticoagulant medication in order to decrease the risk of future clots (i.e., secondary prevention). The independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found enough evidence to recommend against routine testing for FVL and PT gene variants in adults who have idiopathic venous thromboembolism, since longer term preventive treatment with anticoagulant medication offers similar benefits to patients whether or not they have these genetic variations. They also recommend against routine testing for adult family members who do not have a history or symptoms of venous thromboembolism, when the testing is conducted to help decide whether to treat them preventively with anticoagulant

medication [50]. However, for patients with venous thromboembolism associated with commonly recognized modifiable risk factors (e.g., contraceptive use, estrogen replacement), genetic testing may help guide preventive treatment decisions.

CLINICAL SCORING SYSTEMS

The Wells criteria (***Table 2***) and the PE Rule-Out Criteria (PERC) assist clinicians with determining clinical probability for PE [14]. One of the important criteria in the determination of PE is if there is a more likely alternate diagnosis, and this is somewhat subjective. If the Wells criteria are used, a score greater than 6 is considered high probability of PE, 2–6 is moderate probability, and less than 2 is low probability. A modification of the Wells criteria simplifies scoring to either likely (>4) or unlikely (≤4).

WELLS CRITERIA	
Clinical Features	**Points**
Clinical symptoms of deep vein thromboembolism	3
Other diagnosis less likely than PE	3
Tachycardia (>100 beats per minute)	1.5
Immobilization for three or more days OR surgery in the past four weeks	1.5
Previous deep vein thromboembolism or PE	1.5
Hemoptysis	1
Malignancy	1
Source: [25]	*Table 2*

The PERC rule was developed for use in emergency care to rule-out PE in patients whose likelihood of PE is low (<15%), so unnecessary diagnostic workups can be avoided. The PERC rule includes [26]:

- Age younger than 50 years
- Heart rate less than 100 beats per minute
- Oxygen saturation of at least 95%
- No prior deep vein thrombosis or PE
- No unilateral leg swelling
- No hormonal estrogen use
- No hemoptysis
- No history of surgery or trauma requiring prior hospitalization in the previous four weeks

If all eight criteria are fulfilled, the patient's risk for PE can be considered sufficiently low and further testing is not necessary [10; 11; 13; 17]. In practice, clinicians tend to overestimate the probability of PE. In cases in which the clinician judges that the patient is very unlikely to have PE but is uncertain whether the estimated likelihood is <15%, the PERC rule or Wells score ≤4 in combination with a normal D-dimer level is reassuring and can be used to safely rule out PE.

TREATMENT

INITIAL MANAGEMENT

The mainstays of initial PE management focus on rapid assessment of clinical severity and stabilization of the patient. As noted, when a patient initially presents, the most critical pieces of information lie in their vital signs (e.g., heart rate, blood pressure, oxygenation). The initial goal for the patient with PE is to maintain oxygen levels. If mechanical circulatory support is required, cardiopulmonary bypass permits right ventricular recovery by decompressing the dilated and dysfunctional ventricle through diversion of the cardiac output to a pump and oxygenator [51]. Alternatively, venoarterial extracorporeal membrane oxygenation (VA-ECMO) functions similarly but is more mobile, allowing for support to be initiated and continued in more diverse settings.

For patients who are hemodynamically unstable, intravenous fluid should be given with caution, because this can lead to right ventricular overload. Hemodynamically stable, low-risk patients should receive anticoagulation alone; those who are at high risk and have hemodynamic compromise may require systemic thrombolysis or surgical- versus catheter-directed therapy. Those who are at intermediate risk have more complicated cases and can be treated with either anticoagulation alone or anticoagulation with potential procedures. As discussed, the risk level will depend on the severity of right ventricular dysfunction on echocardiography, the degree of troponin elevation, the amount of oxygen and vasopressor required, and clot burden and location [10; 11; 12; 13]. The American Society of Hematology (ASH) recommends that patients with PE at low risk for complications be offered home treatment rather than hospital treatment [27].

The therapeutic treatment strategy for patients with a new diagnosis of PE, and venous thromboembolism in general, can be divided into three phases: initial treatment (the first three weeks after diagnosis), primary treatment (three to six months, or longer), and secondary prevention (beginning upon completion of primary therapy and continuing indefinitely) [27]. For primary treatment of patients with PE, whether unprovoked or provoked by a transient or chronic risk factor, the ASH suggests a shorter course of anticoagulation therapy (3 to 6 months) be preferred over a longer course (6 to 12 months). Anticoagulation therapy may be continued indefinitely in select patients for whom the risk for bleeding complications is less than the risk of recurrent PE.

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PRIMARY PHARMACOTHERAPY

In selecting initial pharmacotherapy, European guidelines and a 2022 clinical practice review recommend that treatment be guided by risk stratification of PE as high, intermediate, or low based on the patient's clinical presentation [36; 55]. Approximately 5% of patients present with signs of high-risk PE (e.g., shock, end-organ hypoperfusion/dysfunction, blood pressure <90 mm Hg) not caused by arrhythmia, hypovolemia, or intrinsic heart failure [55]. Intermediate-risk patients are those who present with echocardiographic evidence of right heart strain, elevated cardiac biomarkers, or both; those who are hemodynamically stable with normal cardiac biomarkers and no evidence of right ventricular strain are classified as having low-risk PE. Patients classified as having high-risk PE are candidates for initial reperfusion (thrombolytic) therapy; those with intermediate- and low-risk PE should receive immediate anticoagulation therapy [36; 55]. Treatment should be started promptly whenever PE is strongly suspected and the patient's risk of serious bleeding complications is low. Pharmacotherapy options for initial anticoagulation include intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, subcutaneous fondaparinux, factor Xa inhibitors (e.g., apixaban, rivaroxaban), direct thrombin inhibitors (e.g., dabigatran), and intravenous argatroban for patients with heparin-induced thrombocytopenia.

Thrombolytic Therapy

Patients who present with high-risk PE warrant consideration for immediate reperfusion therapy, there being no contraindications (e.g., brain metastases, bleeding disorders, recent surgery) [36; 55]. Intravenous systemic thrombolysis is a readily available option for reperfusion. Thrombolytic agents act to dissolve the thrombus by converting plasminogen into plasmin. With early thrombus resolution, the elevated pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction improve rapidly. Thrombus resolution within the first 24 hours in particular is much faster in thrombolytic therapy than with heparin [52].

The first recombinant tissue plasminogen activator, and the most commonly used thrombolytic agent used in patients with PE, is alteplase (rtPA); other available agents include streptokinase, urokinase, reteplase, and tenecteplase. The main indication for thrombolysis is high-risk PE with thrombus and hemodynamic instability. rtPA is administered at a rate of 50 mg per hour for two hours; the dose should be reduced for patients with weight less than 65 kg. If streptokinase, is used, a loading dose of 250,000 IU is given, followed by and infusion of 100,000 IU per hour for 24 hours. Urokinase is started with a loading dose of 4,400 IU and an infusion of 4,400 IU/kg/hour for 12 hours [29; 52].

According to the American College of Physicians, catheter-directed thrombolytic therapy can be considered if cardiopulmonary deterioration is imminent [53]. There is some evidence that ultrasound-assisted catheter-directed thrombolysis is superior to heparin anticoagulation alone in improving right ventricular dilatation within 24 hours without major bleeding complications or recurrent embolism. Absolute contraindications to thrombolytic therapy include history of intracranial hemorrhage, known structural cerebral vascular lesion, known malignant intracranial neoplasm, recent history (within past three months) ischemic stroke, active bleeding (excluding menses), and recent history (within past three months) significant closed-head trauma or facial trauma [52; 53].

Oral Anticoagulants

Direct oral anticoagulants (DOACs) (factor Xa inhibitors or direct thrombin inhibitors) are recommended over vitamin K antagonists (e.g., warfarin) for most patients; however, those with renal insufficiency (i.e., creatinine clearance <30 mL/min), moderate-to-severe liver disease, or antiphospholipid syndrome are not good candidates for DOAC therapy [27].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Society of Cardiology (ESC) and European Respiratory Society (ERS) recommends direct oral anticoagulants (DOACs) as first choice anticoagulants over warfarin even in those who are warfarin eligible.

(https://academic.oup.com/eurheartj/article/41/4/543/5556136. Last accessed August 18, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Factor Xa inhibitors such as apixaban and rivaroxaban have the advantage of fixed dosing and no need for monitoring laboratory values, both of which are required of vitamin K antagonists. Rivaroxaban and apixaban do not require any kind of overlap with an intravenous agent. Dose reductions are indicated for those with renal insufficiency. Apixaban can be used in patients with renal insufficiency and is safe for patients on dialysis [2; 28]. Reversal agents are available: idarucizumab for reversal of dabigatran, and andexanet alfa for apixaban and rivaroxaban.

The half-life of factor Xa inhibitors is much shorter than the half-life of warfarin. If bleeding develops and requires reversal, a four-factor prothrombin complex concentrate can be used. Direct thrombin inhibitors such as dabigatran can also be used for treatment for these patients. For those with heparin-induced thrombocytopenia, intravenous argatroban or subcutaneous fondaparinux can be used for anticoagulation. The dosage varies according to agent (***Table 3***).

ORAL ANTICOAGULATION THERAPY	
Agent	**Dosage**
Vitamin K Antagonist	
Warfarin	5 mg once daily for most patients[a]
Direct Thrombin Inhibitor	
Dabigatran etexilate	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to oral 150 mg twice daily.
Factor Xa Inhibitors	
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily
Edoxaban	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to once-daily oral 60 mg for patients >60 kg or 30 mg for patients ≤60 kg.
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg once daily with food
[a]For patients who are expected to be more sensitive to warfarin, a starting dose of 2.5 mg daily is recommended. After three days of treatment, dosage should be adjusted based on INR values.	
Source: [29]	*Table 3*

Drug-drug interactions with DOACs are common and may increase risk of bleeding or thrombosis. Important DOAC interactions are often due to medications that affect cytochrome P450 (CYP450) enzymes or transport proteins or increase bleeding propensity.

Warfarin, which used to be the mainstay of therapy, is no longer considered first choice, as the other DOACs have better safety profiles and patient satisfaction. Bleeding is common with warfarin usage and is more likely to be develop in patients who are older (65 years of age and older) and with comorbidities, such as diabetes, recent myocardial infarction, and other chronic conditions (e.g., kidney disease, stroke). If it develops, bleeding can be reversed with vitamin K at a dose of 2.5–10 mg intravenously or orally. Fresh frozen plasma can also be used with elevated prothrombin complex concentrates [5; 30; 31]. Drug interactions are also a concern with warfarin. Another potential complication is warfarin-induced necrosis, which is more likely to occur in patients with a history of heparin-induced thrombocytopenia. If warfarin is used, the dose should be adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0–3.0).

Heparin

Intravenous unfractionated heparin has a short half-life and can be reversed with protamine [28]. An initial bolus is given followed by an infusion, during which partial thromboplastin time (PTT) values are monitored. The dosage is based on a weight-based protocol. Although relatively safe to use, the pharmacokinetics of this drug are unpredictable, resulting in the need for close clinical monitoring. However, due to its short half-life, it can quickly be reversed, if needed.

Subcutaneous low-molecular-weight heparin has several advantages, including increased bioavailability and more predictable anticoagulation, as opposed to intravenous unfractionated heparin [28; 32]. There is also decreased incidence of bleeding and potentially better outcomes. Low-molecular-weight heparin is given at a dosage of 1 mg/kg body weight. All heparin products include similar bleeding risk profiles as well as a risk for thrombocytopenia, urticaria, and anaphylaxis. For patients with breakthrough deep vein thrombosis and/or PE during therapeutic warfarin treatment, the ASH suggests using low-molecular-weight heparin over DOAC therapy [27].

Fondaparinux

Fondaparinux is a factor Xa antagonist given subcutaneously in the management of acute PE instead of heparin. Advantages include fixed-dose administration once or twice per day, lack of need for clinical monitoring, and lower risk of thrombocytopenia. The dose is 5 mg for patients who weigh less than 50 kg, 7.5 mg for patients weighing 50–100 kg, and 10 mg for those weighing more than 100 kg. The dose should be adjusted in persons with kidney disease. It is contraindicated for patients with a creatinine clearance less than 30 mL/minute. When used for thromboprophylaxis, some experts recommend a 50% dose reduction or use of low-dose heparin instead [29].

SURGICAL MANAGEMENT

Pulmonary embolectomy is indicated for patients that have high- or intermediate-risk PE with contraindications to thrombolysis; failed thrombolysis or catheter-assisted embolectomy; or hemodynamic shock that is likely to cause death before thrombolysis can take effect [52]. Surgical pulmonary embolectomy is a procedure performed on cardiopulmonary bypass through a midline sternotomy, involving either central

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or femoral vessel initiation. Management involves moderate hypothermia for better visualization and protection during moments of reduced cardiopulmonary bypass flows. Aortic cross-clamping and cardioplegic arrest are sometimes unnecessary to prevent negative effects on right ventricular recovery [51]. Dual incisions offer improved visualization and better clot extraction. Various methods, such as suction, retrograde perfusion, manual manipulation, or balloon-tipped catheters, can aid clot extraction, but balloon catheters may lead to increased postprocedural complications [51].

SECONDARY PREVENTION

Maintenance anticoagulation for secondary prevention is done for patients who have extensive clot burden or to reduce the risk of new clot formation. There are multiple pharmacotherapeutic options for this phase of treatment, including factor Xa inhibitors (e.g., apixaban), dabigatran, and aspirin. Warfarin and low-molecular-weight heparin are second-line options.

Factor Xa anticoagulants, such as apixaban and rivaroxaban, are the most common first-line option for secondary prevention. Though warfarin was previously used, research has shown a decreased risk for intracranial hemorrhage with factor Xa anticoagulants compared with warfarin. When used for maintenance therapy, the dosage of apixaban is 2.5 mg twice per day; the dosage of rivaroxaban is 10 mg once per day. Cessation of therapy should be considered again after 6 to 12 months [4; 5].

Those with incidental PE, very small clot burdens, and minimal symptoms should likely be treated in an outpatient setting—unless other risk factors are present. However, patients with hemodynamically unstable PE (e.g., extensive clot burden, low blood pressure, abrupt clinical deterioration) often require an intensive care stay.

Aspirin has also been studied for long-term maintenance therapy and is more effective than placebo. However, anticoagulation is typically preferred over aspirin. When anticoagulation therapy is initiated in patients with PE with stable cardiovascular disease who were previously taking aspirin for cardiovascular risk modification, clinicians should consider suspending the aspirin during anticoagulation therapy. Enoxaparin sodium or low-molecular-weight heparin may be used in high-risk cancer patients with recurrent PE [2; 28].

Duration of Pharmacotherapy for Secondary Prevention

How long should anticoagulation therapy continue in patients who have experienced PE?

As noted, the duration of anticoagulation therapy for secondary prevention is dependent on a variety of factors, such as bleeding risk and risk factors for PE, and can range from three months to lifelong therapy [3; 28; 32]. If the patient experienced PE following a transient risk factor (i.e., a provoked event), such as immobilization or recent surgery or trauma, at least three months of treatment is warranted, after which therapy should be reassessed. However, those who have chronic provoked factors for PE, such as active cancer, a hypercoagulable state, or chronic immobility, may benefit from long-term (indefinite) anticoagulation therapy. When creating the treatment plan, the goal is to weigh the benefits of PE and deep vein thrombosis prevention with the risk of anticoagulation events (e.g., bleeding). Risk factors for bleeding include age 65 years or older, frequent falls, alcohol abuse, renal failure, previous stroke, diabetes, and anemia.

For patients who develop PE provoked by a transient risk factor and who have a history of a previous thrombotic event also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of the primary treatment phase of therapy [27].

PE IN THE OUTPATIENT SETTING

When possible, patients at assessed low risk for complications (i.e., minimal risk of PE-related death) should be discharged from the hospital and continue to receive treatment at home. Such patients are hemodynamically stable, with have no right heart strain and normal cardiac biomarkers. Most patients with low-risk PE can be treated with an oral anticoagulant or a brief period of low-molecular-weight heparin followed by oral therapy. The presence or absence of comorbidities and proper care and anticoagulation therapy, which can be provided on an outpatient basis, should be noted. Scoring systems have been developed to stratify these patients, including the HESTIA rule (***Table 4***), the PE Severity Index (PESI), and its simplified version (sPESI) (***Table 5***) [33; 34; 35].

The PESI scales identify those with a low risk of 30-day mortality [33]. The criteria used include age, sex, history of cancer, history of chronic pulmonary disease, heart rate, systolic blood pressure, and oxygen saturation [33]. The scales relate the risk stratification score to an associated 30-day mortality and risk of death and can assist in identifying patients who may appropriately be managed at home. The patient's social situation, access to supportive care, and ability to transfer to higher level care should all be considered before shifting to outpatient management.

Anticoagulation options to manage confirmed PE in an outpatient setting include subcutaneous low-molecular-weight heparin, fondaparinux, unfractionated heparin, or DOACs [28; 32; 38; 39]. The treatment duration is generally three to six months [38; 39]. Following the initial three-month period, the decision of whether or not to continue treatment will be made based on continued risk of recurrent thromboembolic balanced against the risks of continued anticoagulation [4; 5; 40].

HESTIA EXCLUSION CRITERIA FOR OUTPATIENT TREATMENT	
Criteria	**Points[a]**
Hemodynamically unstable	1
Thrombolysis or embolectomy needed	1
Active bleeding or high risk of bleeding	1
More than 24 hours on supplemental oxygen needed to maintain oxygen saturation >90%	1
PE diagnosed during anticoagulant treatment	1
Severe pain requiring IV pain medication for more than 24 hours	1
Medical or social reason for hospital treatment for more than 24 hours (e.g., infection, malignancy, no support system)	1
Creatinine clearance of <30 mL/min	1
Severe liver impairment	1
Pregnancy	1
History of heparin-induced thrombocytopenia	1
[a]A score of 1 or more is defined as high risk and rules out outpatient treatment.	
Source: [36]	*Table 4*

THE ORIGINAL PULMONARY EMBOLISM SEVERITY INDEX (PESI) AND THE SIMPLIFIED PESI (sPESI) CLINICAL RISK SCORES		
Parameter	**PESI**	**sPESI**
Age	Age in years	1 if older than 80 years
Male sex	10	–
Cancer diagnosis	30	1
Chronic heart failure Chronic pulmonary disease	10 10	1
Pulse ≥110 beats per minute	20	1
Systolic blood pressure <100 mm Hg	30	1
Respiratory rate ≥30 breaths per minute	20	–
Temperature <36°C	20	–
Altered mental status	60	–
Arterial oxyhemoglobin saturation <90%	20	1
Risk Stratification (PESI)		
Class I (≤65 points)	Very low 30-day mortality risk (0% to 1.5%)	
Class II (66–85 points)	Low mortality risk (1.7% to 3.5%)	
Class III (86–105 points)	Moderate mortality risk (3.2% to 7.1%)	
Class IV (106–125 points)	High mortality risk (4% to 11.4%)	
Class V (>125 points)	Very high mortality risk (10% to 24.5%)	
sPESI Score		
0 points	30-day mortality risk 1%	
1 or more points	30-day mortality risk 10.9%	
Source: [37; 56; 57]		*Table 5*

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PE AND COVID-19

Hospitalized patients with advanced COVID-19 may have laboratory signs of a coagulopathy and increased risk for arterial and venous thromboembolic complications, including PE [41; 42; 43]. The pathogenesis is unknown but likely involves some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [43]. The earliest abnormalities are elevated D-dimer levels and mild thrombocytopenia; with disease progression, fibrin degradation products are elevated and prothrombin time becomes prolonged. Laboratory measure of coagulation factors in patients hospitalized with COVID-19 provides a way to track disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, intensive care unit admission, and mortality [43; 44]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis and PE. In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed deep vein thrombosis, despite prophylactic anticoagulation [45]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [46]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [47]. The National Institutes of Health recommends all hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion be evaluated for thromboembolic disease [48].

At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [41]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [43]. The National Institutes of Health recommends that hospitalized, nonpregnant adults with COVID-19 who do not require intensive-level care and have no evidence of venous thromboembolism receive a therapeutic dose of heparin if their D-dimer levels are above the upper normal limit and they require low-flow oxygen, as long as they do not have an increased risk of bleeding [48].

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include [48]:

- Platelet count <50 x 10^9/L
- Hemoglobin <8 g/dL
- Need for dual antiplatelet therapy
- Bleeding within the past 30 days that required an emergency department visit or hospitalization
- History of a bleeding disorder or an inherited or active acquired bleeding disorder

Low-molecular-weight heparin is preferred over unfractionated heparin because of its ease of administration and because low-molecular-weight heparin was the predominant form of heparin used in the clinical trials for COVID-19 [48].

In patients without venous thromboembolism who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to intensive care or discharged from the hospital, whichever comes first. A prophylactic dose of heparin is also recommended for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists [48].

For those patients who develop a PE in the setting of a COVID-19 infection, about 50% will report persistent fatigue, reduced exercise tolerance, and dyspnea [14; 23]. Of these patients, one-half will also have signs of right ventricular dysfunction on echocardiogram after the diagnosis is made, referred to as post-PE syndrome. This further leads to dyspnea on exertion, damage to the venous valves in the leg, prolonged lower extremity swelling and aching, venous ulcers, and impaired quality of life.

CONCLUSION

PE is a common cause of acute-onset breathlessness and chest pain, often confused for many other diagnoses. It should remain on one's clinical differential due to the fact that it can be life-threatening and is treatable if caught and managed early. A variety of treatment options are at the forefront for ensuring that patients are given the best possible outcome.

Customer Information/Evaluation insert located between pages 32–33.

Falls and Fall Prevention

Audience
This course is designed for nurses and other allied professionals involved in the care of patients at risk for falls.

Course Objective
The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to intervene to reduce fall risk in their patients.

Learning Objectives
Upon completion of this course, you should be able to:

1. Discuss the epidemiology of falls and fall injuries.
2. Anticipate types and settings of fall injuries and associated cost reimbursement issues.
3. Assess community-dwelling older adults and hospital inpatients for fall risks, using office-based tools (techniques) to evaluate strength and balance.
4. Recognize the importance and lend support to health system efforts to implement an effective fall prevention program.

Faculty
Mary Franks, MSN, APRN, FNP-C, is a board-certified Family Nurse Practitioner and NetCE Nurse Planner. She works as a Nurse Division Planner for NetCE and a per diem nurse practitioner in urgent care in Central Illinois. Mary graduated with her Associate's degree in nursing from Carl Sandburg College, her BSN from OSF Saint Francis Medical Center College of Nursing in 2013, and her MSN with a focus on nursing education from Chamberlain University in 2017. She received a second master's degree in nursing as a Family Nurse Practitioner from Chamberlain University in 2019. She is an adjunct faculty member for a local university in Central Illinois in the MSN FNP program. Her previous nursing experience includes emergency/trauma nursing, critical care nursing, surgery, pediatrics, and urgent care. As a nurse practitioner, she has practiced as a primary care provider for long-term care facilities and school-based health services. She enjoys caring for minor illnesses and injuries, prevention of disease processes, health, and wellness. In her spare time, she stays busy with her two children and husband, coaching baseball, staying active with her own personal fitness journey, and cooking. She is a member of the American Association of Nurse Practitioners and the Illinois Society of Advanced Practice Nursing, for which she is a member of the bylaws committee.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his postgraduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure
Contributing faculty, Mary Franks, MSN, APRN, FNP-C, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Sharon Cannon, RN, EdD, ANEF

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Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

The ability to remain upright on the varied terrain of the physical world, whether at rest or in motion, depends on the interplay of multiple faculties: awareness, vision, memory, balance, coordination, strength, and agility. These faculties are acquired and honed during youth and undergo an inexorable erosion during old age. Simple maneuvers, once negotiated effortlessly and with little conscious attention, become unpredictable and less reliable as one grows older. Witness an older man hurrying up a flight of stairs. At first nothing appears amiss, when suddenly the toe of his right shoe fails to clear the ledge of the next step and he trips forward in disbelief—this has never happened before. Imperceptible quadriceps atrophy and gradual general deconditioning likely accounts for the failure lifting the advancing foot just far enough to clear the step. Consider an older woman descending the same staircase cautiously, less sure whether she can negotiate every step-down safely, unaware that her hesitancy arises from the subtle changes in vision imposed by cataracts. The strength and agility required to maintain an upright posture while carrying out the usual tasks of work and play dissipate with age. Other factors can also contribute to deficits in the skills necessary to maintain balance and gait, including disorders of the nervous system, infection, muscular weakness/wasting, and intoxication.

Injuries sustained by falling, especially falls among older adults, can lead to immediate and long-term sequelae, including death. Health professionals responsible for hospital and long-term facility care have increasingly worked to develop programs that reduce fall risk among inpatients. Given the growing expansion of the aging population, it is equally important that primary care providers pay close attention to risk assessment and fall prevention among community-dwelling older adults. This course will review the epidemiology and scope of falls and fall-related injuries, available clinical guidance for screening and fall risk assessment, and management strategies for fall prevention in community and healthcare settings, emphasizing the fall burden associated with aging.

EPIDEMIOLOGY

Falls and fall-related injuries are common worldwide and have the heaviest impact in low-income communities and communal settings with a preponderance of older adults. Falls can cause severe injury such as hip fractures and head trauma. Among older adults, injurious falls may heighten the risk for further loss of mobility and early death. The World Health Organization estimates that 37.3 million falls severe enough to require medical attention occur each year and notes that falls are the second leading cause of unintentional injury deaths worldwide, after road traffic injuries [7]. Because the number of falls is so high, the resultant loss of disability-adjusted life years (DALYs) is significant—more lives lived with disability than results from transport injury, drowning, burns, and poisoning combined [7]. Not only is the individual economic burden related to falls and fall injuries increasing, healthcare system costs have skyrocketed. Approximately 40% of the total DALYs lost due to falls globally occurs in children [7].

The Centers for Disease Control and Prevention (CDC) conducts surveillance of falls in the United States, including the incidence rate of reported falls by state. While there is variability in the fall rate per state, those with the highest recorded number of falls among older adults are California, Texas, and Florida [3]. CDC surveillance data indicate that about 30 million falls occur annually across the country, of which 37% require medical attention. Of those individuals needing medical treatment, many also need to restrict their activity for a minimum of one day. These data show that, on average, there are 8 million fall injuries per year in the United States [3].

Falling imposes an economic hardship not only for individual patients but also the healthcare system in general. Approximately 800,000 patients each year are hospitalized because of fall-related injuries. According to National Council on Aging estimates, the 2015 cost of nonfatal falls was documented at $50 billion [4]. The cost related to fall treatment is expected to reach an estimated $101 billion by 2030. Fatal falls incur nearly $754 million in healthcare costs alone [4]. Individual groups at highest risk of falling are those 65 years of age and older, young children, and women; men are at higher risk of death associated with falls [7].

FALLS AMONG OLDER ADULTS

Of falls that result in injury severe enough to require medical attention, what proportion require treatment for fracture?

As noted, falls are a common occurrence in the frail older adult population, causing injuries that may result in disability, institutionalization (e.g., long-term care facility admission), or even death. Older adults are particularly prone to falling because of age-associated, gradual onset of lower body muscle weakness, disturbances of gait, and balance deficits. More than 14 million, or 1 in 4, older adults in the United States report falling every year. About 30% of falls result in injury severe enough to require medical attention; of these, approximately 50% require treatment for bone fracture. The most common skeletal fracture sites are the hip, spine, forearm, leg, pelvis, arm, and hand. Hip fractures from falling occur at the rate of about 1 per 100 falls in older adults, a serious complication that requires hospitalization, surgery, and often results in long-term disability. Even in the absence of injury, many older people who fall then develop a fear of falling, which may prompt additional restriction of physical activity, leading to further loss of physical fitness and agility, thereby increasing the risk of falling.

According to the World Falls Guidelines Task Force, clinicians should routinely ask about falls in their interactions with older adults, as they often will not be spontaneously reported.

(https://academic.oup.com/ageing/article/51/9/afac205/6730755. Last accessed March 26, 2024.)

Strength of Recommendation/Level of Evidence: 1A (Strong recommendation based on high-quality evidence)

In 2020, emergency departments recorded 3 million visits for falls involving older adults; falls among adults older than 65 years of age caused more than 36,000 deaths, making it the leading cause of injury-related death in that age group [3]. Women are statistically more likely to report a fall injury compared with men of the same age. Most falls occur in the home (60%), followed by community public areas (30%) and healthcare settings (10%), such as hospitals and long-term care facilities [13]. Community-dwelling adults 65 years of age or older account for one-third of those who experience falls each year.

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Fall risk increases gradually with aging, associated with onset of chronic diseases and eventually with the aging process itself. The most robust correlation with fall risk is found among those with comorbidities of the central nervous system, heart disease, rheumatoid disease, osteoporosis, and chronic pain [5]. Obesity is observed to convey an increased risk of falls, related to sarcopenia and coinciding with a more sedentary lifestyle as one ages [6]. A systematic review and meta-analysis confirmed that obesity increases the risk of falls and multiple falls in people 60 years of age and older; however, there was insufficient evidence of an association with fall-related injuries or fractures [8]. In fact, data collated from the subset of cohort studies suggested that obese older persons are actually less likely to experience a fall injury or hip fracture.

FALLS AMONG CHILDREN

Among those 19 years of age or younger, falls are the most common cause of nonfatal injuries each year. Children younger than 6 years of age have the highest proportion of visits for falls, with 1.2 million emergency department visits per year [13]. Falls threaten the safety of children, and they are fourth among causes of unintentional death in children and adolescents. There is concern that childhood falls are under-reported events in health institutions [27].

TYPES OF FALLS

What are the three main categories of falls?

Falls are defined by the World Health Organization as "events that result in a person coming to rest inadvertently on the ground, floor, or other lower level" [7]. Falls can be categorized into three types: physiological anticipated, physiological unanticipated, and accidental. It is important that the types of falls and risks of falling, whether living at home or residing in healthcare facilities, are well understood so appropriate fall prevention measures can be undertaken [9]. Fall prevention strategies designed for community-dwelling persons and healthcare facility inpatients and residents will be discussed later in this course.

The category of physiologically anticipated falls includes individuals who are at risk because of age and/or health status, as for example those with altered mental status, high-risk medication (e.g., sedative, epidural post-delivery), and frequent toileting needs (e.g., diarrhea, frequent urination) due to medications or intercurrent illness. Healthcare providers in the ambulatory setting as well as hospital and nursing home staff should be cognizant of individual risk and vigilant for the possibility of falls in this category. At-risk patients should be identified and closely monitored to address risk factors and ensure that preventive measures are in place [9]. Examples of anticipated falls include a patient with Parkinson disease falling from a toilet, a patient with dementia who falls trying to get up from bed, or a patient with a large volume loss having a syncopal episode in the bathroom unattended.

Unanticipated physiologic falls are fall events wherein the individual has no inherent (physiological) risk or reason for anticipating a fall under usual circumstances. In the inpatient/in-residence setting with fall protocols in place, these patients should be documented as low risk for falling [9]. Examples of patients who might experience this category fall event would be a patient who develops stroke symptoms while sitting in a chair, or a patient who has a syncopal episode while straining for a bowel movement in the bathroom. Patients with new-onset seizures would also belong in this type of fall category.

Accidental falls are those caused mainly by slips and trips, but other incidents could occur [9]. As an example, a hospital inpatient trips over the IV tubing or IV pump power cable, or another patient trips over the footrest of a wheelchair. These types of falls are accidental; whether or not they are predictable, thus preventable, depends on considerations of the environment, age, strength, and clinical condition [9].

FALL INJURIES AND REIMBURSEMENT

The Joint Commission (TJC) published a sentinel event alert to assist in preventing falls and fall-related injuries in healthcare settings. A sentinel event is "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof" [10]. Falls resulting in serious injury or death are among the top 10 sentinel events reported to TJC. Of the 465 falls reported to TJC between 2009 and 2015, 63% resulted in death, while the remaining 37% resulted in injuries only [11].

FALL INJURIES

Children between 0 and 5 years of age are learning new skills, such as walking and climbing, which can result in falls from ground level surfaces to several feet, such as off chairs or stairs. Many of these can result in serious injury, including open wounds, fractures, or even severe brain injury [13].

Fractures are a common injury in the older adult population, with approximately 20% sustaining major injuries (e.g., a head injury). Fractures of the hip occur in 1% of all falls in the older adult population [12]. While this is a small percentage, it significantly increases the risk of morbidity and mortality. After 65 years of age, the observed mortality rate within the first year after a hip fracture repair is 15% to 36%. A prospective cohort study of 728 patients who underwent surgery for hip fractures between 2013 and 2015 found that 121 died within one year post-fracture, a mortality rate of 17% [14]. One-year mortality risk following hip fracture was associated with the development of pressure ulcers, inability to recover pre-fracture ambulation, postoperative anemia, and the development of urosepsis [14].

As noted, other common fracture locations that result from falling are the proximal humerus, pelvis, distal radius, and vertebral bodies. Prosthetic fractures, which occur around joint replacement prostheses, have become more common in the older adult population as well [12]. Many require surgical intervention to repair. Femur fractures are common in the older adult population related to falls. The overall functional decline of older adults post-femur fracture is 50% within the first year [12].

Falls are also the leading cause of traumatic brain injury in patients 65 years of age or older. The extent of head injuries resulting from a fall may be inapparent initially; delayed onset of symptoms and altered mentation may emerge over a few days post-fall [12]. Head injuries involving elderly patients warrant a careful history, taking into account the possibility of secondary hemorrhagic complications resulting from prior anticoagulant and antiplatelet drug usage. Subdural hematomas, subarachnoid hemorrhage, skull fractures, and diffuse axonal injury are all potential injuries. Management decisions for head injury should be based on a detailed history of the fall event itself, not just the patient's initial clinical presentation. Falls from different heights influence whether rapid assessment with head computed tomography (CT) imaging (within certain time frames) is advisable, especially if there are suspected open or depressed skull fractures, focal deficits, vomiting, or history of prior anticoagulants or antiplatelet medications [15]. The presence of any of these features warrants specialized care with neurosurgery consultation to ensure proper treatment and care is provided.

FALL INJURY REIMBURSEMENT

Reimbursement to hospitals and long-term care facility for costs related to fall injuries is no longer covered by the Centers for Medicare and Medicaid Services (CMS) as of 2008 [16]. However, CMS does reimburse for fall risk assessments and fall prevention programs. Falls were not originally included in the CMS no-pay policy, and the addition of falls to the policy was originally questioned due to lack of supporting evidence of fall prevention efficacy. However, the decision was made to add falls to the no-pay policy in hopes of increasing research efforts to further prevent falls. The CMS has stated, "...we believe these types of injuries and trauma should not occur in the hospital, and we look forward to...identifying research... that will assist hospitals in following the appropriate steps to prevent these conditions from occurring after admission" [17].

Hospitals and clinics also cannot bill the patient for any services related to a "never event," such as a fall. Any injury costs incurred from a never-event fall (e.g., a humeral fracture) would not be billed to the patient, and the hospital would not receive reimbursement from Medicare regarding these services. They would still, however, receive reimbursement for the treatment received related to the original hospitalizing event (e.g., myocardial infarction) [18].

The National Council on Aging (NCOA) notes that although defined fall risk-related services, such as fall risk assessments, in the clinical setting may be lacking, providers should counsel their patients on potential risks of falling [17]. All healthcare providers can boost reimbursement to the hospital by providing and documenting that approximately 50% of a given daily visit was dedicated to education and or counseling on fall risk. These reimbursements for patient education regarding fall risk also apply to Medicare Annual Wellness visits (initial and subsequent) and general offices for follow-ups or illnesses [17].

FALL RISKS

Which fall risk factors are intrinsic?

Personal fall risks can be organized into two categories: those associated with environmental (extrinsic) hazards and those related to age, general health, and mobility (intrinsic factors). Extrinsic factors include poor lighting, lack of personal ambulation aids (if needed), loose carpets, slippery floors, low objects (e.g., low toilets), steps, cords, or improper footwear. Intrinsic factors are those associated with aging, intoxication, and/or chronic disease, such as weakness, disturbances of gait and balance, declining vision, and medication side effects. Examples of intrinsic factors that lead to an increased risk of falling are gait abnormalities associated with Parkinson or vestibular diseases; bradycardia from beta blockers; drowsiness associated with sedative medication; reduced visual acuity from retinopathy or cataracts; hypotension (postural, medication induced, or hypovolemic); delirium and orthostatic instability related to acute infection and febrile states; and general loss of functional capacity associated with aging [2; 12].

Fall risk assessment and prevention is a matter of increasing concern for hospitals, given that falls among inpatients occur often, particularly in acute care settings [24]. One study demonstrated that the highest incidence of falling was among patients admitted with neurologic diagnoses; the lowest incidence of falls was among those on the surgical service. Important risk factors identified by the study were advanced age, emergency arrival, hospital-to-hospital transfers, and prolonged hospital stay [24]. Fall prevention in hospitals and long-term care facilities has been more difficult following the onset of the COVID-19 pandemic. Since 2020, patient-nurse ratios have increased, along with high turnover rates in organizations. High turnover rates and frequent change of staff have been associated with an increased incidence of adverse events, including increased fall rates, especially in nursing home settings [2]. This scenario is concerning, because staff who are not able to be fully aware of a resident's functional abilities are less apt to intervene with preventive measures or timely assistance [2].

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Situational factors (e.g., activities, habits) can also impact fall risk associated with any setting and type of fall [12]. The likelihood of falling is dependent on a person's strength, agility, and capacity to maintain mobility and an upright posture in response to sudden situational challenges. Unfamiliarity when traversing new terrain or visiting new locations may also increase the risk of falling. Distractions (e.g., walking and talking at the same time), missing a step or curb, or rushing to get from place to place (e.g., the telephone or restroom) increase risk [12]. Fear of repeated falls can cause situational anxiety that also increases risk of another fall. While falls are multifactorial, history of previous falls is the best predictor of the likelihood of future fall events.

FALL RISK SCREENING, ASSESSMENT, AND INTERVENTION

Several approaches to fall prevention have been developed by specialty societies and public health agencies to assist care providers and healthcare systems reduce the likelihood of falls and fall-related injuries. Strategies differ somewhat in reference to the clinical context: those applicable to persons residing in the community and those applicable to patients residing in hospitals and long-term care facilities. However, certain interventions have been identified as useful in all residential settings, whether community or inpatient care facility [12]:

- Safety devices (e.g., grab handles, high friction floors, appropriate footwear)
- Regular exercise, leg muscle strengthening, gait training, and balance exercises
- Medication review and management
- Vitamin D supplementation to improve bone health and muscle strength
- Review of environmental issues, including evaluation of the current living conditions

COMMUNITY FALL PREVENTION PRACTICES

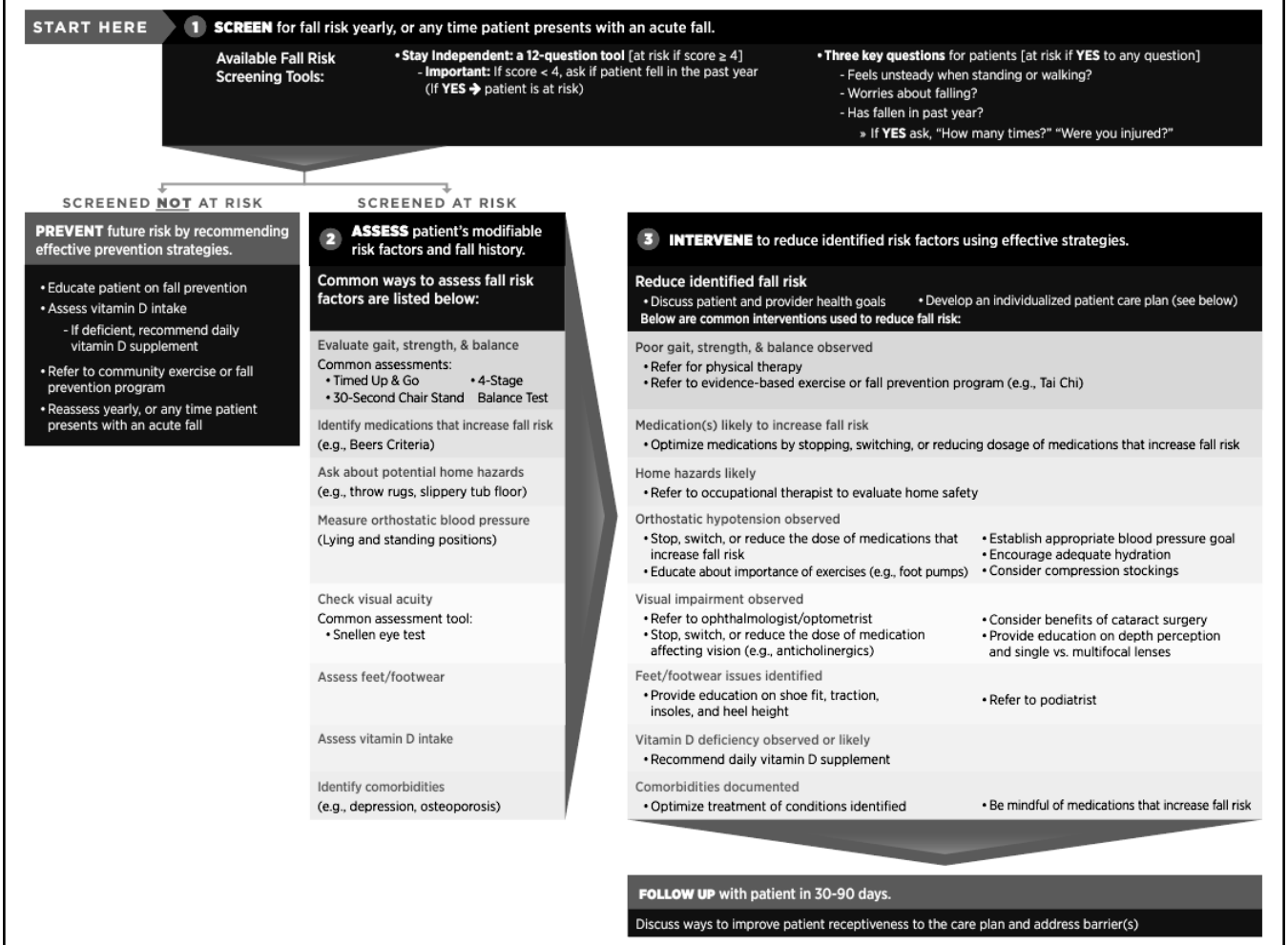
The development of best practices for fall prevention in community-dwelling adults is the purview of primary care providers and centers on preventive care of the older adult patient. Reducing the risk of falls and fall injury in older adults is part of the CDC's Stopping Elderly Accidents, Deaths, & Injuries (SEADI) program [29]. The CDC SEADI program has developed clinical materials and a toolkit (assessment techniques) designed help care providers assess and manage risk in their older patients. Included is a streamlined algorithm for fall risk screening, assessment, and intervention (***Figure 1***). Office-based screening of older patients is recommended yearly, and a brief questionnaire is provided for this purpose. Patients identified as being at increased risk should receive an assessment for prior fall events and modifiable risk factors. SEADI has also developed an assessment protocol designed for evaluating functional strength and balance (e.g., Timed Up and Go Test; 4-Stage Balance Test), reviewing medication side effects, asking about home hazards (e.g., throw rugs, slippery tub floor), measuring orthostatic blood pressure (lying and standing positions), and checking for visual acuity. Specific interventions to reduce fall risk are guided by the results of risk assessment, paying attention to other factors such as footwear (e.g., shoe fit, traction, heel height), likelihood of vitamin D deficiency, and potential impact of comorbidities.

Interventions

Exercise interventions are the cornerstone for fall risk reduction and prevention of fall-related injury in community-dwelling older adults. According to the U.S. Preventive Services Task Force (USPSTF), both supervised individual and group classes are effective when functional training is included [31]. Older adults should set a weekly goal of 150 minutes of moderate-intensity exercise (or 75 minutes of vigorous physical activity) combined with muscle-strengthening activities twice each week. A meta-analysis of 59 randomized trials found that fall prevention exercise programs are beneficial for adults at average or high risk of falls [32]. The rate of falls in this study was 23% lower among participants in an exercise program compared with those in control groups. Exercise programs effective in reducing falls are those that include functional exercises, balance training, and resistance exercises.

Other interventions for reducing fall risk are guided by the patient's individual fall risk assessment. Important considerations include prescription and over-the-counter medications that may result in side effects such as drowsiness, dizziness, and orthostatic hypotension; regular visual acuity testing at 1- to 2-year intervals, in order to update eyeglasses when needed and manage cataracts in a timely fashion; and improving home safety by eliminating tripping hazards, improving lighting, and adding grab bars in the tub or shower. Routine vitamin D and calcium supplementations have not been found effective, nor are they recommended by the USPSTF, for reducing fall risk in older adults without evidence of deficiency [30]. However, in select older women at risk for hip fracture, it may be prudent to consider calcium and vitamin D supplementation, screening for osteoporosis (recommended for all women older than 65 years of age), and weight-bearing exercises.

STEADI ALGORITHM FOR FALL RISK SCREENING, ASSESSMENT, AND INTERVENTION AMONG COMMUNITY-DWELLING ADULTS 65 YEARS AND OLDER



Source: [29] *Figure 1*

The World Falls Guidelines Task Force recommends providing advice on how to maintain safe mobility and optimize physical functioning to older adults at low risk of falls from a clinician trained to do so. Such advice should consider the circumstances, priorities, preferences and resources of the older adult. This advice should reinforce health promotion/prevention messaging relevant to falls and fracture risks such as those on physical activity, lifestyle habits and nutrition including vitamin D intake.

(https://academic.oup.com/ageing/article/51/9/afac205/6730755. Last accessed March 26, 2024.)

Strength of Recommendation/Level of Evidence: E (Expert opinion)

INPATIENT AND RESIDENT FALL PREVENTION PRACTICES

For inpatients or residents, when should fall risk assessment and preventive interventions start?

The Agency for Healthcare Research and Quality (AHRQ) estimates that each year between 700,000 and 1 million people in the United States fall in the hospital [21]. Many of these falls cause fractures, lacerations, or internal bleeding, leading to increased healthcare utilization. Fall prevention involves managing a patient's underlying fall risk factors and optimizing the facility's physical design and environment [21]. The AHRQ has developed hospital training programs, a fall prevention toolkit, and other materials to help inpatient facilities overcome the challenges associated with developing, implementing, and sustaining a fall prevention program [21].

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Fall risk assessment and preventive interventions should start at initial admission to the hospital or long-term care facility. Within hospitals, bed alarms, sitters, and physical restraint orders have been used in the past to reduce the likelihood of patients falling [17]. However, restraints have been noted to pose an increased risk for severe injury (and aspiration) and are used only very rarely. Restraints must have 1:1 observation and a physician order [28]. While employing a bedside sitter seems a reasonable precaution, one study found that evidence is inconclusive whether the presence of a sitter decreases the number of falls [16].

While many precautions are of benefit to all patients in preventing falls, the AHRQ recommends fall prevention measures should be individualized, considering the patient's age, fall history, and risk factors. The goal is to assure patient safety from falls, preventing additional harm during the period of hospitalization. Outpatient clinic administrators and staff can use similar prevention measures to ensure patient safety against falls in the home [21]. Although the following precautions were developed for reducing risk of inpatient falls, they may be applicable to the ambulatory clinic and home environment as well [21]:

- A call light within reach and instruction to the patient on proper use
- Sturdy handrails in restrooms, patient rooms, and hallways
- Hospital or exam tables in the lowest position, with brakes locked
- Wheelchair locks used when inactive
- Appropriate footwear (e.g., nonskid soles, avoiding slippers with open backs or open-toed sandals)
- Appropriate supplemental lighting
- Clean and dry flooring
- Safe handling practices of patients, including assistance with transferring and ambulation

Fall Prevention Programs

Inpatient or resident fall prevention programs have been implemented broadly, often in association with regular exercise routines for residents of long-term care facilities. Hospital interventions have been demonstrated as effective for decreasing fall rates [20]. The AHRQ Fall Prevention in Hospitals training program supports staff in the development and implementation of their own fall prevention programs with standardized tools to prevent falls [21]. The training consists of five modules with various practices, including information on why change is needed and how to manage change, best practices in fall prevention, how to implement the program, and how to measure fall rates [21]. The AHRQ training program also addresses discharge planning, including strategies for fall prevention after discharge of at-risk patients back into the community.

In addition, the CDC STEADI initiative includes a fall prevention toolkit specifically designed for inpatient use. This was developed to help inpatient organizations integrate fall prevention programs into their current practices. The STEADI initiative includes 10 practical steps identified by research findings and provider practices to [22]:

- Reduce patient falls during and after hospital stays
- Foster better partnership with outside providers for post-hospital discharge care
- Upgrade hospital practices and records
- Recognize and appropriately manage medications that place patients at an increased fall risk

The STEADI initiative also outlines suggested tasks for all members of the interprofessional team in support of safe mobility and fall prevention (***Table 1***).

The NCOA has initiatives for fall prevention programs that are geared toward the home settings. This Falls Free Initiative is led by the National Falls Prevention Resource Center. The Falls Free Initiative works with more than 70 organizations nationwide to develop strategies to prevent falls, fall-related injuries, and fall-related deaths. The Falls Free Initiative can be accessed online at https://www.ncoa.org/article/get-the-facts-on-falls-prevention [23].

PEDIATRIC FALL PREVENTION

The Humpty Dumpty Falls Scale (HDFS) serves as an international tool to help assess pediatric fall risk. Developed in Brazil, this tool is used within the inpatient setting with patients birth to 21 years of age. The parameters include age, gender, diagnosis, impairments, environmental factors, response to surgery/anesthesia (if applicable), and medication usage responses are scored on a 1–4 scale. Scores less than 12 indicate low risk, while scores of 12 or greater are considered at high risk for falls. The HDFS is used at admission, daily, and with any changes in level of care [27].

CONCLUSION

Falling is among life's earliest and most common experiences. Is there anyone who has not fallen while learning to walk, or not stumbled when in too much of a hurry? When we are young, like "Jack and Jill (who) went up the hill to fetch a pail of water," falling can be painful but is often of little consequence to life and limb; moreover, falling down teaches resilience and the importance of being careful. Jack and Jill likely jumped up no worse for the wear and later went right back up the hill again. It is worth noting here that these two were out and about, active at play or doing chores. The tale of Jack and Jill connotes youth, energy, exuberance, companionship; their danger of falling came from being too much in a hurry.

SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION PROGRAM TEAM MEMBERS	
Team Member	**Suggested Tasks**
STEADI safe mobility champion (from any profession)	• Proactively encourage early mobilization of patients to reduce fall risks during hospitalization • Work with team to incorporate the safe mobility and fall prevention program into the patient care workflow • Work with available unit-based or hospital educators to establish a training program for current and future employees • Be available to troubleshoot issues during implementation • Provide feedback to team members • Monitor and report results of program implementation • Communicate with hospital leadership about the program • Assign and train staff to discuss fall prevention strategies with patients and caregivers
Nurse and/or certified nursing assistant	• Screen patients for fall risk using a screening tool (e.g., Stay Independent checklist, three key questions, STRATIFY Risk Assessment Tool) • Perform gait testing (e.g., Timed Up and Go Test, 30-Second Chair Stand Test, or 4-Stage Balance Test) • Check orthostatic blood pressure • Educate patients about orthostatic hypotension and related fall risk • Discuss fall prevention strategies with patients and caregivers • Perform vision assessment (e.g., Snellen eye chart) • Counsel about using single distance lenses when walking outside (e.g. avoid bifocals) • Assess feet and footwear • Conduct cognitive assessment (e.g., Mini-Cog) • Ensure each patient has optimal independence in instrumental activities of daily living (IADLs) and activities of daily living (ADLs) during hospital stay • Mobilize patient at least three times a day as tolerated • Give patient appropriate STEADI patient educational materials • Follow up during their hospital stay to ensure patients are making progress as part of fall prevention care plan
Physician, nurse practitioner, physician assistant, clinical nurse specialist	• Take a fall history, including circumstances of previous falls • During physical exam include an observation of gait to identify medical issues that could increase fall risk (e.g., cardiac or neurologic disease) • Review results of fall risk assessments performed by other team members • Avoid prescribing and manage medications that increase fall risk (collaborate with pharmacists) • Order appropriate labs and imaging specific to fall risk • Recommend and provide referrals specific to fall risk • Discuss fall prevention strategies with patients and caregivers • Engage patients and caregivers in developing and implementing individual fall prevention care plans • Avoid issuing bed rest orders or discontinue them as soon as not clinically indicated • Discontinue tethers (IV lines, urinary catheters, etc.) as soon as not clinically indicated • Recommend community exercise or fall prevention programs
Pharmacist	• Review medications to identify those that increase fall risk • Notify safe mobility and fall prevention program team of any medications that might increase fall risk and set up alerts to providers for those medications • Make recommendations for dose reduction or safer alternatives for medications that increase fall risk • Raise awareness about medication-related fall risks • Discuss fall prevention strategies with patients and caregivers

Table 1 continues on next page.

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SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION PROGRAM TEAM MEMBERS *(Continued)*	
Team Member	**Suggested Tasks**
Physical therapist	• Assess or inquire about baseline functional status • Discuss fall prevention strategies with patients and caregivers • Perform detailed gait and balance testing • Design a rehabilitation care plan or exercise program to improve mobility and balance during hospitalization • Educate patients about community-based fall prevention programs, such as tai chi classes or Stepping On
Occupational therapist	• Discuss fall prevention strategies with patients and caregivers • Educate patients about home trip hazards (e.g. throw rugs, stairs) • Recommend fall prevention safety features (e.g., grab bars, lighting, railings) • Educate patients and caregivers about behavioral and functional changes that impact fall risk
Source: [22]	*Table 1*

Humpty Dumpty, on the other hand, tells a more somber tale. He was not out and about at all, just simply sitting on the wall; and when he fell it was a "great fall" (of serious consequence). All the king's horses and all the king's men couldn't put Humpty together again! Perhaps Humpty Dumpty is a nursery rhyme for the aging, a cautionary tale on the importance of staying active and the hidden danger in simply sitting still. Humpty Dumpty can connote age, inactivity, weight gain, solitude, and fragility. Sedentary life has the appearance of safety but the place where one sits is not always safe, and the consequences of falling can be dire.

Falls are common in older adults, and the risk of falling increases with aging. While this course has focused on the older adult population, persons of all ages can be at risk for falls for a variety of reasons. Preventive measures can be used for any adult and all patients with limited mobility. Strategies for effective prevention of falls begin with proper assessment of predisposing factors and comorbidities, focusing on managing extrinsic and intrinsic factors that increase risk. Timely education of patients and families is recommended in the primary and secondary prevention of falls. By striving for the goal of zero falls, healthcare facilities and providers can achieve a significant reduction in number of injuries and loss of life. A given patient's fall risk can be reduced significantly in a single healthcare contact, using a prepared strategy (e.g., STEADI algorithm) to address potential medication side effects and need for vitamin D; home safety review, visual acuity testing, and lower body strength and balance testing; and education and advice regarding regular exercise for maintaining strength and mobility. Select patients benefit from referral to physical and/or occupational therapy for training to improve balance.

RESOURCES

CDC STEADI Initiative

This site provides links to office-based clinical tools and functional assessment instruction, including video demonstration.

https://www.cdc.gov/steadi/materials.html

Algorithm for Fall Risk Screening, Assessment, and Intervention
https://www.cdc.gov/steadi/pdf/STEADI-Algorithm-508.pdf

Timed Up and Go (TUG) Test
https://www.cdc.gov/steadi/pdf/STEADI-Assessment-TUG-508.pdf

4-Stage Balance Test
https://www.cdc.gov/steadi/pdf/STEADI-Assessment-4Stage-508.pdf

National Institute on Aging
This site provides educational and instructive articles for aging adults, including exercises with video instruction for enhancing strength and balance.

https://www.nia.nih.gov/health/exercise-and-physical-activity

Customer Information/Evaluation insert located between pages 32–33.

Influenza: A Comprehensive Review

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed to help healthcare professionals and allied personnel understand influenza and their role in its prevention.

Course Objective

The purpose of this course is to provide healthcare professionals with an updated review of influenza, including clinical aspects, public health issues, and strategies for prevention. The goals are to minimize the burden of influenza on patients and communities, prevent complications and hospitalizations, and save healthcare dollars.

Learning Objectives

Upon completion of this course, you should be able to:

1. Articulate the history and burden of influenza on the community.
2. Explain the types of influenza viruses, including the H and N designations.
3. Describe the symptoms, transmission, and diagnosis of influenza.
4. Distinguish between influenza and influenza-like illnesses.
5. Identify complications of influenza.
6. Articulate the effectiveness and importance of the influenza vaccines.
7. Implement a strategy to increase vaccine administration to vulnerable patients.
8. Describe the best method of hand hygiene and other ways of protecting against influenza.
9. List the current antiviral medications available and their use.
10. Teach family members how to care for people with the flu, including interventions for non-English-proficient patients and caregivers.
11. Identify the significance of avian and swine influenza, particularly issues related to pandemic disease.

Faculty

Elizabeth T. Murane, PHN, BSN, MA, received her Bachelor's degree in nursing from the Frances Payne Bolton School of Nursing, Case Western Reserve University in Cleveland, Ohio and a Master of Arts in Nursing Education from Teachers College, Columbia University, New York, New York.

Her nursing experience includes hospital nursing on pediatric, medical, and surgical units. She lived for 15 years in a village in Eastern Papua New Guinea providing medical and linguistic/literacy services for the villagers. She was a public health nurse for a year with the Brooklyn, New York Health Department and 20 years with the Shasta County Public Health Department in Redding, California. As a public health nursing director, she developed response plans for environmental and health issue disasters for both Shasta County and adjacent Tehama County Public Health Departments.

Faculty Disclosure

Contributing faculty, Elizabeth T. Murane, PHN, BSN, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

In this course, the term "influenza" is defined strictly as an acute viral respiratory illness caused by influenza A or B, occurring in seasonal outbreaks and periodic epidemics and characterized by the abrupt onset of systemic symptoms (e.g., malaise, fever, myalgia, headache) and cough. (Note: This is not to be confused with the gastroenteritis syndrome of nausea, vomiting, and diarrhea often erroneously referred to as "flu" or "stomach flu.") Influenza occurs mainly in winter months (October to March) in temperate climates north of the equator. In the United States, "flu season" usually begins in November, peaks in late December or January, and is generally over by March. However, earlier outbreaks in October can also occur and peak activity may continue as late as mid-March and April. Each summer some localized outbreaks and sporadic cases occur. Often, there is no history of recent travel or epidemiologic links between such outbreaks.

Based on a statistical analysis for the period 2010 to 2016, the incidence of symptomatic influenza among United States residents, including both medically attended and nonattended infections, is approximately 8% and varies from 3% to 11% among seasons [9]. All age groups are susceptible to influenza, but the median incidence among children younger than 18 years of age (9.3%) is somewhat higher than for adults 18 to 64 years of age (8.9%) [9].

Influenza is a disease that is often accepted as "a part of life." While considered bothersome, it is not perceived to be a "serious" clinical or public health issue, in contrast to newly emerging infections that make headlines because of hospitalizations and fatalities. Historically, much effort and money was expended to contain or find a way to prevent new diseases like sudden acute respiratory syndrome (SARS), Ebola virus disease, and Zika virus infection, but little notice was given to the fact that in the United States influenza and pneumonia are leading causes of hospitalization and death each year [1; 2]. While this may still be the case, the emergence of COVID-19 and the resulting coronavirus pandemic significantly changed many aspects of health care and public health. For the purposes of this course, the pandemic's effect on influenza circulation, the surveillance of influenza, and the somewhat renewed interest in influenza as a cause of morbidity and mortality will be discussed. Many individuals now have a greater awareness of the impact of these two viral respiratory illnesses and the measures that can prevent transmission and deaths.

In 2019, pneumonia/influenza was listed as one of the top 10 causes of death in most age groups [7]. As the cause of death, pneumonia/influenza ranked sixth in children 1 to 4 years of age, seventh in children 5 to 9 years of age, eighth in those 10 to 14 years of age, seventh in those 15 to 19 years of age, and seventh in those 85 years of age and older. When all age groupings were combined, pneumonia/influenza ranked ninth as a leading cause of death, between nephritis and intentional self-harm (8th and 10th, respectively) [7]. Influenza was the only communicable disease still listed as a leading cause of death in the United States in 2019.

Rates of serious illness and death from seasonal influenza are higher among those who are 65 years of age and older with medical conditions that place them at increased risk for complications from influenza. Approximately 90% of the annual fatalities resulting from influenza occur in this age group [2; 3]. However, much media attention is directed to fatalities among children. Pediatric deaths increased markedly during the 2009–2010 H1N1 (swine flu) pandemic, with 276 deaths reported [12]. During flu pandemics, the burden of disease has skewed toward younger individuals; in the 2009 H1N1 pandemic, which caused illness in 60 million Americans, 90% of hospitalizations and deaths were in persons younger than 65 years of age [3].

The cost of a flu epidemic is estimated to be $12 billion [3]. The pain and suffering caused by influenza is often not considered when discussing costs [3; 4]. Between 1957 and 1986, 19 different annual influenza epidemics in the United States caused up to 40,000 deaths per year. Direct annual costs for medical care alone were between $1 billion and $3 billion [4]. A study based on 2010 Census data found that the annual economic costs of influenza varied from $13,900 to $957.5 million across U.S. counties, with a median of $2.47 million [5]. It has been estimated that the economic costs of the next influenza pandemic in the United States will be $713 million to $166.5 billion in direct healthcare costs (e.g., outpatient visits, hospitalization) alone [6]. Large amounts of time, energy, and money have been spent to find a vaccine against COVID-19 while the flu vaccine, though not perfect, is markedly underused.

Surveillance conducted by the Centers for Disease Control and Prevention (CDC) of laboratories and outpatient facilities in 2017–2018 showed that influenza activity began to increase in November and remained at high levels for several weeks during January and February [2]. Influenza A (H3N2) viruses predominated through February, and influenza B viruses were more commonly reported starting in March. The burden of illness during the 2017–2018 season was unusually high, with an estimated 48.8 million influenza illnesses, 22.7 million healthcare provider visits, 959,000 hospitalizations, and 79,400 deaths attributed to influenza. The 2018–2019 season had an estimated 29 million flu illnesses, 13 million flu-related medical visits, 380,000 flu-related hospitalizations, and 28,000 flu deaths [2; 191]. More than 48,000 hospitalizations occurred in children; however, 70% of hospitalizations and 90% of deaths occurred in older adults 65 years of age or older.

The precautions taken by much of the public during the first year of the COVID-19 pandemic, including masking and "social distancing," succeeded in reducing coronavirus infections and deaths, and it had the additional effect of drastically reducing circulating influenza, flu infections, and flu deaths [192; 193]. The CDC had so few reported flu hospitalizations that it could not make an accurate account of the 2020–2021 flu season. One comparison that the CDC was able to provide showed that by week 34 of the flu seasons, 2020–2021 had 2,265 (0.15%) flu-positive samples out of 1,480,295 clinical laboratory tests, compared with the 2019–2020 season in which 250,396 (16.8%) samples were positive out of 1,491,430 tests [193]. The cumulative influenza hospitalization rate was 0.8 per 100,000 in 2020–2021, compared with 66.2 per 100,000 in 2019–2020.

The economic burden of influenza on the community, the potential excess mortality among vulnerable members of the population, and the benefit to be derived from simple preventive measures and regular immunization are often under-recognized by the public and medical professionals alike. Vaccination provides protection from influenza illness, its complications, and the spread of infection to others. During the six influenza seasons from 2010–2011 through 2015–2016, influenza vaccination prevented an estimated average 1.6 to 6.7 million illnesses, 790,000 to 3.1 million outpatient medical visits, 39,000 to 87,000 hospitalizations, and 3,000 to 10,000 respiratory and circulatory deaths each season in the United States [8].

Because it takes two weeks to develop the immunity provided by the flu vaccine, most campaigns to immunize the population occur from the middle of October through November.

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However, immunization through December and early January is encouraged for those who have not been vaccinated earlier. Persons of any age with chronic conditions that increase their risk of complications from influenza should be immunized as early as September.

HISTORY

Where do new influenza viruses evolve?

The term "influenza" originated in Italy sometime in the 15th century from an epidemic that was attributed to the "influence of the stars." In 1580, there was a worldwide epidemic that, from written description, was most likely caused by the influenza virus. Several other pandemics have occurred throughout the centuries. The most famous of these pandemics, the "Spanish flu," lasted for 10 months in 1918–1919 and resulted in an estimated 21 million deaths worldwide, with approximately 500,000 of these deaths in the United States [3]. Other more recent influenza pandemics include the "Asian flu" (1957), "Hong Kong flu" (1968), "Swine flu" (1976), and "Swine flu" (2009).

Influenza A and B are the two virus types that cause disease in humans. Influenza A virus was first isolated in 1933 by Smith, Andrews, and Laidlaw in ferrets. In 1936, influenza B virus was isolated by Francis. Swine influenza viruses (closely related to human influenza viruses) were isolated in 1930 [14]. In that same decade, researchers discovered that influenza virus could be grown in embryonated chicken eggs. These discoveries led to the development of inactivated (killed) vaccines [3].

For many years, the proposed influenza epicenter has been thought to be Southeast Asia. Farming practices there bring pigs, fowl, and people into close contact, allowing swine, avian, and human flu viruses to mix. The cycle is thought to be birds to pigs to humans. Now it is clear that this cycle can occur at any place in the world where there is the domestication of animals [14].

INFLUENZA VIRUS

INFLUENZA VIRUS TYPES

Influenza belongs to the orthomyxovirus family and consists of a single-stranded, helically shaped ribonucleic acid (RNA) virus. There are three types of influenza viruses designated A, B, and C. The differentiation is made by the type of proteins within the nucleus, specifically antigenic properties in their internal nucleocapsid and matrix proteins. The individual types have different effects on the humans who become infected.

Influenza type A is the virus that causes moderate-to-severe illness in all age groups and is highly infectious, with an attack rate of 10% to 20%. It also causes influenza in pigs, birds, and other animals. There are several subtypes of influenza A.

Influenza type B generally causes milder disease. It primarily affects children but has also caused outbreaks in military camps and occasionally in long-term care facilities. It does not cause illness in animals and birds and, as a result, tends to be more stable with less antigenic change. Subtypes have not been defined for influenza B.

Influenza type C is rarely ever reported, probably because any disease it causes is usually subclinical or mild. It does not affect animals and birds.

Because type A influenza virus causes more severe illness and also occurs in animal and birds, this course will focus on influenza A.

INFLUENZA A SUBTYPES AND ANTIGENIC SHIFT

What is antigenic shift?

Influenza A subtypes are defined by the occurrence of the glycoproteins hemagglutinin (H) and neuraminidase (N), which are surface antigens on the virus. The hemagglutinins H1, H2, and H3 are involved in attaching the virus to cells. The neuraminidases N1 and N2 facilitate virus penetration into cells. There are 15 different subtypes of hemagglutinins and 9 different subtypes of neuraminidases leading to several possible combinations, which are indicated in the name of the virus (e.g., H1N2, H2N3). Many combinations of the various hemagglutinin and neuraminidase antigen subtypes are possible. However, H1N1, H1N2, H2N2, and H3N2 have historically occurred in humans.

Pigs are susceptible to three of the same subtypes of influenza. Historically, they have not been infected by the H2N2 subtype. Wild waterfowl, in contrast, appear to acquire all influenza A subtypes. An additional difference is that the virus causes respiratory illness in humans, pigs, and other mammals but infects the gastrointestinal tract in wild birds without causing disease. However, the virus is shed in the bird droppings, leading to the contamination of water supplies, barnyards, farms, fields, and animal food supplies.

The genes of influenza viruses are carried on eight separate segments of RNA rather than on one long single molecule. This means that if two or more subtypes of influenza virus infect the same cell in a host, these viruses can exchange RNA segments during replication and create viruses with new gene combinations. This reassortment is termed "antigenic shift." It often occurs in pigs and is the source of influenza epidemics because the human population has little immunity to the new subtype that results.

In comparison, "antigenic drift" refers to changes in the surface glycoproteins. This does not result in a new subtype but does influence the choice of the particular influenza viral subtypes for the annual influenza vaccine. Depending on the degree of antigenic drift, immunity developed to one virus may be adequate to protect against the related virus. In other situations, the drift has resulted in enough change that there is little protection.

In the past, the influenza subtypes present in birds did not directly infect humans. A different host was usually required to complete the shift from an avian subtype to a subtype capable of infecting humans. This host has been the pig, which can be infected with avian, human, and swine influenza viruses. A possible scenario is that the food or water supply of the pig is contaminated by bird feces containing a subtype or subtypes of influenza A. The pig also acquires different influenza subtypes from other pigs and/or humans. Reassortment of the viral RNA occurs in the pig host, thus infecting other pigs. Farm workers catch the new subtype from the pigs and develop highly contagious influenza because they do not have immunity against this new subtype. Thus, a new influenza strain is launched [14]. It is possible that antigenic shift could occur in a person who acquires a strain from a bird and also has a human strain. Realignment of H and N in the person's cells would result in a new strain. This new strain could become a pandemic if there is very little or no immunity in the human population and there is efficient, effective transmission from person to person [3].

Major pandemics of 1889–1891, 1918–1920, 1957–1958, and 1968–1969 have resulted from antigenic shifts. Characteristics of a pandemic are high attack rates in all age groups and a high mortality rate. Historically, pandemics have moved along trade routes, with rapidity of spread matching available transportation methods [3]. Rapid movement of people around the world by aircraft and fewer border restrictions by partners such as the European Union allow new influenza subtypes to spread quickly. However, cooperation among the World Health Organization (WHO), the CDC in the United States, and the European Centre for Disease Prevention and Control, which was established in 2005, has contributed to slowing the spread of the virus. Also, minimizing the transmission of influenza virus from any of the hosts to any of the other hosts (e.g., birds, pigs, humans) will decrease the antigenic shift and lessen the development of new subtypes to which the population has not developed immunity [14].

Research has shown that work-related travel rates affect the spread of influenza more than geographical distance or air travel [15]. Based on 30 years of weekly data, influenza imported into a state with many inflows and outflows of workers, such as California, spreads much faster than if it enters a less-connected state, such as Wyoming. Epidemics also tend to start and spread from more populated states. This information is especially important in the event of the appearance of a new virus to which most of the population is susceptible. It usually takes five to seven weeks for annual influenza disease to spread across the continent. However, if a new strain originates in a highly connected state, it could spread to all states within two to four weeks. The study also revealed that adults, not children, are responsible for the transmission of influenza across regions because they travel farther and more frequently. One proposed intervention is to limit interregional travel to slow the spread [15].

VIRUS NAMING

The name of each influenza virus is developed following this formula [3]:

- Virus type (A or B): A/
- Geographic origin (place where virus was first isolated): Wuhan/
- Strain number: 395/
- Year of isolation: 95/
- Virus subtype (based on combination of hemagglutinin [H] and neuraminidase [N] antigens): (H3N2)

This was the principal virus isolated in the United States during most of the 1997–1998 influenza season.

Thus A/New Caledonia/20/99/(H1N1) would be read influenza A, which was first isolated in New Caledonia, strain number 20, isolated in 1999, with hemagglutinin subtype 1 antigen and neuraminidase subtype 1antigen.

INFLUENZA DISEASE

As discussed, a brief definition for influenza is "respiratory illness with fever." Before COVID-19, this was a quick way for healthcare providers participating in the annual surveillance of influenza activity to categorize each of their patients; now, it is necessary for providers to administer flu and COVID-19 tests to confirm influenza disease. It is, of course, possible to have concurrent flu and COVID-19. Approximately 1,000 sentinel medical practitioners in the United States participate in the U.S. Influenza Sentinel Provider Surveillance System by providing statistics about the number of "respiratory illness with fever" cases that have been seen each week. These figures are collected weekly by designated local health departments and reported to the CDC by the corresponding state health department. The CDC compiles and publishes these figures, which give a current view and contribute to a historical picture of influenza activity for that week. Monitoring and analyzing these figures also alerts medical professionals to changes in patterns. Any change in the historical pattern is especially important in early detection of a biologic change, whether introduced naturally or by terrorist activity. Several biologic agents that could be used by a terrorist first manifest their presence with flu-like symptoms.

SYMPTOMS AND SIGNS

What are the major symptoms of influenza?

As noted, before the emergence of COVID-19, it was relatively easy to diagnose influenza. This is no longer the case, as the viral infections cause similar symptoms [194]. Uncomplicated influenza (and COVID-19) is characterized by an abrupt onset of:

- Constitutional symptoms: Fever, chills, myalgia, headache, severe and persistent malaise, eye pain, light sensitivity, and substernal burning in the chest

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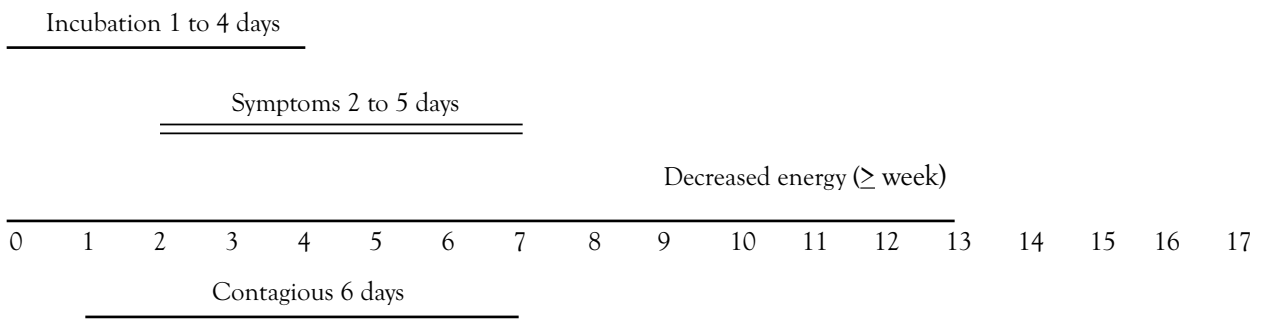
COURSE OF INFLUENZA IN ADULTS



Day 0	Infected
Day 1 to 4	Incubation (average: 2 days)
Day 1 to 6	Contagious (1 day before symptoms to 5 days after symptom onset)
Day 2 to 9	Symptomatic (usual: 2 to 5 days)
Day 4 to ?	Decreased energy (1 or more weeks)

Source: Author *Figure 1*

- Respiratory symptoms: Nonproductive cough, shortness of breath, sore throat, and rhinitis

Initially, there are more constitutional than respiratory symptoms. If there are no complications, the chest is usually clear to auscultation.

Children may also experience any of the accompanying effects of fever, such as listlessness, irritability, anorexia, and convulsions. In addition, otitis media, nausea, vomiting, and diarrhea are frequently reported in children with influenza [8]. Pneumonia and encephalopathy are serious complications in children with influenza [17]. Elderly patients may exhibit confusion in addition to other symptoms.

The patient with influenza usually appears febrile and fatigued with hot, moist skin, a flushed face, and red watery eyes. More than half of patients infected with the influenza virus will have nasal discharge with obstruction and pharyngeal redness. Younger patients may have nontender cervical lymphadenopathy [18].

Influenza onset is so abrupt that many patients can pinpoint the hour in which they became ill. This is an important feature that helps distinguish influenza from other diseases with flu-like symptoms. The fever is generally 101 to 102 degrees F (38.3 to 39 degrees C). Children may run higher fevers. Patients may complain of body aches. Myalgia often localizes in the back muscles. These systemic symptoms usually last from two to three days and may persist as long as five days. Most systemic symptoms respond to antipyretics and analgesics. It is important to remember that any medications containing aspirin should never be used in children or teenagers because of the risk of Reye syndrome [3]. This will be discussed in more detail later in this course.

Uncomplicated influenza is generally a self-limiting illness. Fever, myalgia, and respiratory symptoms usually resolve in five to seven days, but most patients experience some degree of malaise and fatigue for a week or more after resolution of acute symptoms (***Figure 1***).

TRANSMISSION

Influenza is highly contagious, with an attack rate of 10% to 20% from the day before symptoms begin through approximately five days after onset in adults. It is spread from person to person through coughing and sneezing by the infected individual. Influenza is spread by the airborne route, which means that a person coughing in the room can transmit the virus to others in the room without close personal contact. This is in contrast to droplet transmission in which heavier particles (droplets) are transmitted to those with close contact (less than 3–6 feet, depending on the organism). Droplet transmission also probably occurs in influenza. Airborne transmission is especially significant in congregate situations like institutions, daycare facilities, airplanes, and cruise ships [19].

As noted, the influenza virus may be transmitted between humans and pigs. More than 25 examples of transmission from pigs to humans have been documented in the medical literature [14]. It is assumed that many more undocumented cases occur in individuals who work with swine. Usually, this swine-human connection is missed because the flu seasons in both pigs and people overlap. However, this connection should not be minimized. Its influence in antigenic drift or shift and the introduction of new subtypes is important to traditional transmission patterns.

Contaminated hands are a frequent source of transmission and infection. Contagious individuals cough or sneeze into their hands and deposit virus on whatever they touch. Or, they cough or sneeze the virus into the air, which settles on objects in the area. Others handle these objects and then touch their eyes, nose, or mouth and are infected. Following an incubation period of one to four days (average: two days), the individual develops symptoms. Another major factor in the spread of influenza is that it is transmitted to others before infected individuals even realize that they are sick [20].

Children are another source of infection, as they can be contagious for 10 or more days. In addition, young children can shed virus for up to six days before illness onset [16]. This is one reason to discourage the practice of kissing infants and children on the mouth.

DIAGNOSTIC TESTS FOR INFLUENZA

Obviously, an accurate diagnosis of influenza on the basis of symptoms alone is difficult. The quickest way to decide if the patient has influenza, COVID-19, or some other disease, is to use rapid diagnostic tests for influenza and COVID-19. However, medical practitioners should be aware that false-negative and false-positive results do occur. All patients with flu-like symptoms should now be administered rapid diagnostic tests to identify influenza and/or COVID-19 infection(s) [194].

Within three to four days after onset of influenza, the virus can be found from throat and/or nasopharyngeal swabs. Highest viral shedding occurs during the first four days of illness. Nasopharyngeal specimens generally are more accurate. There are several rapid diagnostic tests available, and these tests usually require only about 15 minutes of laboratory time [22; 23]. The specimen to collect and the information provided by the results vary according to the test being used. These various rapid diagnostic tests for influenza A are 65% to 95% accurate [21]. The accuracy rate depends on the particular rapid diagnostic test used and collection of the specimen at the optimum time [22]. Other factors that may improve the accuracy of these tests include knowledge that influenza is circulating in the community and obtaining the specimen from a patient within the first four days of illness [23]. The package insert should always be consulted as to the percentage of inaccurate results for the specific test. The rapid diagnostic test, therefore, can leave the medical practitioner with the need to base decisions about diagnosis and treatment on his or her clinical judgment [22]. Recent immunization with intramuscular (IM) influenza vaccine will not affect a rapid diagnostic test. Intranasal vaccine will affect any serology test [24]. In an institutional setting, such as a nursing home, use of a rapid test combined with a viral culture will help provide more effective treatment and allow for rapid prevention and control measures [21].

The Advisory Committee on Immunization Practices recommends clinicians should use rapid molecular assays (i.e., nucleic acid amplification tests) over rapid influenza diagnostic tests in outpatients to improve detection of influenza virus infection.

(https://academic.oup.com/cid/article/68/6/e1/5251935. Last accessed May 7, 2024.)

Level of Evidence: A-II (Good evidence to support a recommendation based on one or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time-series; or from dramatic results from uncontrolled experiments)

Culture of the virus takes a minimum of 48 hours. Another one to two days are needed to identify the virus type. Viral culture can take as long as 10 days to complete. Obviously, these tests provide information as to the virus responsible for the illness but are not practical for individual case management. Knowing the virus or viruses responsible, however, allows more accurate planning for vaccine preparations. This information also helps evaluate the effectiveness of the formulation used in the current vaccine [3].

There are several ways that the influenza diagnosis can be confirmed [23; 25]:

- Rapid test
- Viral culture
- Direct or indirect immunofluorescent antibody staining
- Reverse transcriptase polymerase chain reaction
- Immunohistochemical analysis of tissues collected during autopsy
- Paired serology (comparison of antibody levels during acute and convalescent—two to three weeks later—phases). Antibodies in the convalescent specimen should be at least four times greater than in the acute specimen to confirm influenza.

For more information on available tests, please refer to the CDC's website at https://www.cdc.gov/flu/professionals/diagnosis. Monitoring the status of influenza circulating in the community through the information provided by the CDC can also assist the practitioner in the diagnosis [23].

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INFLUENZA COMPARED TO COMMON COLD		
Clinical Presentation	**Influenza**	**Common Cold**
Prodrome	None	One or more days
Onset	Sudden	Gradual
Fever	101 to 102 degrees F	Rare in adults
Headache	May be severe	Rare
Myalgia	Usual, often severe	Mild
Extreme exhaustion	Usual	Never
Tiredness/weakness	May last longer than two weeks	Mild
Sore throat	Common	Often
Sneezing	Occasionally	Usual
Rhinitis	Occasionally	Usual
Cough	Usual, nonproductive	Mild hacking

Source: Author *Table 1*

INFLUENZA-LIKE ILLNESSES

Making the correct diagnosis when a patient presents with flu-like symptoms has become more critical in the wake of the COVID-19 pandemic. As discussed, COVID-19 cannot be reliably differentiated from influenza based on symptoms or history alone [194]. The purpose of the discussion below is to highlight the importance of making a careful observation of the patient and obtaining an accurate history of the illness.

INFLUENZA COMPARED TO THE COMMON COLD

How do the symptoms of influenza and the common cold differ?

Because both influenza and the common cold are caused by viruses that affect the respiratory tract, distinguishing between them is important. Adults rarely develop fever with a cold (coryza) but usually have a fever of 101 to 102 degrees F (38.3 to 39 degrees C) with the flu. Headaches, muscle aches, and extreme exhaustion are mild or nonexistent with a cold but are usual and severe with the flu. The prodromal signs of sneezing, runny nose, and sore throat signal that a cold is developing and may be present for one or more days before onset. These symptoms may occur with influenza but usually occur concurrently with the sudden onset rather than signaling an approaching illness. The flu develops suddenly, without warning. Like influenza, a cold may have a dry (nonproductive) cough. Some use a simple rule to distinguish between a cold, in which symptoms are from the neck up, and influenza, which is systemic (***Table 1***).

OTHER FLU-LIKE ILLNESSES

There are many other illnesses that initially look like influenza. For discussion and consideration in making a diagnosis, these diseases are sometimes grouped into influenza-like illnesses (ILI). Adults will average one to three ILI a year. Children can average three to six ILI in a year. The common cold is one of these, and the differences between influenza and colds have been discussed above. Other bacteria that cause ILI are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, and *Legionella pneumophila*. In addition, respiratory syncytial virus (RSV) has similar symptoms. None of these ILIs are as significant as biologic agents that may be used by a terrorist, such as anthrax, ricin, plague, and smallpox, all of which may present with influenza-like symptoms. However, they are a significant source of disease and should be considered when deciding if a patient has influenza or something else. Because bacterial diseases are treatable with antibiotics, but influenza is not, an accurate diagnosis is important. Much of the overuse of antibiotics occurs when patients request them for any illness or when careful diagnosis is not made between viral and bacterial diseases.

It may be helpful to consider the time of year in which the diagnosis is being made. Generally, pneumococcal disease peaks in the winter, as does influenza and RSV. Mycoplasma and legionellosis are more common during the summer and fall. Rhinoviruses and parainfluenza virus peak during the fall and spring. Adenoviruses circulate throughout the year [21]. COVID-19 has had severe winter peaks but has been unpredictable thus far, with lesser peaks several times each year, corresponding with the emergence and spread of new variants [47]. Information on the presence of influenza and predominant strains in the community can usually be found from the surveillance system maintained by the local health department [16].

Other information to consider is that, in healthy individuals, influenza is a self-limiting disease that strikes suddenly with most of its fury, maintains that level of illness for three to five days, and then shows improvement, even though the aftereffects of weakness and tiredness may persist for a week or more. In most other ILI diseases the patient's condition continues to worsen.

These last two considerations are not meant to figure in the diagnosis but to guide thinking about the patient's illness. For instance, if a greater than usual number of cases of ILI are being seen and it is the wrong time of year for influenza, another disease or a terrorist attack should be considered.

COMPLICATIONS OF INFLUENZA

What are the most common complications of influenza infection?

Complications of influenza leading to hospitalizations and death are greater in persons 50 years of age and older, in young children, in pregnant women in the second and third trimester, and in persons of any age with underlying medical conditions. Data for the 2017–2018 influenza season show that laboratory-confirmed influenza virus infection was responsible for 183 deaths in children younger than 18 years of age [2]. Since becoming a nationally notifiable condition in 2004–2005, the number of annual pediatric deaths has ranged from 37 to 171, excluding the 2009–2010 H1N1 epidemic, which will be discussed later in this course.

PNEUMONIA

The major complication of influenza is pneumonia, and three types have been well-described in association with influenza epidemics: primary influenza (viral) pneumonia, secondary bacterial pneumonia, and mixed influenza/bacterial pneumonia. The incidence and mortality are highest in the elderly and in persons with underlying chronic illness, especially those with heart, lung, and renal diseases. However, in pandemic periods, half the deaths from pneumonia are seen in persons younger than 65 years of age [18].

Primary influenza pneumonia is the least common but most devastating form. It arises when the virus directly invades lung parenchyma and tends to present early as a rapidly deteriorating illness with high fever, profound dyspnea, and progressive respiratory failure. Patients with conditions that cause elevated left atrial pressures, such as heart failure and third-trimester pregnancy, are particularly at risk. Chest radiographs show bilateral diffuse reticulonodular opacities and basal (lower lobe) consolidation. Mortality is high.

Secondary bacterial pneumonia is the most common type and constitutes the major cause of excess morbidity and mortality in the elderly. The typical clinical presentation is a patient who appears to be convalescing from influenza only to experience an exacerbation of symptoms with renewed fever, worsening cough, purulent sputum, pleuritic chest pain, and radiographic evidence of a localized pulmonary infiltrate. The pathogens most often responsible are *Streptococcus pneumoniae* (50%), *Staphylococcus aureus* (20%), and *Haemophilus influenzae*. A number of factors affecting lung defense mechanisms are at play in the pathogenesis of bacterial superinfection, including [18]:

- The prime target cell for influenza virus in humans is the ciliated epithelial cell of the tracheobronchial tree.
- Damage to this epithelium leads to impaired mucociliary clearance of any potential pathogens that happen to be colonizing the upper respiratory tract.
- Alveolar macrophage phagocytosis is transiently impaired.

As might be expected, mixed influenza/bacterial pneumonia is a third type encountered during influenza outbreaks. This type of patient is vulnerable to severe, direct infection of the lung and happens, at the same time, to be colonized by a virulent respiratory bacterial pathogen (e.g., pneumococcus or staphylococcus).

Signs that a patient has developed pneumonia are [18]:

- Symptoms continue after the expected five to seven days
- Symptoms worsen after the patient has started to improve
- Fever returns and is higher than with the initial illness
- Dyspnea
- Productive cough
- Abnormal x-ray (pulmonary infiltrates)
- Rales on auscultation

REYE SYNDROME

An unfortunate complication of influenza in patients younger than 18 years of age is Reye syndrome. Much education for parents has focused on the danger of giving aspirin to anyone younger than 18 years of age with a fever. This education has led to a decrease in Reye syndrome. Unfortunately, acetylsalicylic acid or salicylic acid is a component in some over-the-counter preparations and may be unintentionally given to a child with a fever. Influenza virus, especially influenza A virus, and varicella (chicken pox) interact with acetylsalicylic acid to produce Reye syndrome. Symptoms are nausea and vomiting, decreased consciousness and/or convulsions caused by cerebral edema, hypoglycemia, and liver failure. Parents must be reminded to read the labels of all medications and that aspirin is listed as acetylsalicylic acid [18].

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MYOSITIS AND RHABDOMYOLYSIS

Myositis (inflammation of muscle tissue) and rhabdomyolysis (involving striated muscle tissue) can be complications of influenza. These complications occur most often in children and are manifested by extreme muscle tenderness, especially in the legs. Myoglobulinuria may lead to renal failure in these patients. Serum creatinine phosphokinase (CPK) is markedly increased [18].

STAPHYLOCOCCUS AUREUS SUPERINFECTION

Influenza can be complicated by *Staphylococcus aureus*, leading to pneumonia as discussed above. Superinfection with *S. aureus*, leading to bacteremia, endocarditis, or epidural abscess, can also occur following influenza. Influenza B and *S. aureus* have led to toxic shock.

CARDIAC COMPLICATIONS

Other less common complications from influenza are myocarditis (inflammation of the cardiac tissues), and pericarditis (inflammation of the pericardial lining). A study conducted in Australia from 2008 to 2010 showed that recent influenza vaccination was significantly protective against acute myocardial infarction [26].

PULMONARY COMPLICATIONS

Besides the more common complication of bacterial or viral pneumonia, influenza can lead to the worsening of chronic bronchitis and other chronic pulmonary diseases.

CENTRAL NERVOUS SYSTEM COMPLICATIONS

Encephalitis, postencephalitic Parkinson disease, transverse myelitis, Guillain-Barré syndrome (GBS), and possibly amyotrophic lateral sclerosis have followed cases of influenza. There has been research suggesting that cases of Parkinson disease resulted from the "Spanish flu" pandemic of 1918–1919 [55; 56; 57; 58; 59; 60].

Any person with a serious medical condition can be placed in jeopardy by influenza, not only from the complications listed above, but also from exacerbation of the underlying condition [18].

INFLUENZA VACCINE

Who should receive annual influenza vaccination?

Influenza vaccine is the primary preventive measure against the virus. It is efficacious in preventing influenza. Among those at higher risk, it lessens the severity of the illness, decreases complications, reduces hospitalizations, and lowers the fatality rate. It is disappointing that a vaccine with such benefits and few side effects is not used more widely. With a highly communicable disease like influenza, children are the most likely to contract and spread the infection. Nearly all children must be immune to achieve community (herd) immunity [4]. The Advisory Committee on Immunization Practices (ACIP) recommends routine annual influenza vaccination for all persons 6 months of age and older who do not have contraindications [8]. A licensed, recommended, and age-appropriate vaccine should be used.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Centers for Disease Control and Prevention asserts that routine annual influenza vaccination is recommended for all persons 6 months of age and older. (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm. Last accessed May 7, 2024.)

Level of Evidence: Consensus Statement and/or Expert Opinion

The timing of vaccination is predicated on timing of onset of the influenza season balanced against concerns that vaccine-induced immunity might wane over the course of a season. The 2023–2024 recommendation is that vaccination begin to be offered in September and October [8]. Children 6 months through 8 years of age who require two doses should receive their first dose as soon as possible after the vaccine becomes available. This approach is based on clinical trials that suggest protection from the influenza viruses covered by the vaccine lasts six to eight months and may last up to one year in college students. Because those 50 years of age and older have a diminished response to the vaccine, the immunity probably does not last as long [8].

HIGH-DOSE INFLUENZA VACCINE

A vaccine containing an increased amount of the hemagglutinin antigen of the influenza virus was licensed by the U.S. Food and Drug Administration (FDA) in 2009 [4]. In 2021, the trivalent version was replaced with a quadrivalent formulation [8]. It is a single-dose, inactivated, quadrivalent, injectable vaccine sold under the brand name Fluzone High-Dose, manufactured by Sanofi-Pasteur. This high-dose vaccine was developed for individuals 65 years of age and older who are at a greater risk of hospitalization and death from seasonal flu and are known to develop lower antibody titers to the influenza virus. The vaccine is available for the 2023–2024 flu season [8].

Prelicensure clinical trials showed no preference for the new vaccine over other inactivated trivalent influenza vaccines. All were equally safe and equally effective at producing immunity [4]. However, the high-dose formulation resulted in significantly higher hemagglutination inhibition titers against each strain than the standard formulation [8]. A 2014 trial showed that recipients had 25% greater protection against influenza illness. A comparison between the standard and high-dose flu vaccines showed that in each 0.5-mL dose the standard vaccine contained 45 mcg while the high-dose vaccine had 180 mcg [8].

As with the standard vaccine, the high-dose should not be given to anyone with a known severe reaction to egg proteins or other components of the vaccine. Vaccination with the high-dose formulation produced more frequent injection site reactions and systemic adverse events than the standard formulation, but typically they were mild and transient [4; 8].

HIGH-RISK GROUPS WHO SHOULD RECEIVE THE INFLUENZA VACCINE

In the event of a vaccine shortage, the following high-risk groups should receive the vaccination first.

Persons 50 years of age and older have the highest fatality and hospitalization rate from influenza and its complications. Of the annual deaths from influenza, 90% occur in those 65 years of age and older. In addition, 58% of the hospitalizations are in this age bracket [2]. Those who are between 50 and 64 years of age are high risk because of the high prevalence of chronic diseases in this population. These patients often do not receive the vaccine because the publicity about the need to receive the vaccine has tended to focus on those 65 years of age and older. Only 48.1% of persons 50 to 64 years of age receive the vaccination; the vaccination rate among persons 65 years of age and older is 69.1% [183]. In addition, Medicare pays for the vaccine after the person reaches 65 years of age. Therefore, individuals who fall into the 50 to 64 age group may be disinclined to receive the vaccine.

Persons with chronic health problems who are 6 months of age or older are at high risk for complications from influenza or exacerbation of their condition. Such chronic conditions include:

- Cardiac disease, such as congestive heart failure
- Pulmonary disease, such as chronic obstructive pulmonary disease, cystic fibrosis, or asthma
- Renal disease
- Diabetes and other metabolic diseases
- Hepatic disorders
- Neurologic disorders
- Anemia and blood disorders, such as sickle cell disease

Persons with compromised immune systems from any cause—human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), autoimmune conditions, cancer, long-term steroid treatment, and medications—should receive the inactivated vaccine [8]. Because the vaccine is inactivated (killed), it can and should be given to immunosuppressed people. However, because of the depressed immune system of this group of people, the expected antibody response may not be obtained. HIV-infected patients with minimal AIDS-related symptoms and high CD4 T-lymphocyte cell counts have been shown to develop substantial antibody titers against influenza. For those with more advanced HIV disease and low CD4 T-cell counts, the vaccine might not induce protective antibody titers, and a second dose has not been shown to increase the titer. Some studies have shown that there is a temporary (two- to four-week) increase in replication of HIV after receiving the influenza vaccine [62]. However, other studies have not demonstrated this increase nor has progression of HIV disease been shown to occur following the administration of the influenza vaccine. Each immunocompromised individual should be evaluated before the vaccine is administered because an increase in plasma HIV levels and/or a decrease in CD4 count has been transient in most, but not all, cases of those receiving the influenza vaccine [62].

Persons with conditions or diseases that may compromise respiratory function or increase the risk of aspiration should also be vaccinated against influenza to prevent any possible complications or damage.

All healthcare providers should receive the influenza vaccine annually. Additionally, healthcare facilities are encouraged to make available the vaccine to their workers. In its 2012 recommendations, the ACIP encouraged healthcare facilities to obtain a signed declination form from healthcare workers who refuse influenza vaccination [63]. Those who refuse vaccination may be required to wear a mask during influenza season. This issue is not specifically discussed in the 2023–2024 recommendations [8].

Persons who reside in skilled nursing facilities (nursing homes) or other chronic care facilities are at high risk for influenza-related problems because of their weakened physical state and close living arrangements.

Persons 6 months to 18 years of age on long-term aspirin therapy should be immunized against influenza because of the interaction of the influenza virus and aspirin that can lead to Reye syndrome.

Women who are pregnant during influenza season have the same complication and hospitalization rate from influenza as persons with chronic diseases and, therefore, should receive the vaccine. This would include women who will deliver from the beginning of October through the end of May. Increased severity of influenza among pregnant women was reported during the pandemics of 1918–1919, 1957–1958, and 2009–2010 [8]. Severe infections among postpartum women also were observed in the 2009–2010 pandemic, and 56 deaths (36 during the third trimester) were reported among 280 pregnant women admitted to intensive care units. Although there are some recommendations that a woman should not receive the influenza vaccine before the 14th week of gestation, the ACIP and the American Congress of Obstetricians and Gynecologists (ACOG) recommend influenza vaccination for all women who are or will be pregnant during the influenza season, regardless of trimester [8; 64]. There is a coincidental association of spontaneous abortion, which is common in the first trimester. Also, many practitioners avoid any exposure to vaccines during the first trimester. However, no adverse fetal

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effects have been associated with influenza immunization [8; 65]. Infants born to women who contracted the 1918 flu during their second and third trimesters had higher rates of cardiovascular disease at 60 to 82 years of age [66]. For men this rate of increase was 23.1%; for women, it was 17%. In addition, individuals exposed prenatally were less successful economically and educationally. Studies of other influenza pandemics have shown schizophrenia risk is three times higher in those exposed to influenza in utero [66]. This information should help healthcare workers to recognize the importance of immunizing pregnant women.

Persons aged ≥6 months with egg allergy should receive influenza vaccine. Any influenza vaccine (egg-based or nonegg-based) that is otherwise appropriate for the recipient's age and health status can be used [8]. It is no longer recommended that persons who have had an allergic reaction to egg involving symptoms other than urticaria should be vaccinated in an inpatient or outpatient medical setting supervised by a healthcare provider who is able to recognize and manage severe allergic reactions if an egg-based vaccine is used. Egg allergy alone necessitates no additional safety measures for influenza vaccination beyond those recommended for any recipient of any vaccine, regardless of severity of previous reaction to egg. All vaccines should be administered in settings in which personnel and equipment needed for rapid recognition and treatment of acute hypersensitivity reactions are available.

Of note, severe allergic reactions after administration of the egg-free vaccine RIV to egg-allergic persons have been noted in VAERS reports [185]. These reports highlight both the possibility that observed reactions after egg-based influenza vaccines might be caused by substances other than egg proteins and the importance of being prepared to recognize and manage serious hypersensitivity reactions when administering any vaccine to any recipient (regardless of allergy history) [8].

All children 6 to 59 months of age, especially children 6 to 23 months of age, even without any chronic conditions, should receive the annual influenza immunization because they are at a substantially increased risk for influenza-related hospitalizations [8]. Many of the hospitalizations are due to dehydration that can occur rapidly in a child who has a fever and will not drink fluids. The hospitalization rate in this age group matches the hospitalization rate for other groups at high risk for complications and death from influenza. At this point, these higher hospitalization rates cannot be totally assigned to influenza because RSV circulates at the same time. Since 2003, the Vaccines for Children (VFC) program has covered the cost of the influenza vaccine for all eligible children 6 to 23 months of age and all eligible children 2 to 18 years of age who are household contacts of a child 0 to 23 months of age [16]. The ACIP, the American Academy of Pediatrics, the ACOG, and the American Academy of Family Physicians (AAFP) published the Recommended Immunization Schedule for Persons Age 0 Through 18 Years, which includes a recommended yearly influenza immunization for all children 6 months of age and older [8; 67]. Data from two studies showed that a side benefit from the influenza vaccine has been a reduction in otitis media [8].

Other groups who should receive vaccine during a shortage include American Indians/Alaskan Natives; the morbidly obese (body mass index ≥40); household contacts/caregivers of children younger than 6 months of age for whom there is no vaccine; and persons with medial conditions that put them at higher risk for severe complications from influenza [8].

Before 2004, influenza-related deaths in children were not on the list of deaths that should be reported. When it became apparent that a significant number of children were dying, the CDC requested that all influenza-related deaths of children younger than 18 years of age be reported to the appropriate state health department. Any postmortem tissue specimens that were collected or autopsy reports that were completed were also asked to be sent to the CDC [25]. However, in the subsequent years there have been even more deaths of children. As noted, in the 2017–2018 flu season, there were 183 deaths among persons younger than 18 years of age [2]. During the 2009 H1N1 pandemic, 32% of hospitalizations and 10% of deaths (approximately 1,250 deaths) were children younger than 18 years of age [68].

OTHER GROUPS ADVISED TO RECEIVE THE INFLUENZA VACCINE

Persons who provide essential services, such as law enforcement personnel and firefighters, should be immunized. This is especially important in a pandemic situation. Students living in dormitories should receive the vaccine in order to avoid disruption of their studies.

Travelers should be evaluated for influenza immunization when "travel shots" are being recommended. Influenza in temperate climates occurs in the winter months (October through March in the Northern hemisphere; April through September in the Southern hemisphere); it occurs year-round in tropical climates. People taking a cruise could be infected with influenza at any time of the year because many of the service crew members are from tropical areas and a cruise ship is a closed community, which helps to assist in the spread of the virus [65].

The need for healthcare workers to be immunized against influenza cannot be overemphasized. All healthcare workers should receive the influenza vaccine. Not only does it protect the patient, but it also protects the healthcare worker. Healthcare workers who have been immunized tend to remember to advise their patients to get the immunization. This can strengthen the advice by example and can also provide anecdotal reassurance about the pain or side effects experienced. Studies have shown that residents in long-term care facilities have fewer deaths from influenza when their caregivers have been immunized against influenza [16].

GROUPS WHO SHOULD NOT RECEIVE THE INFLUENZA VACCINE

Persons with acute respiratory or other active infections or illnesses should be advised to wait until they have recovered to receive the vaccine [8].

Persons with a history of GBS are more prone to another episode of this syndrome [8]. Because GBS is such a rare condition, it is impossible to know if the influenza vaccine is involved in its occurrence. During the 1976 swine flu epidemic, there was an increase of GBS (1 additional case per 100,000 vaccinated) in those who had received the vaccine [8]. However, an increased incidence of GBS following administration of other influenza vaccine formulations since 1976 is extremely low (1 additional case per 1 million vaccinated). According to the package insert for Fluzone, for patients who have recovered from GBS, it is better to err on the side of caution and avoid giving them the influenza vaccine until more information is available [65]. *The Epidemiology and Prevention of Vaccine-Preventable Diseases*, known as the "Pink Book," states that persons who have developed GBS within six weeks of receiving the influenza vaccine would be wise to avoid a subsequent flu shot [3; 8]. However, the recommendation of the ACIP is that recovered GBS persons with risk factors that increase their vulnerability to the complications of influenza should receive the vaccine because the risk of complications is greater than the risk of a recurrence of GBS [8].

Persons with an allergic reaction to dry natural latex rubber should be evaluated before being given the vaccine because the stopper in some of the vials contains dry natural latex rubber [8]. According to data provided to CDC, Fluvirin and Fluad (manufactured by Seqirus) are the only vials that are expected to possibly contain latex.

Note: Influenza immunization is NOT contraindicated in breastfeeding persons. In fact, it should be encouraged because the patient could transmit influenza to a vulnerable infant if she gets the disease [8]. The patient could also be liable to a decreased milk supply because of decreased fluid intake and fever and would have the added burden of infant care and breastfeeding while experiencing exhaustion and other flu symptoms.

MANUFACTURE OF THE VACCINE

Because of antigenic drift, each year the ACIP and the FDA must decide which influenza strains to include in the formulation of the season's vaccine. Because the formulation changes each year to provide protection against the expected circulating strains, an annual influenza immunization is needed. Obviously, the point is to include the strains that will be expected to spread globally. There are two type A strains included in the trivalent formulations, because type A influenza strains are usually those that lead to more complications, hospitalizations, and deaths. The third strain included is always a type B; the quadrivalent formulation includes a second type B strain. In the 2003–2004 influenza season, the expected dominant strain killed the embryonated egg where the virus was grown due to the virulence of the strain [17]. A virus that was close to the expected circulating strain was chosen instead. However, the match was not close enough to the circulating strain for the vaccine to be as effective as it usually is. To the credit of the ACIP, this was only the second mismatch in 15 years [74; 75]. In some cases, antibodies produced against one strain can overcome another strain, but the strains must be closely related. Antibodies produced by the strains in the 2003–2004 formulation were not close enough to the dominant circulating strain to destroy it, so people who had received the vaccine still developed influenza. In fact, the choice of which strains to include is based on the current knowledge as to which will be the most virulent strains in circulation. Due to the fact that there are only three strains in the vaccine and there are multiple influenza strains, people who are vaccinated can still develop illness from a strain of influenza virus that was not included in the vaccine.

Another extremely significant factor in the choice of a strain is the ability to grow the strain so that the vaccine can be produced in millions of doses. When vaccine distribution is delayed, it is often due to the fact that one particular strain would not reproduce well or quickly enough. As noted, some strains kill the culture medium.

Production of influenza vaccine involves the following steps [65]:

1. The chosen strains of influenza virus are incubated in fertilized chicken eggs.
2. Fluids containing the virus are harvested.
3. The virus is inactivated (killed) by formaldehyde.
4. The virus is concentrated.
5. The virus is chemically disrupted to produce a "split virus." (All influenza vaccine used in the United States is split virus.)
6. Further purification of the virus by chemical means is done.
7. The virus is suspended in sodium phosphate-buffered isotonic sodium chloride solution.
8. No antibiotics are used in the preparation of influenza vaccine.

Thimerosal is a preservative used in multi-dose vials to inhibit bacterial growth that might occur because of multiple introductions of needles to withdraw individual doses. It is a compound containing 49.6% mercury. Because of the allegation that thimerosal is connected to conditions such as autism and the fact that there have been warnings to avoid fish that has a high mercury content, thimerosal has been removed from most childhood vaccines. Vaccines without thimerosal are packaged in single-dose vials. However, thimerosal is still used in multi-dose vials (5-mL dose vials) [8]. There are 25 mcg of mercury in

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each 0.5-mL dose of multi-dose vaccine. One should note that there have been no studies proving any link between mercury poisoning and autism. Thimerosal is made from ethyl mercury, which is different from methyl mercury, the compound named in the government warning about consumption of or exposure to mercury [74]. More influenza vaccine without thimerosal has been made each year and should be used for those who have a severe allergic reaction to thimerosal. At least 91% of the 170 million doses of vaccine available for the 2023–2024 flu season will be thimerosal-free or thimerosal-reduced [76].

These production methods have been used for decades and do not apply some of the modern technology available in the production of vaccines against other organisms, such as hepatitis A or hepatitis B. As noted, most influenza vaccine is incubated in fertilized chicken eggs. It takes one egg to produce one dose. More than 80 million doses are made for annual distribution in the United States alone. The number of chickens and eggs needed for this production is almost beyond comprehension. Also sobering is the thought of what would happen if one or more of the major flocks used for producing the eggs for the vaccine became infected with an avian influenza, which would require destruction of the flock(s).

Another issue involved is the amount of time required to produce the annual influenza vaccine—about six to eight months. Any new strain of influenza could circulate around the world much faster than the vaccine could be produced, resulting in a pandemic. Experimentation is being conducted on faster ways to produce the vaccine. Some companies are experimenting with caterpillar cells to incubate the virus. Experiments have indicated that the vaccine can be produced more quickly and that it would be available to protect people against emerging strains. Phase I trials indicated that the vaccine incubated in caterpillar cells is safe. In a clinical trial of 400 elderly people, the vaccine stimulated the production of nearly twice the number of antibodies as the vaccine produced using eggs. In addition, there were no adverse effects. Phase II trials in 400 elderly participants showed that 97% of them developed antibodies if the highest dose of the vaccine was used [77; 78].

Another approach being explored in influenza vaccine production is to genetically engineer cells to replicate continuously. Such a process would lead to faster production and a more consistent vaccine [79]. One example of this is the Flublok vaccine, which uses protein-producing machines to make hundreds of copies of hemagglutinin, the small piece of the influenza virus needed for immunity [80]. Flublok is available for the 2023–2024 influenza season.

Other experimentation is being done using DNA-based approaches to develop a broadly protective vaccine that utilizes influenza virus proteins from multiple strains. Several companies are working to develop new ways to grow the antigens that cause the immune system to fight infection [79; 81].

Using the reverse genetics method, in which genomes of the influenza viruses are manipulated in order to transfer genes between viral strains, seed viruses for vaccine manufacture can be rapidly generated. In addition, highly pathogenic influenza viruses can be altered so that they are safer for vaccine manufacturers to handle [81].

Another method of vaccine development, cell culture, has been well tolerated and has successfully led to antibody development in trials. Some research has shown that vaccines developed based on cell culture have been efficacious against all strains of influenza A, including H5N1 [81]. Using cell-based vaccines creates a more consistent manufacturing process and could reduce production time to 9 to 12 weeks. Although there are some side effects from cell-based vaccines, including headaches and injection site reactions, they appear to have a similar tolerability profile to egg-based vaccines [27].

In another area, one small study has been conducted that indicates that mild exercise before having a flu shot may make the vaccine more effective. Lifting weights before a flu shot increased antibody response in women but reduced the response in men. However, the cell-mediated response in men was increased by weight lifting. The researchers suggest that exercise increases the number of immune cells in muscle tissues, which in turn increases activity in the lymph nodes and creates a more efficient immune response [29; 30].

HANDLING AND STORAGE OF THE VACCINE

The following information pertains to the egg-based vaccine in use. As is the case for all vaccines, the package insert should be consulted for proper handling and storage in order to preserve its effectiveness. Influenza vaccine should be stored at a temperature of 36 to 46 degrees F (2 to 8 degrees C) [8]. It should be transported in insulated containers with cold packs; however, it should not be directly in contact with the cold packs nor should it be placed anywhere in a refrigerator where it can be frozen. Freezing destroys the effectiveness of influenza vaccine. The vaccine can tolerate being out of the refrigerator while an influenza clinic is being prepared or conducted. However, only enough vaccine for the first half hour should be taken from the refrigerator at a time. When immunizing individual patients in an office setting, the vaccine vial should be returned to the refrigerator as soon as the dose has been withdrawn.

It is important that the temperature of the vaccine storage refrigerator be checked and recorded each morning before starting to dispense immunizations and each evening before leaving for the day. Older refrigerators can develop cold spots where items can freeze, or they may not maintain a constant temperature. All inactivated vaccines, like influenza vaccine, are destroyed by freezing. Large bottles of water should be kept in the refrigerator at all times to help maintain an even temperature and to preserve cold longer in case of a power outage. Some live vaccines, such as chickenpox and oral polio (no longer used in the United States), must be kept frozen. Vaccine should never be stored on the shelves in the door as the temperature there is erratic.

VACCINE PREVENTION OF SEASONAL INFLUENZA, 2023–2024

Each year the CDC and the ACIP provide updated recommendations for the prevention and control of seasonal influenza [8]. A variety of vaccines are available for the 2023–2024 flu season. These include standard-dose inactivated vaccines, high-dose inactivated vaccines, and recombinant and live attenuated vaccine, all of which are quadrivalent formulations. U.S.-licensed influenza vaccines for the 2023–2024 season contain hemagglutinin derived from an influenza A/Victoria/4897/2022 (H1N1)pdm09-like virus (for egg-based vaccines) or an influenza A/Wisconsin/67/2022 (H1N1) pdm09-like virus (for cell culture-based and recombinant vaccines); an influenza A/Darwin/9/2021 (H3N2)-like virus (for egg-based vaccines) or an influenza A/Darwin/6/2021 (H3N2)-like virus (for cell culture-based and recombinant vaccines); an influenza B/Austria/1359417/2021 (Victoria lineage)-like virus; and an influenza B/Phuket/3073/2013 (Yamagata lineage)-like virus [8]..

In 2022–2023 , the age indication for Flucelvax Quadrivalent was expanded from 2 years of age or older to 6 months of age or older [8]. The approved dose volume is 0.5 mL per dose for all patients.

Various influenza vaccines have been licensed and approved for the 2023–2024 season. More than one type or brand might be appropriate within approved indications and ACIP recommendations. Current prescribing information should be consulted for authoritative, up-to-date information. Children younger than 18 years of age should not receive Flublok (IM) or Afluria administered with a jet injector [8]. The following inactivated or recombinant influenza vaccines (all quadrivalent) are expected to be available for the 2023–2024 influenza season: Fluad, Fluarix, Flublok, Fluzone High-Dose, Fluzone, Flucelvax, and Afluria; the live, attenuated vaccine FluMist will also be available (***Table 2***).

Monitoring the 2010 influenza season in Australia produced data indicating that Afluria (marketed as Fluvax in the Southern Hemisphere) was associated with increased frequency of fever and febrile seizures in children 6 months through 4 years of age when compared to previous years [33]. Generally, the fever occurs 4 to 24 hours after the vaccine is given [33]. It would be prudent to instruct the parents or caregivers of these children to monitor the child's temperature and give nonaspirin fever-reducing medication as needed. In some public health immunization clinics, parents are instructed to give a dose of a fever-reducing medication to the child as soon as they get home, as a preventive measure. In a 2009 clinical trial in the United States, increased fever was noted among recipients of Afluria 6 months through 8 years of age. For the 2010–2011 influenza season, the U.S. Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink reviewed adverse event reports carefully for febrile seizures in children younger than 9 years of age [33].

ADMINISTERING THE VACCINE

The influenza vaccine discussed in this section is for IM use only; the intranasal and intradermal preparations are discussed later in the course. The IM vaccine is for all people 6 months of age or older. In order to assure that the vaccine is given IM, it is necessary to use needles of the proper length. Vaccine that is administered subcutaneously because of improper technique or a needle that is too short is ineffective.

The recommended site for adults and for children 3 years of age and older is the deltoid muscle [8]. A 1-inch needle will reach the deltoid in most children and adults. Some patients with large arms will need a 1.5-inch needle. One should be careful to make sure that the patient's sleeve can go high enough so that the needle can be inserted in the middle of the arm, about 1.5 inches below the top of the shoulder. Usually the firmness of the deltoid can be felt in that area. In patients who are very thin, it is wise to squeeze the deltoid between the thumb and finger to avoid hitting the bone. Administration of the vaccine distal in the deltoid is more painful. The posterior portion of the arm should not be used.

In children younger than 3 years of age, the deltoid is usually not big enough to receive the vaccine. The vastus lateralis muscle should be used [8]. This is the muscle on the outer aspect of the child's thigh and can usually be palpated. At times, when the infant kicks, the outline of the muscle can be seen. Two key elements to administering an injection to a child are to have the child properly and quickly restrained. An assistant, either the parent or a helper, should position the child so that the leg or arm where the injection will be given will not move. The upper body, the leg not being used for the shot, and the foot of the leg being used should be held tightly by the parent. Young children 3 years of age and older should sit sideways on the parent's lap so that the child's legs can be clamped between the parent's knees. The arm that will not be used for the injection should go around the parent's waist and be clamped under the parent's arm. The hand of the arm being used for the injection should be held by the parent. The person giving the vaccination should have all injections prepared so that they can be administered quickly. It is also good to distract the older child by having them blow, count, or see how loudly they can say "ouch."

Children should receive split-virus vaccine. This is not an issue in the United States as all vaccines are split-virus. Because some influenza vaccine comes in multidose vials, a small amount of thimerosal is in the vaccine [8]. For parents who are unwilling to accept the studies showing no connection between thimerosal and autism or other negative health effects, several thimerosal-free preparations are available [8; 65].

FluMist, Fluarix, Flulaval (single-dose), Fluzone (single-dose), and Flublok do not contain thimerosal. There are additional vaccines in use with reduced or no thimerosal. Information on the amount of thimerosal present in each vaccine dose is available on the CDC website [8].

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INFLUENZA VACCINES—UNITED STATES, 2023–2024 INFLUENZA SEASON				
Trade Name	**Supplied As**	**Age Indication**	**Route**	**Mercury (from Thimerosal)**
IIV4 (Standard dose, egg-based)				
Afluria Quadrivalent	0.25-mL prefilled syringe	6 through 35 months	IM	–
	0.5-mL prefilled syringe	≥3 years		–
	5.0-mL multidose vial	≥6 months (needle/syringe) 18 through 64 years (jet injector)		24.5 mcg/0.5mL
Fluarix Quadrivalent	0.5-mL prefilled syringe	≥6 months	IM	–
FluLaval Quadrivalent	0.5-mL prefilled syringe	≥6 months	IM	–
Fluzone Quadrivalent	0.5-mL prefilled syringe	≥6 months	IM	–
	0.5-mL single-dose vial	≥6 months		–
	5.0-mL multidose vial	≥6 months		25 mcg/0.5mL
ccIIV4 (Standard dose, cell culture-based)				
Flucelvax Quadrivalent	0.5-mL prefilled syringe	≥2 years	IM	–
	5.0-mL multidose vial	≥2 years		25 mcg/0.5mL
HD-IIV4 (High dose, egg-based)				
Fluzone High-Dose Quadrivalent	0.7-mL prefilled syringe	≥65 years	IM	–
aIIV4 (Standard dose, egg-based with MF59 adjuvant)				
Fluad Quadrivalent	0.5-mL prefilled syringe	≥65 years	IM	–
RIV4 (Recombinant HA)				
Flublok Quadrivalent	0.5-mL prefilled syringe	≥18 years	IM	–
LAIV4 (Egg-based)				
FluMist Quadrivalent	0.2-mL prefilled single-use intranasal sprayer	2 through 49 years	Nasal	–

Source: [8] *Table 2*

Children younger than 9 years of age receiving influenza vaccine for the first time should receive two doses, one month apart. The dose for a child is age-related [35]. Children from 6 to 35 months of age should be given 0.25 mL administered IM with a 1-inch needle in the outer aspect of the thigh. If it is the first time the child has received a flu shot, a second 0.25 mL dose IM should be given one month later [35]. In subsequent years, the child will receive only one influenza vaccine each year. Children 3 years of age and older should be given 0.5 mL IM using a 1-inch needle in the deltoid. Children who are 3 to 8 years of age receiving influenza vaccine for the first time will need a second vaccine in one month. These second doses in those not previously immunized against influenza are given to maximize a satisfactory antibody response to all antigens in the vaccine. Preferably, the series should be started as soon as possible after the vaccine becomes available [8; 36; 74]. Late-season immunization is acceptable and should be encouraged for those who have not received the vaccine [63].

As an inactivated vaccine, influenza can be administered with other vaccines if required. Separate needles and separate sites should always be used. In fact, for patients 65 years of age or older who have never received the immunization against pneumococcal disease, that vaccine should be given at the same visit. This is also an excellent time to check on the status of the patient's tetanus immunization. Tetanus vaccine should be given every 10 years, a fact that is often forgotten in adults, especially older individuals.

All patients or their parent/guardian must receive the Vaccine Information Statement (VIS) appropriate to the vaccine being administered. The patient signs that he or she has read the VIS. The record the patient signs must contain the date that the VIS was provided to the patient. Many people think that they are signing permission for the vaccine to be given. Actually, they are signing that they have read the VIS [37].

Children younger than 18 years of age should not be given any vaccines without a parent/guardian present. Grandparents who are not legal guardians frequently bring children to immunization clinics. A written permission from the child's parent/guardian should be presented to the staff before the vaccine is administered.

INFLUENZA VACCINES AND COVID-19

During the 2023–2024 influenza season, it is expected that SARS-CoV-2 will continue to circulate in the United States, and COVID-19 vaccinations are expected to continue. Current guidance for the use of COVID-19 vaccines indicates that these vaccines can be coadministered with other vaccines, including influenza vaccines [8]. Influenza vaccination during the COVID-19 pandemic is particularly important, as preventing influenza will avoid burdening and already stressed healthcare system. There is also evidence that respiratory virus activity increased in 2022 and 2023, leading some to predict a worse-than-usual influenza season [189]. If influenza and COVID-19 vaccines are administered at the same visit, they should be given at different sites (separated by at least 1 inch [190]. If used, high-dose or adjuvant influenza vaccines should be administered on a separate limb from the COVID-19 vaccine, if possible. There is no requirements regarding which vaccine is administered first.

There is little experience to guide recommendations for providing influenza vaccines to persons with COVID-19. In general, those who are in quarantine or isolation should not be brought to a vaccination setting if doing so could expose others to COVID-19. For those who have moderate or severe COVID-19, vaccination should generally be deferred until they have recovered [8]. For persons who have mild or asymptomatic COVID-19, further deferral might be considered to avoid confusing COVID-19 illness symptoms with postvaccination reactions.

SIDE EFFECTS OF THE INFLUENZA VACCINE

The most common side effect following influenza immunization is a local reaction—soreness, redness, or induration at the injection site—that occurs in 15% to 20% of the recipients. Generally, these effects last only one or two days. Some people (<1%) experience fever, chills, malaise, and myalgias, usually within 6 to 12 hours. This effect occurs most often in those receiving the vaccine for the first time. As with the local reaction, these systemic reactions last only one to two days. In a comparative study with a placebo, the systemic reactions occurred as often with the placebo as with the influenza injection. Neurologic reactions to influenza do occur, but they are rare [8].

A certain percentage of people will be incubating an influenza virus when they receive the influenza injection. When they have symptoms of influenza within a few days of vaccination, they are certain it is the result of the flu shot. Healthcare workers should try to reassure their patients that the vaccine cannot be responsible because the virus in it is split and dead.

Immediate severe allergic reactions can occur after administration of influenza vaccine. These reactions are probably due to hypersensitivity to a component of the vaccine, usually a severe egg allergy. As noted, this concern may be eliminated with new technologies that have become available. The CDC recommends that all patients receiving the influenza vaccine, especially for the first time, should be carefully screened for severe egg allergy. However, the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology updated their practice parameter in 2017 and now assent that any appropriate, licensed influenza vaccine may be safely used for persons with egg allergy of any severity, eliminating the need for careful prescreening [186]. If a person has a severe allergic reaction to thimerosal, a thimerosal-free vaccine should be used. For those allergic to eggs but who have factors that increase their risk of complications from influenza infection, protocols to vaccinate them are available. Flublok or Flucelvax may be used in these patients as they are egg-free [8]. A sheet with the symptoms of anaphylaxis and the dosage of therapeutic epinephrine should be posted near the preloaded epinephrine syringe and should be readily available and known to all staff. In addition, crushable packets of ammonia should be available in any area in which immunizations will be administered. It should be noted that anaphylactic reactions are extremely rare. Patients, especially teenagers, may faint and the crushed ammonia passed quickly under the nose is enough to revive them. Never ignore a patient who verbalizes fear of shots or mentions that they have fainted in the past. Make sure such a patient is seated or lying down if in an exam room. Reassure the patient and administer the vaccine as quickly as possible. Position your body in such a way as to be able to support the patient if he or she begins to faint.

ADVERSE EVENTS

Adverse events are any unusual conditions, such as fever, dizziness, behavior change, or serious allergic reactions (e.g., difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, tachycardia), following influenza vaccine. The National Childhood Vaccine Injury Act of 1986 mandates that healthcare providers report adverse events following vaccination to VAERS. Providers are additionally encouraged to report any clinically significant adverse event following vaccination to VAERS [8]. Any person can report an adverse event following the administration of any vaccine by calling VAERS or by obtaining a form online. Adverse events usually occur within 48 hours of vaccine administration. However, GBS may occur as long as six weeks after administration. The VAERS form will ask for detailed information on the vaccine, such as lot number, administration site, administrator, and date. Patients to whom

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influenza vaccine is administered should be instructed to call a physician if there is an adverse event. Careful investigation follows the receipt of a VAERS report. The provider is notified of the results of the investigation usually several months after the report was made. Therefore, it is important to keep a copy of the report in the patient's file and a copy in a special file for VAERS reports. As the report is investigated, the provider may be contacted for clarification or additional information.

EFFECTIVENESS OF THE INFLUENZA VACCINE

The effectiveness of any vaccine depends upon the age and immunocompetence of the person receiving the vaccine. Most children and young adults receiving the vaccine have a good antibody response to the strains included in the vaccine and develop titers sufficient to protect them against those strains. For healthy adults younger than 65 years of age, if the vaccine strains match the circulating strains, illness will be prevented in 70% to 90% of those adults. In children, various studies have shown that children as young as 6 months of age develop antibodies. Children at high risk to develop complications with influenza may have a lower antibody response than healthy children. Also, children receiving the vaccine in the second year exhibit lower attack rates. Otitis media rates are lowered in some studies but not in others. Overall, because the vaccine is beneficial to children in preventing disease and lowering hospitalization rates, the ACIP recommends a yearly influenza immunization for all children 6 months of age and older [4; 8].

In adults 60 years of age and older who are not institutionalized, a randomized trial showed that the vaccine was 58% effective against influenza respiratory illness. Efficacy might be lower in those older than 70 years of age. However, the vaccine appears to be effective in preventing secondary complications, hospitalization, and death among older adults, both those who are healthy and those with chronic medical conditions. Among noninstitutionalized older adults, the vaccine prevented hospitalization for pneumonia and influenza 30% to 70% of the time. Among institutionalized older adults, the vaccine can be 50% to 60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death even though it is only 20% to 40% effective in preventing respiratory illness among this population [8]. Overall, in those 65 years of age and older, influenza immunizations have reduced hospitalization by 70% and death by 85% [36].

COST-EFFECTIVENESS OF THE INFLUENZA VACCINE

In preventing illness among younger workers, the vaccine may help reduce economic losses caused by absenteeism. Decreasing hospitalization rates of healthy infants and toddlers, of older noninstitutionalized and institutionalized adults, and of persons with chronic conditions is cost-effective. Studies have demonstrated that flu-related hospitalizations are decreased 40% to 42% overall with vaccination, that there is a 25% decrease in antibiotic usage for secondary illness associated with influenza, and that there is possibly a decrease in lost workdays. A 2014 study found that a vaccinated child's risk of being hospitalized due to influenza was reduced 74%; for individuals 50 years of age or older, flu-related hospitalization risk was reduced 57% [84]. These statistics indicate a significant annual savings of healthcare dollars for each person who received influenza vaccine. In an era of escalating healthcare costs and increasing antibiotic resistance, these are important figures [8].

NASAL SPRAY INFLUENZA VACCINE

Live attenuated influenza vaccines (LAIVs) have been in development in the United States since the 1960s [43; 44]. FluMist (a LAIV trivalent formulation), manufactured by MedImmune, LLC, was originally approved in June 2003. FluMist quadrivalent LAIV contains two subtype A strains and two subtype B strains. It was approved by the FDA in February 2012 and was first available for the 2013–2014 flu season [45; 46]. FluMist, which is delivered intranasally, is licensed only for healthy, nonpregnant persons 2 to 49 years of age. Live vaccines are unsuitable for healthcare workers who care for immunocompromised patients [8].

For two flu seasons, FluMist was not recommended based on data indicating inefficacy of the formulation. However, FluMist was reintroduced in the 2018–2019 season [8; 187]. People with chronic health conditions should not be given the intranasal vaccine. The ACIP does not recommend the use of LAIV in immunosuppressed patients, and family members of close contacts of severely immunocompromised individuals are advised to avoid contact with them for at least seven days following vaccination [45]. LAIV can be administered at the same time with other vaccines, live and inactivated, but if not given at the same time, should be given four weeks after any other vaccine. Family members or close contacts of severely immunocompromised patients should not be given LAIV [45; 61].

LAIV appears to induce both mucosal and serum antibodies. It is easier to administer than an IM injection, and it is preferred in some cases. In addition, no serious illnesses have been reported among unvaccinated contacts who were infected by those who had received the live vaccine [8].

Who Should Not Receive LAIV

The following groups of people should not be given LAIV [8; 31; 43; 45; 46; 61]:

- Anyone younger than 2 years of age or older than 49 years of age
- Children 2 through 4 years of age who have received the diagnosis of asthma or have had a wheezing episode within the past 12 months
- Anyone with chronic underlying medical conditions, such as cardiac or pulmonary disease, diabetes, renal dysfunction, or a compromised immune system
- Children on long-term aspirin therapy
- Persons with a history of GBS

- Pregnant women
- Persons with hypersensitivity to any of the components of LAIV, including eggs
- Persons who have been on antiviral medications in the previous 48 hours
- Persons with a history of asthma or other reactive airway disease

Administration and Dosage

Intranasal influenza vaccine is supplied in prefilled single-use sprayers containing 0.2 mL of vaccine and must be refrigerated at 2 to 8 degrees C (35 to 46 degrees F) [46]. Half of the dose in the sprayer, approximately 0.1 mL, is sprayed into one nostril while the patient is sitting upright. The attached dose-divider clip is removed so the rest of the dose can be sprayed into the other nostril. The dose is not repeated if the person sneezes [45].

PROMOTING THE USE OF INFLUENZA VACCINE

The Healthy People 2030 objective is to increase the proportion of persons who are vaccinated annually against seasonal influenza to at least 70% of the target population, but obviously 100% coverage is preferable [82]. To emphasize the importance of flu vaccinations, the CDC has established the National Influenza Vaccination Week. In 2024, the week is scheduled for December 6 through 12 [73]. While improvements in vaccination coverage were observed in children from the 2010–2011 season to the 2019–2020 season (from 51% to 64%), the 2021–2022 season vaccination coverage was 6% lower (58%) [184]. A significant increase has not occurred in the adult population over the same time period (from 41% to 50%) and dipped to as low as 37% during the 2017–2018 flu season. Vaccination rates are particularly low among adults 18 to 49 years of age (increasing from 31% to 38% in the past decade) [184].

Among people 65 years of age and older, the overall influenza vaccination rate was 73.9% in 2022. However, people of color (in all age groups) have much lower rates [36]. There are several high-risk groups, discussed previously in this course, that fall far short of the 90% influenza immunization rate goal. According to data from the National Health Interview Survey, only 49.2% of high-risk people 6 months to 64 years of age were immunized against influenza in 2017 [82]. Since 1999, in years without vaccine shortages, immunization levels have ranged between 63% to 66% for high-risk individuals [70; 87]. In 2022, only 50.4% of high-risk individuals 18 to 64 years of age were vaccinated [184].

Data from the 2010 Internet Panel Survey of healthcare personnel indicated that only 49% of healthcare workers were immunized against influenza, in spite of the fact that vaccination reduced work absenteeism and resulted in fewer deaths among nursing home residents [69]. In the 2011–2012 season, only 67% were immunized. That percentage rose to 72% during the 2012–2013 season and then to 76% in the 2020–2021 season [70; 87]. The lowest rate of vaccinations among healthcare personnel are in those working in long-term care facilities and home health care settings (66.0%) [87].

Studies have also shown that ill workers account for as much as 60% of corporate healthcare costs. To respond to these situations, many companies now offer free influenza vaccinations and expanded telecommuting options [71].

FACTORS INFLUENCING INFLUENZA IMMUNIZATION

One of the major factors influencing people with conditions that put them at high-risk for complications, hospitalization, and death from influenza is the misconception that the flu shot will give them the flu. This misconception is fueled by the fact that, in such a large cohort receiving the influenza immunization, a certain percentage will already be incubating the virus. When the symptoms of influenza appear one day or so after getting the shot, the natural assumption is that the illness came from the shot. Some take the opposite view that the flu shot will protect them against colds, so they are disappointed the "the flu shot didn't work" when they get a cold [84]. The same would be true about a bacterial infection or another ILI, such as RSV.

Another factor is that patients rely on their physician's advice. Unfortunately, physicians may not specifically recommend that their patients get the influenza vaccine. This leads the patient to think that it is not important or it would have been mentioned. Physicians can assess whether needle fears or phobias are preventing vaccination and could suggest or offer the LAIV4 vaccine. The CDC estimates that 2 in 3 children and 1 in 4 adults have a strong fear of needles [195]. It can be helpful to understand needle-fear triggers and have a variety of strategies to help patients manage the fear and pain.

Cost may be a prohibitive factor for those too young for Medicare, which covers influenza and pneumococcal immunizations. Some people may assume that the influenza immunization is effective for several years. Others feel that a healthy person should not take anything, like a flu shot, that might make them sick or may have side effects [84]. Some patients do not realize how effective the influenza vaccine is in preventing complications, hospitalizations, deaths, and actual influenza disease when the vaccine antigens correspond to the circulating antigens.

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Probably one of the biggest factors affecting influenza immunization rates is the fact that influenza is so common—a true illustration of "familiarity breeds contempt." Few are aware of the number of hospitalizations and deaths and the economic burden associated with influenza. Additionally, vaccine hesitancy for a number of reasons, including distrust of medicine and science, compounded by misinformation found in certain media and now proliferated online, has had a negative influence on vaccine uptake.

IMPROVING INFLUENZA VACCINE USAGE

Start Administration As Soon As Vaccine is Available

What is the most effective way to increase the use of influenza vaccine?

Now that studies have shown that the immunity produced by the vaccine lasts several months, the ACIP recommends that influenza immunizations start as soon as the vaccine is available. Thus, patients who are seen infrequently by their healthcare providers can receive the vaccine when they have an appointment and avoid a special visit just for the immunization. Providers should offer the vaccine to all patients, especially children 6 months to 8 years of age, as soon as they have a supply. The CDC also recommends that the offer of the vaccine and its refusal be documented in the patient's medical record [8].

The Role of the Healthcare Provider

One of the major factors in increasing the number of administrations of influenza vaccine is the involvement of the medical practitioner providing care in a variety of settings, such as physicians' offices, clinics, outpatient rehabilitation programs, or any place where there is contact between medical providers and their patients. To encourage practitioner involvement, providers should be informed of the reimbursement for the vaccine and its administration by Medicare and Medicaid and should be instructed as to billing methods, especially roster billing.

The majority of flu shots given are administrated by the person's personal healthcare provider, and studies have shown that a healthcare provider's recommendation plays a critical role in a patient's decision to get a seasonal flu vaccine [85]. As many as 75% of patients at high risk for influenza or for death from a complication of influenza have seen a healthcare provider in the last year. One of the most effective methods of encouraging a high-risk patient to receive the flu shot is a verbal recommendation from the patient's physician [85].

To ensure that high-risk patients receive the recommendation, a variety of reminder techniques might be employed, such as placing stickers on the charts of high-risk patients, creating computer-generated lists of patients not scheduled to be seen, sending reminders via email or regular mail, and telephoning patients. Educational efforts by public health departments through media and personnel could encourage high-risk people to ask their healthcare provider for the flu shot [86]. Beginning in September, emergency rooms and walk-in clinics should display posters and educational materials about the need for the flu shot and either provide the vaccine or provide information about where it may be obtained [16].

Influenza immunization is also recommended for all people who have contact with high-risk populations. Obviously, this includes all healthcare professionals, a group for which the ACIP recommends annual influenza vaccination [8]. According to results of a survey conducted by the CDC among 2,391 self-selected healthcare personnel, 76% of survey participants reported having had an influenza vaccination for the 2020–2021 season, a significant increase from 67% during the 2011–2012 season [70; 87]. Vaccination coverage was highest among hospital-based healthcare personnel (91.6%) and lowest among healthcare personnel at long-term care facilities (66%). Coverage was also higher in occupational settings that offered no-cost, onsite vaccination for one or more days compared with settings that did not offer no-cost coverage. Vaccination coverage was 95.9% overall among healthcare personnel in all occupational settings who reported an employer mandate to receive vaccination [70; 87].

Immunization lowers worker absenteeism and transmission to vulnerable patients. Those who supervise or manage other healthcare personnel should set an example for their staff and patients by making sure to get a flu shot each year. It seems that those who have received the vaccine are more aware of the need to inform patients of the value of the flu shot, and their example is an encouragement.

As noted, LAIV should not be used to immunize contacts of severely immunocompromised patients unless no contact for seven days following receipt of LAIV can be assured [8]. There have been no reported instances in which a healthcare professional immunized with LAIV has transmitted influenza to a patient. Unvaccinated healthcare workers are more likely to transmit the virus [88]. To encourage more healthcare professionals and allied personnel to get the flu shot, it should be provided at the work site free of charge [16].

Standing Orders

Implementation of standing orders in acute care hospitals is another way to help increase influenza vaccine coverage. Patients who are hospitalized as flu season approaches, or during flu season, should have their records checked for chronic illness that is impacted by influenza and for influenza vaccine status. Those who have risk factors for complications and have not received the influenza immunization should receive the flu shot before discharge, as covered by the standing order. Such standing orders would have to be developed and implemented by the medical board of the hospital. All medical personnel connected with the hospital should be made aware of the standing order and reminded by posters or other means during influenza season. A study of Medicare patients hospitalized during flu season showed that only 31.6% had received the flu vaccine before admission, 1.9% during admission, and 10.6% after admission [43].

In long-term care facilities, there should be a standing order for each patient to receive a flu shot in October. When a patient is admitted to the facility, the attending medical professional and family member(s) should be informed of the standing order. If there is a reason that the patient should not receive the influenza vaccine, the physician can so order or the family member can so request. All residents should be immunized on the same day, if possible, before flu season. Those admitted after this day should receive the vaccine upon admission [43]. One study showed that only 62% of residents in nursing homes received influenza immunization in spite of its demonstrated effectiveness in preventing complications, hospitalization, and death in long-term care patients. Another study showed that if 80% or more of the residents in the facility were immunized against influenza, hospitalization from all causes was reduced regardless of the vaccination status of the individual resident [89]. As noted, another protective measure for residents of institutions is for the care providers to receive an influenza immunization.

Home healthcare agencies should also have protocols in place to immunize patients under their care during the flu season and to inform the in-home caregivers of their need to be immunized. Staff members with patient contact should also be immunized [43].

All healthcare providers of patients in hospitals, long-term care facilities, and home health agencies should be aware that the Centers for Medicare and Medicaid Services has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to patients covered by Medicare and Medicaid [43].

The Role of Community Agencies

Religious meeting places are a point of contact for many groups. Patient education materials can be included in the organization's bulletin. In some areas, the local public health department will provide an influenza immunization clinic in conjunction with a religious service.

Reminder posters and educational materials can also be displayed at banks, grocery stores, and community centers. These materials are available from the local public health department or on the CDC website. Organizations such as Lions, Kiwanis, Rotary, and the AARP, that are interested in controlling the cost of health care, should be enlisted to help encourage their friends and neighbors to be immunized against influenza.

Many public health departments provide influenza immunizations in community settings, such as churches, community centers, meetings of minority groups, airports, and malls—any place where a clinic can be temporarily set up. Some even provide "drive-up clinics" where the person does not need to get out of the car to receive the flu shot. These clinics are especially helpful for a person who cannot wait in line or walk easily and may help those with fear of needles [195].

OTHER METHODS TO PREVENT INFLUENZA

What hygiene practices are effective in preventing the spread of influenza?

The primary and most effective way to prevent influenza is vaccination. However, in cases when antigens of the vaccine are not close enough to the circulating antigen, when there is a shortage of vaccine, or when a new strain has emerged and is circulating before the vaccine can be made and distributed, people will have to resort to other ways to protect themselves from infection.

HANDWASHING

Good handwashing is difficult to practice, is rarely known or taught, and is one of the single most effective ways to prevent transmission of many diseases, including influenza. Everyone knows to wash their hands before eating and after using the restroom. However, few do little more than remove obvious dirt. Good handwashing involves removing the skin oils where organisms can remain even when the hands look clean. A quick pass under the water faucet and fast dry with a towel removes visible dirt, but the oils and organisms remain.

To effectively remove the oils and organisms, the process should take at least 20 seconds (e.g., the amount of time that it takes to sing "Twinkle, Twinkle Little Star"). The hands should be soaped and rubbed vigorously for 15 seconds to create a good lather and to assure that all parts of each hand are soaped and rubbed well. Then the hands should be rinsed thoroughly and dried, preferably with a paper towel. The towel should be used to turn off the water and then properly thrown away. Such handwashing removes the oils that harbor the organisms, but 20 seconds can seem like a long time in the busy life of a healthcare provider. If there is no visible dirt or contamination, a waterless hand sanitizer with at least 60% alcohol can be used between patients. However, nothing is as good as washing well with soap and water. Some mistakenly think that hot water must be used to kill the organisms. Water hot enough to kill organisms would be too hot to touch. Warm water mainly adds to comfort and hopefully encourages better washing technique. Careful attention to handwashing and cleansing may result in chapped skin, so medical professionals should find the proper lotions to care for their hands [90; 91].

AVOID TOUCHING EYES, NOSE, OR MOUTH

The eyes, nose, and mouth are entryways for bacteria and viruses. Everyone tends to unconsciously touch their eyes, nose, and mouth when going about their activities. Because organisms are not visible and handwashing is often less than adequate, infection occurs. Though difficult, persons trying to prevent illness should make a conscious effort to avoid touching their face [92].

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PROPER COVER FOR A COUGH OR SNEEZE

Covering a cough or sneeze is of primary importance however it is done [93]. Ideally, disposable paper tissues will be readily available during cold and flu season and used to cover the nose and mouth when coughing or sneezing. Patients and children should be instructed that, when this is not possible, they should cough or sneeze into their upper sleeve or elbow instead of into their hands. This will avoid contaminating the hands with an offending virus or bacteria [93]. In those instances when coughs and sneezes are covered with only the bare hands, the hands should be cleaned with soap and water or with an alcohol-based hand sanitizer as soon as possible to prevent transfer of the organisms to another person. Coughing, sneezing, or blowing nasal secretions into a cloth handkerchief is not recommended as this results in creating a moist, viable culture that is then carried in the pocket or purse, potentially resulting in prolonged episodes of re-infection or transfer from cross-contamination.

AVOID PEOPLE WITH RESPIRATORY SYMPTOMS

During cold and flu season, trips to the store, school, church, and workplace bring contact with those who are coughing and sneezing. If at all possible, avoid close contact. This is an excellent time to consciously work on keeping your hands away from your face. Good handwashing should be done as soon as possible after contact with high-touch surfaces or someone exhibiting symptoms of respiratory illness. Help the immune system to overcome the organisms by getting enough rest, drinking six to eight glasses of water per day, and eating fresh fruits and vegetables [94]. Healthcare providers can lessen the spread of influenza by utilizing proper cough etiquette, providing tissues and safe disposal, using rapid diagnostic tests and antiviral chemoprophylaxis for suspected flu in healthcare workers, and recommending that influenza sufferers stay home [95].

ANTIVIRAL MEDICATIONS AS PREVENTION

Antiviral medications can also be used to prevent influenza. Three of the four antiviral drugs used to treat illness due to influenza can also be used to prevent it, although this is complicated by growing resistance to available agents. Amantadine (Symmetrel) and rimantadine (Flumadine) have been approved for treatment and prevention, but both of these agents have also been associated with decreasing effectiveness due to viral resistance and are no longer recommended for these uses [45; 96; 97]. Oseltamivir (Tamiflu) is an effective treatment of uncomplicated acute illness due to influenza A and B viruses in adults and children older than 2 weeks of age, and it is approved as a preventive treatment in persons 1 year of age and older. In 2007, the Japanese Ministry of Health, Labor, and Welfare issued a warning that oseltamivir may cause psychiatric problems and suicide in patients 10 to 19 years of age [98]. This warning has been the subject of much controversy, and no such warning has been issued in the United States. Zanamivir (Relenza) is approved for prophylaxis in persons 5 years of age and older; ACIP recommends that prophylaxis with zanamivir be considered for individuals at high risk of influenza complications, for unvaccinated healthcare workers exposed to influenza, and for eligible residents of institutions that house high-risk patients when outbreak control is needed [45].

A physician's order is required to obtain antivirals. In the past, amantadine and rimantadine prevented influenza A illness 70% to 90% of the time [16]. However, the increasing incidence of amantadine- and rimantadine-resistant strains of influenza in the United States has made these medications less effective [96]. Therefore, they are no longer recommended for treatment or prophylaxis of circulating influenza A strains [45; 97].

Antiviral medications can make a person less contagious to others, so they are prescribed for contacts of people who are at high risk for complications from the flu. A subclinical infection may develop in a patient taking an antiviral. This allows the body to make antibodies against the virus. If any antiviral medication is to be totally effective, it must be taken as long as influenza is active in the community. Some studies indicate that taking an antiviral during peak influenza activity in a community is also effective. Of course, the less expensive single application vaccine is the best choice in preventing influenza in contacts of high-risk persons. However, in situations in which the individual has a hypersensitivity to one of components of the vaccine, or the needed two weeks to develop immunity are not available before contact, an antiviral medication can be used. Another reason to use an antiviral prophylaxis would be if the available vaccine does not match the circulating virus.

Antivirals are also used in closed environments, such as institutions or cruise ships, to control flu outbreaks. In such cases, it is best to combine the vaccine with an antiviral to provide protection for those exposed but who have not developed illness until the vaccine can stimulate the immune system to make protective antibodies. This also avoids the protracted use of the antiviral medication. The antiviral will not interfere with the antibody response elicited by the vaccine [3; 16; 99].

ANTIVIRAL MEDICATIONS

Which antiviral medications are approved to treat influenza A and B?

The antiviral medications zanamivir and oseltamivir are also used to treat acute illness due to influenza (***Table 3***). To be effective, any of these medications must be started within 48 hours of symptom onset. Generally, a course of one of these antivirals will reduce the illness by one to two days, prevent serious complications, and make the patient less contagious to others. These medications are effective only against influenza viruses and will not affect the common cold or other ILI of viral origin [16; 99; 100]. All require a prescription from a physician.

COMPARISON OF ANTIVIRALS USED IN INFLUENZA				
Characteristics	**Zanamivir**	**Oseltamivir**	**Peramivir**	**Baloxavir**
Type of antiviral	Neuraminidase inhibitor	Neuraminidase inhibitor	Neuraminidase inhibitor	Endonuclease inhibitor
Effective for type	Influenza types A and B	Influenza types A and B	Influenza types A and B[a]	Influenza type A and B, including avian strains and strains resistant to oseltamivir
Route of administration	Inhaled	Oral	IV	Oral
Age that can receive	Treatment: 7 years of age and older Prevention: 5 years of age and older	Treatment: 14 days of age and older Prevention: 13 years of age and older	Treatment: 6 months of age and older Prevention: NA	Treatment: 5 years of age and older Prevention: 5 years of age and older
Action	Decrease symptoms	Decrease symptoms Decrease antibiotic use	Decrease symptoms	Decrease symptoms
Side effects	Throat/tonsil pain, nasal symptoms, diarrhea, nausea, headache, cough	Nausea and vomiting	Diarrhea	Diarrhea, nasopharyngitis
Sold as	Relenza	Tamiflu	Rapivab	Xofluza

[a]Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

Source: [45; 96; 97; 121] *Table 3*

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Advisory Committee on Immunization Practices, clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:

- Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization
- Outpatients of any age with severe or progressive illness, regardless of illness duration
- Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients
- Children younger than 2 years and adults 65 years of age or older
- Pregnant women and those within two weeks postpartum

(https://academic.oup.com/cid/article/68/6/e1/5251935. Last accessed May 7, 2024.)

Level of Evidence: A-II (Good evidence to support a recommendation based on one or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time-series; or from dramatic results from uncontrolled experiments) and A-III (Good evidence to support a recommendation based on opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

ZANAMIVIR

Zanamivir belongs to the antiviral group of neuraminidase inhibitors. It is effective against both influenza A and B and was approved in 1999 to treat uncomplicated illness due to influenza virus in adults and children 7 years of age and older. The dosage is 10 mg twice daily by inhalation for five days. Doses should be 12 hours apart. It may also be used to prevent influenza virus in adults and children 5 years of age and older. The dosage is two 10-mg inhalations once daily for seven days after last known exposure [45; 101]. Zanamivir can lead to a decrease in respiratory function and bronchospasm. It is not recommended for patients with asthma, obstructive pulmonary

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disease, or other chronic lung diseases. More common (>10%) side effects include headache, throat/tonsil discomfort or pain, nasal signs and symptoms, and cough. Other effects that occur in less than 10% of patients include diarrhea, nausea, headache, dizziness, nasal infections, sinusitis, and bronchitis [45]. Some allergic responses of oropharyngeal or facial edema have also occurred [16; 22; 100; 102].

OSELTAMIVIR

Oseltamivir also is a neuraminidase inhibitor and effective against both influenza A and B viruses. It is marketed as Tamiflu, which should not be confused with Theraflu. Like zanamivir, it was approved in 1999. It can be used as treatment in adults and children who have been symptomatic for no more than two days. The treatment dosing for adults and children 13 years of age and older is 75 mg twice daily. The treatment dosing for children younger than 13 year of age is weight dependent [101]:

- 3 mg twice daily for children aged 2 weeks to younger than one year
- 30 mg twice daily for children aged 1 year and older who weigh ≤15 kg
- 45 mg twice daily for children who weigh >15 kg and up to 23 kg
- 60 mg twice daily for children who weigh >23 and up to 40 kg
- 75 mg twice daily for children who weigh >40 kg

Oseltamivir can also be used as a preventive in anyone 1 year of age or older, but such usage should be rare [97]. The dose is 75 mg twice daily by mouth for adults and once daily for children and adolescents who weigh more than 40 kg (88 lbs.) [45]. Studies have shown that oseltamivir reduces the incidence of complications that may require antibiotics. Although the neuraminidase inhibitors promote a drug-resistant mutant of the virus, less resistance appears to occur with oseltamivir than with zanamivir. The reported side effects with oseltamivir are nausea and vomiting, which are lessened if the medication is taken with food [8; 16; 22; 100; 102].

Since 2005, some resistance to all of the antivirals has been documented. However, the 2009 H1N1 outbreak remained sensitive to oseltamivir except in a few cases [8]. Serious reactions to the four antiviral medications should be reported to the FDA MedWatch program.

PERAMIVIR

Peramivir is a neuraminidase inhibitor for use in patients 6 months of age or older with acute uncomplicated influenza who have shown symptoms for no longer that two days [45; 97]. Peramivir injection preparation is a 200 mg/20 mL single-use vial, stored at 59 to 86 degrees F (15 to 30 degrees C). After being diluted, it should either be administered immediately or refrigerated and administered within 24 hours [159]. Peramivir is typically given in a single 600-mg dose; the dose should be adjusted based on renal function. The most common side effect is diarrhea (8%) [45]. An efficacy study showed that overall symptoms were relieved 21 hours sooner in participants given peramivir compared to those given placebo [32]. Efficacy studies have primarily been conducted in patients with A type influenza viruses, and it is effective for 2009 H1N1 [45; 159].

BALOXAVIR

In 2018, the FDA approved the first antiviral influenza treatment with a novel mechanism of action in nearly 20 years—baloxavir. Baloxavir is a selective inhibitor of influenza cap-dependent endonuclease. It is approved for use in persons 5 years of age and older if administered within 48 hours of onset of symptoms [121]. It is also approved for avian influenza strains and strains with proven resistance to oseltamivir. In 2022, approval of baloxavir was extended to include post-exposure prevention in persons 5 years of age or older who have been exposed to influenza [45]. Studies indicate that baloxavir, which has the advantage of once-a-day dosage, is as effective as oseltamivir in alleviating symptoms and shortening the duration of illness [10]. Baloxavir is administered as a single oral dose of 40 mg for persons 40 to <80 kg or 80 mg for persons ≥80 kg. The most common side effects are diarrhea and nasopharyngitis [121].

AMANTADINE AND RIMANTADINE

Amantadine was approved in 1966 as a treatment for uncomplicated respiratory tract illness caused by influenza. It belongs to a group of chemically related drugs called adamantanes (tricyclic amines) and is effective only against influenza A viruses. Rimantadine, approved in 1993, is also in the adamantanes group. Therefore, it is also only effective against influenza A. However, circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes. As a result, these medications are no longer recommended for the treatment or prophylaxis of influenza A [45; 103].

TREATMENT OF ACUTE ILLNESS RESULTING FROM INFLUENZA

All antiviral treatment for influenza should begin within 48 hours of symptom onset to be effective [45; 97]. In most individuals without underlying medical conditions, influenza is a self-limiting disease. Recovery usually occurs after one week, although fatigue and malaise may persist two or more weeks. The decision to use an antiviral is influenced by the type of work the patient does. In an epidemic or pandemic, persons providing critical services should be treated because shortening their absence by one or two days is important. For other personnel, the decision should be based on the comparison between the wages that would be lost and the cost of the medication [100]. If an outbreak of influenza occurs in an institution, antiviral medications should be used for both treatment and prophylaxis [104].

Some people may desire treatment because of upcoming plans or because they do not like to be sick. These individuals should be encouraged to obtain the annual influenza vaccine in the future, as disease that develops in spite of the vaccine is usually milder unless the vaccine strains do not match the circulating strains.

Antiviral treatment with oral or enterically administered oseltamivir is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization [97]. Oral oseltamivir is also recommended for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions [96; 97]. Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.

Pregnancy should not be considered a contraindication to the use of oseltamivir or zanamivir; however, peramivir and baloxavir are not recommended for these patients. Pregnant women are known to be at higher risk for complications from infection with seasonal influenza viruses, and if influenza is confirmed or suspected in these patients, it should be treated with oseltamivir or zanamivir; fever should be treated with acetaminophen. [101]. Because antivirals have a potential but unknown risk during pregnancy, it is important to continue to vaccinate pregnant women. The seasonal flu shot has been given to pregnant women for many years without any harm to the women or their fetuses. Vaccines that contain thimerosal result in exposure to only trace amounts of mercury and are not associated with toxicity; however, most (93%) of available vaccines are thimerosal-free or thimerosal-reduced formulation. All single-use vaccines are thimerosal-free, and the LAIV4 nasal vaccine is also thimerosal-free [45; 76].

CARE OF THE PATIENT WITH INFLUENZA

AT HOME

Family members or friends should be located to care for the high-risk patient who lives alone. With enough community support (e.g., home health, neighbors, "Meals on Wheels"), a patient might be able to remain alone, but it would require careful planning and coordination among all involved. During an epidemic or a pandemic, it may be necessary to set up temporary facilities, such as a shelter for medically fragile patients, to provide care. A normally healthy adult living alone may only need help in the form of shopping.

Points in the care of the patient include: careful observation, providing symptomatic relief, help with activities of daily living, helping the patient remain hydrated, and emotional support (***Appendix 1***).

PREVENTIVE MEASURES FOR THE CAREGIVER

What precautions should be taken when caring for a high-risk patient during flu season?

Attention should also be given to the person(s) caring for the patient with influenza in the home to protect him/her from the disease. This would include influenza immunization, with or without an antiviral medication for two weeks, instruction on effective handwashing, wearing a mask when providing care or when the patient is coughing, getting adequate rest, consuming five to nine or more fruits, fruit juices, and vegetables each day, and drinking eight glasses of water every day (***Appendix 2***).

SELF-CARE

Of course, the most important aspect of self-care is obtaining the immunization. However, should one develop influenza and not be at high risk for complications, there are a few general steps to speed recovery and protect others [105]:

- Consider obtaining an antiviral if flu is in the first or second day of illness.
- Stay home to protect others from infection.
- Get plenty of rest.
- Drink plenty of liquids.
- Do not drink alcohol or use tobacco products.
- Consider over-the-counter medications to relieve the symptoms.
- Cover coughs and sneezes.
- Wash hands well and frequently, especially after coughing or sneezing.

OBSERVATIONS INDICATING URGENT MEDICAL HELP IS NEEDED

By keeping a written record of observations, a patient's subtle changes become more apparent, and the information will also help a physician. As discussed, there are many diseases that initially present like influenza or conditions that can be complicated by influenza; therefore, each person with influenza should be watched. The patient with influenza usually starts to improve after a few days. Patients and/or caregivers should be given a list of symptoms that indicate when a physician should be notified (***Appendix 3***). Any difficulty in breathing, a fever that is not responding to antipyretics, change in mental state, inability to maintain hydration, or worsening of symptoms should be reported to a physician, or the patient should be taken to the emergency room if a physician is unavailable.

The healthcare professional should review the following items with patients with influenza or their family member(s), so a physician can be notified appropriately and promptly [105]:

- High or prolonged fever
- Breathing (fast or difficult with retractions in children, or cyanosis, labored breathing, shortness of breath, or pain or pressure in the chest in adults)

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- Inadequate fluid intake (e.g., fewer wet diapers, darker urine)
- Changes in mental status (e.g., hard to arouse, confusion, too irritable to be comforted)
- Fainting or near-fainting, seizures
- Severe or persistent vomiting
- Worsening of a chronic disease
- Worsening of influenza symptoms, increasing weakness
- Any rash or jaundice
- Dry cough that becomes productive

THE PATIENT WITH INFLUENZA IN THE HOSPITAL, MEDICAL OFFICE, OR CLINIC

Infection control procedures should be followed carefully as soon as any contact with a patient with influenza or an ILI occurs so that transmission can be prevented. In order to protect staff, posters prominently displayed or warning signs at the sign-in desk should request that the staff be informed if the patient has any respiratory symptoms.

Patient education posters about flu, the vaccine, and cough etiquette should be displayed in emergency rooms, waiting rooms, exam rooms, elevators, and other appropriate traffic areas used by patients and visitors. Messages should be brief but clear. Pictures could also be included for children who cannot read or for non-English speakers. All education materials should be provided in the major languages of the community.

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such a vital aspect of the prevention and treatment of influenza, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

Educational materials might include:

Cough Etiquette

- Cover your cough.
- Use a tissue.
- Throw the tissue away in the wastebasket.
- Wash your hands.
- Tissues and wastebaskets should be easily accessed.

Handwashing

- Use soap.
- Rub your hands well to make a good lather.
- Rub your hands for 15 seconds.
- Rinse well.
- Dry with a paper towel.
- Turn off water with a paper towel.
- Throw the paper towel in the wastebasket.

If no facilities to wash hands are available, alcohol-based hand sanitizer should be available.

When influenza and COVID-19 are present in the community, patients who are coughing should be given a mask and asked to sit in a separate area. If a separate area is not available, they should be at least 6 feet away from other people. Masks can be the surgical masks with ties or procedural masks with ear loops; they do not need to be respirator N95 masks.

Staff involved with patients who have respiratory symptoms with fever should follow droplet precautions as developed at their work place. For all patient contact, a mask (surgical or procedural) should be worn. Hands should be washed thoroughly following contact. During an epidemic, staff circulating between floors in the hospital should be limited [106].

AVIAN INFLUENZA

What elements are needed for an avian influenza pandemic to occur?

The influenza viruses that are carried by birds, both domesticated and wild, rarely have infected humans. This is partly due to the fact that avian influenza (AI) viruses attach to receptors found on bird cells but not found on human cells. Human viruses prefer the receptors found in the human respiratory tract. Pigs have receptors used by avian, swine, and human influenza viruses and have traditionally been the link between avian and human influenza viruses. Because pigs acquire all three types of viruses, reassortment/antigenic shift of the hemagglutinin and neuraminidase proteins occurs in the pig host, which then transmits the new strain to humans or other pigs [14; 107].

However, there now exists evidence that avian influenza can spread directly to humans [107]. In 2004, areas of Asia experienced large-scale outbreaks of avian influenza, specifically the H5N1 virus, in poultry. The virus went on to infect humans, with a high mortality rate. The number of countries, people, and animals affected by the virus reached unprecedented levels. In 2006, the CDC summarized the H5N1 outbreak. Wild birds and poultry had been infected in Asia, parts of Europe, the

Middle East, and Africa. Human infections continued to be reported in China, Egypt, Indonesia, Azerbaijan, Cambodia, and Djibouti. There were some probable human-to-human transmissions of H5N1, but these were rare. As of March 2024, there had been 888 human cases of H5N1 since 2003, with a continued fatality rate of approximately 52% [108; 109]. In 2013, an outbreak of H7N9 virus in China spread to humans, with 14 reported infections and 6 deaths in the first two months [110]. Both the CDC and the WHO have reported that there is a strong threat of a future pandemic of avian influenza and that preparedness is vital [111; 112].

Although influenza A viruses can infect all birds, domestic poultry flocks are more vulnerable to infections that can reach epidemic proportions. Generally, domesticated fowl transmit the virus in saliva, nasal secretions, and feces. However, it is thought that the fecal-oral route is the common way the virus is spread among flocks. Wild birds rarely become sick but are a source of infection through their droppings because they carry the virus in their intestines. Free-roaming domestic fowl are at more risk from wild bird droppings than housed flocks. Both food and water supplies can be contaminated by droppings or sharing with wild birds. At first it was thought that wild birds spread the virus from farm to farm, but further study indicated that people and equipment probably spread the virus to domesticated flocks [113; 114].

AI viruses are classified as low pathogenic and high pathogenic based on their genetic sequence and the resulting illness in birds. Low pathogenic AI has been detected in wild birds, mostly ducks, geese, and gulls, since 1975 [115]. Low pathogenic AI virus causes only ruffled feathers and a reduction in egg production. Fortunately, most AI viruses are low pathogenic; however, in six to nine months, they can mutate to high pathogenic. High pathogenic AI viruses, first noted in 1878 in Italy, are highly contagious, spread rapidly, and are almost 100% fatal. Fowl can die the same day that they first exhibit symptoms [115; 116; 117].

Whenever an AI virus infects a human directly, there is much concern. Humans rarely have any immunity to AI viruses. Medical resources around the world quickly mobilize when there is a case of AI that skips reassortment in swine and directly infects a human. Fowl within a 2-mile (3-kilometer) radius of the source bird/flock are killed in order to contain the virus. An AI virus in humans usually produces upper respiratory disease and conjunctivitis. The infected humans and their contacts are watched closely for secondary transmission. For a pandemic to follow, these factors are needed:

- Humans do not have immunity to the virus
- Direct transmission from bird to human
- Sustainable transmission from human to human
- Movement of infected/contagious individuals to other geographic locations

Once a new pandemic influenza virus emerges, it generally circulates for many years [113; 116]. Researchers at the University of Wisconsin, Madison, have been combining H5N1 with a seasonal flu strain (H3N2). As a result, they have found such reassortment flu viruses are highly pathogenic; 22 were more pathogenic for mice than the original H5N1, and three caused extremely severe disease [118].

AVIAN INFLUENZA VIRUSES

The hemagglutinin antigens that historically have caused human influenza are H1, H2, and H3. Although all known hemagglutinin subtypes occur in birds, H5, H7, H9, and H10 have been implicated more in recent outbreaks. Various combinations with the neuraminidase antigens occur. All of these AI viruses are type A, as B and C do not infect birds. Some of the cases focused on in the past decades have included the following [111; 119; 120; 125]:

- H5N1 – Hong Kong, 1997, first documented human infection—18 hospitalized, 6 deaths, 1.5 million chickens culled
- H5N1 – Russia/Romania/Turkey/Azerbaijan/Egypt, 2006, some human illness, unknown deaths
- H7N9 – China, 2013–2017, 1,222 confirmed cases, 40% mortality rate
- H5N1 – United States, 2022–2024, nearly 91 million commercial and backyard poultry birds affected (as of May 2024), 36 dairy herds affected, 2 human cases

Fortunately, although in some of these outbreaks bird-to-human transmission did occur, human-to-human transmission has been extremely rare. Limited transmission possibly did occur between humans in the Netherlands, but no sustainable transmission occurred, so an epidemic or pandemic did not follow. There were 14 cases and 12 deaths (11 children) from H5N1 virus in Vietnam. The viruses isolated from those who expired in Vietnam were mostly resistant to amantadine and rimantadine. Studies are continuing as to the effectiveness of oseltamivir and zanamivir against H5N1 viruses. There is some evidence that the 2004 H5N1 virus in Asia is sensitive to oseltamivir [113; 114; 116]. However, some evidence of resistance to oseltamivir has been reported in highly pathogenic avian influenza H5N1 viruses isolated from human cases [122]. Most of the 2004 H5N1 outbreaks were controlled by veterinarian officials or spontaneously died out.

AVIAN INFLUENZA AND HUMANS

Most cases of AI in humans have resulted from contact with infected poultry or contaminated surfaces. It is also possible for the virus to become aerosolized and then land on exposed surfaces of the mouth, nose, or eyes. Aerosolized virus could also be inhaled directly into the lungs. Although no cases have been recorded, eating uncooked or undercooked poultry or beef is believed to be a possible transmission risk [123]. Influenza viruses are destroyed by adequate heat. Because of the

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pathogens found in poultry, all patients should be reminded to cook all poultry, including eggs, thoroughly. Chicken should be cooked until the internal temperature reaches 180 degrees F. All utensils and surfaces that have come in contact with raw poultry should be washed well with soap and water immediately following use. A separate cutting board should be used to cut raw poultry. In order to retard bacterial or viral replication, all poultry products should be defrosted in the refrigerator, not at room temperature. Cooking beef to the appropriate internal temperature kills bacteria and viruses, including AI viruses. All beef products should be cooked thoroughly before eating, and uncooked (raw) beef should be kept separate from cooked foods or foods that will not be cooked to prevent cross-contamination. In addition, people should not eat or drink raw milk or products made with raw milk [123].

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit poultry to be imported from countries in which there were detections of AI, such as China's ban of U.S. chicken in 2015. However, the risk of AI spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or chilled. All documented transmission to date has been from live animals [124; 125].

Humans have no immunity to AI viruses, so illness tends to be severe and the fatality rate high. Prevention is difficult because the viruses tend to be highly contagious. Because of the mobile nature of people and efficient, rapid transport, any virus can spread quickly around the world. The current manufacturing process of influenza vaccine requires several months. The elements are all in place for a pandemic.

In 2007, a team of scientists at the National Institute of Allergy and Infectious Diseases reported that it had developed a way to generate vaccines and therapeutic antibodies that could target constantly mutating influenza viruses, such as H5N1. The team focused on mutations that enable H5N1 hemagglutinin protein to better recognize and enter human cells and those mutations that will elicit antibodies. This information will enable researchers to consider how to design potential vaccines that will protect people from future emerging AI virus mutants, possibly helping to contain a pandemic in its early stages [126].

In order to understand how influenza viruses mutate, researchers have been working to synthesize the hemagglutinin responsible for the 1918 influenza ("Spanish flu") pandemic. The success of this endeavor was reported in 2004, and scientists have since discovered how subtle alterations enabled the virus to move from birds to people [127].

The H5N2 avian influenza virus continues to be monitored around the world by scientists. It is highly virulent but has not been transmitted person to person yet [4; 112]. In 2015, H5N2 avian influenza virus (along with H5N8 and H5N1) were found in more than 200 bird samples, indicating the likelihood that 40 million farm and backyard birds had been infected in 20 states [48]. Starting in 2022 and continuing through 2024, the largest H5N1 avian influenza outbreak in the United States in seven years occurred, affecting nearly 91 million poultry birds and was detected in more than 9,000 wild birds (as of May 2024) [34]. One human case was reported in April 2022, and another was reported in April 2024. Large outbreaks of H5N1 avian influenza were also reported in Europe in 2021–2022, with nearly 48 million poultry birds culled [39]. Canada also experienced a H5N1 large avian influenza outbreak in 2022–204, with at least 11 million birds affected (as of May 2024) [40].

PREVENTING OR LESSENING THE EFFECTS OF A PANDEMIC

Vaccine Development

As with the development of all vaccines, the first step is to isolate the organism. In the case of AI, various research centers and companies around the world are working to make a vaccine. The first step is to isolate the virus (e.g., the H5N1 influenza A virus in 2004). Next, the virus is dismantled so the most virulent elements can be excluded. Then the virus is reassembled without those virulent elements, and attempts are made to produce it [124]. As noted, the virus has been isolated and the virulent elements have been identified to allow vaccine development to proceed. In 2006, a new recombinant H5N1 virus became available for distribution to companies interested in pandemic vaccine development [128]. In 2007, GlaxoSmithKline received a contract from the U.S. Department of Health and Human Services to manufacture 22.5 million doses of AI vaccine in addition to the 5 million doses ordered in 2006 [129]. Since that time, various other AI vaccines have been ordered and delivered to the national stockpile [72]. Research to find novel media or methods (rather than using eggs) is ongoing [130].

In 2007, the FDA approved the first human vaccine for the AI virus H5N1 [131]. This vaccine is intended for individuals 18 to 64 years of age who could be at an increased risk of exposure to the H5N1 influenza virus. The vaccine is not available commercially, but rather has been purchased by the federal government to be distributed if necessary. The vaccine consists of two 1-mL IM doses given 21 to 35 days apart (optimum: 28 days). There is thimerosal in this vaccine [45; 131]. Because this vaccine has been approved by the FDA and found to be safe and effective, it is no longer considered experimental. Therefore, it can be used during a pandemic without the time-consuming protocol and signed informed consent necessary for an experimental drug or vaccine [131]. In 2013, the first adjuvanted H5N1 vaccine, Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, was approved for individuals 18 year of age and older. The vaccine is not for commercial use, but at least 20 million doses are stocked at the Strategic National Stockpile for emergency release [53].

Antiviral Stockpile

Another plan is to gather a supply of effective antiviral medications to use not only to treat AI but also to use as a preventive treatment if a vaccine is not available. As discussed, some testing of the four antivirals available has been done with the H5N1 virus, which produced mass illness in Asia in 2004. So far, only oseltamivir was shown to be effective. More research is needed [114]. Some have suggested combining probenecid and oseltamivir to enhance effectiveness and to stretch limited oseltamivir supplies [132].

It is not known if other AI strains will be sensitive to oseltamivir or to any of the other antivirals. The suggestion has been made to stockpile antivirals so they would be available in a pandemic. Logically, it would make sense to include the effective antiviral medications in the Strategic National Stockpile and use the same distribution system and overall protocol in managing them [133].

Increased Interaction Between Veterinary and Human Disease Experts

Because of the rapid spread of avian influenza among flocks in Asia in the spring of 2004, the need for more involvement and communication between animal and human experts became apparent. No reporting of animal diseases is required by the WHO. However, the Global Early Warning System combines and coordinates the disease intelligence mechanisms of the United Nations Food and Agriculture Organization, the World Organization for Animal Health, and the WHO to provide the international community with information about the prediction, prevention, and control of animal disease threats [134]. In addition, the World Organization for Animal Health monitors avian influenza outbreaks in its member countries (including the United States) [28]. Human medical practitioners are not trained in the subtle indications of animal illnesses, nor are they usually aware of early indications that an epidemic is developing. Veterinarian expertise is also needed to institute the best measures for containing the illness and limiting transmission not only to animals but to humans as well [135].

Travelers

During the outbreaks of AI in poultry in Asia during 2003–2004, people were not restricted from traveling to outbreak areas because of the limited transmission to humans. However, the following recommendations were sent to embassies and Americans living abroad [136]:

- Practice frequent and careful handwashing with soap and water or with a hand cleanser if soap and water are unavailable.
- Avoid bird markets and poultry yards where AI is most likely to be transmitted.
- All poultry and eggs should be cooked well as influenza virus is destroyed by heat.
- Masks and other personal protective equipment in public areas are not recommended.

Travelers should be immunized with the current influenza vaccine against human influenza strains before traveling and should be reminded that winter (i.e., flu season) occurs in the Southern Hemisphere when the Northern Hemisphere is experiencing summer.

Limiting Introduction of Avian Influenza to Other Countries

The CDC has developed guidelines for airline personnel with a suspected case of AI on board an international flight originating in an area in which AI has been reported [137]:

- As much as possible, airline staffs are to keep the sick person separated from close contact with others.
- A surgical or procedural mask should be provided to limit the amount of droplets coughed into the air. If the passenger cannot wear the mask, anyone assisting him/her should be masked.
- Staff should teach the passenger cough etiquette if it is not being practiced.
- Disposable gloves are to be worn for any contact with body fluids, and hands are to be washed well when gloves are removed.

The captain is to report the illness to the nearest U.S. Quarantine Station if the aircraft is coming to the United States. The Quarantine Station will coordinate appropriate medical assistance when the plane lands and will notify the appropriate CDC staff.

In addition, general precautions of handwashing and covering coughs are, as always, important. Should flight personnel or ground staff become ill and believe they have been exposed to AI, they should notify their employer. If they are away from home, they should obtain local medical help. On any visit to a medical practitioner, they should inform the staff of the possible exposure to AI [137].

Limiting Continuing Disease and Transmission Among Fowl

The major way to limit disease and transmission among domesticated fowl is to destroy all diseased birds and their flockmates. Because the virus appears to be carried by people and machines, possibly on shoes and tires, to surrounding areas, the recommendation is that all fowl in a 2-mile (3-kilometer) radius of the diseased flock be culled. Obviously, no shipping of live poultry from the infected areas should occur.

Those culling the flocks are vulnerable to infection because they will be dealing with diseased birds, exposed to their feces, or inhaling dust/dirt contaminated with the feces. Therefore, cullers must have personal protective equipment: coveralls or a surgical gown with long sleeves and an impermeable apron, heavy duty rubber gloves or disposable nitrile or vinyl gloves,

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rubber boots or disposable shoe covers, N95 respirator masks, and safety goggles. Frequent effective handwashing is important. All cullers should have received the current influenza vaccine so they will not acquire the circulating influenza and provide an opportunity for reassortment with the AI strain. Cullers should be monitored by the local health department and be provided information on the ways to prevent infection. They should be instructed when to call the practitioner and to always tell the practitioner that they have been exposed to AI. Persons who are at high risk for complications from influenza should not be employed as cullers. Medical personnel who have contact with cullers should make sure that the cullers have received the current influenza vaccine, understand the symptoms of the flu, realize that eye infections are common, and understand the importance of following the protective guidelines, including how to effectively wash their hands. The CDC states that treatment with an antiviral may be considered for workers involved with culling flocks of known infected birds, but does not recommend routine use of chemoprophylaxis of workers involved in culling non-infected birds as a preventative measure [31]. Whether personal protective equipment was used correctly, the type of exposure, and risk of complications from illness should be part of clinical decision making. Oseltamivir or zanamivir (one dose twice daily) is recommended versus the typical antiviral regimen (once-daily dose) for exposed individuals who require chemoprophylaxis [31].

Those who dispose of the carcasses and those who are cleaning and disinfecting the environment where the flocks were housed are also at risk. The viruses can survive for varying periods of time, in some cases up to weeks or months, depending upon the temperature and humidity. For personal protection, those who dispose of the carcasses should follow the same recommendations as the cullers [31].

All workers involved in eradication efforts should be monitored for respiratory symptoms, fever, and conjunctivitis for one week after the last involvement with the diseased birds or their environment. If they seek medical care, they should be instructed to tell the practitioner that they were working with birds that had AI. Other than seeing the practitioner, all symptomatic personnel should stay home until their temperature has been normal for 24 hours. To protect their families, they should cover all coughs and dispose of the tissues safely, wash their hands well, and try to limit any face-to-face contact with others [151].

In handling environmental cleanup, it is important to note that the virus is killed by heating to 56 degrees C (132.8 degrees F) for three hours or to 60 degrees C (140 degrees F) for 30 minutes. Formalin and iodine compounds will also kill AI. When the temperature is cool, the virus can survive for three months in contaminated manure. It can survive for four days at 22 degrees C (71.6 degrees F) in water and for more than 30 days at 0 degrees C (32 degrees F) [116].

The culling of millions of birds has an economic impact on the owners and countries in which the culling must be done. However, the more widespread the virus is in any country or countries, the more opportunity there is for transmission to humans. Each AI in a human increases the possibility that co-infection with a human influenza virus can occur leading to reassortment of the antigens and a new virulent influenza virus that can be transmitted person-to-person [116].

Limiting Transmission of Influenza by Medical Treatment

If a patient is known to have or is suspected of having respiratory AI, he or she should be segregated in the waiting room, be provided with a surgical or procedural mask, be given tissues and a way to dispose them, and not be kept in the waiting room for an extended period.

A nasopharyngeal swab or aspirate should be collected and sent to the local public health laboratory. It is important to keep the local health authorities aware of any such suspected illness so that the full use of available resources can be made, if necessary. The specimen should then be forwarded to the state laboratory for reverse transcription-polymerase chain reaction (RT-PCR) for influenza A analysis and, if possible, for H1 and H3 analysis. Should the state not have the capacity to perform these tests, or if the tests are positive, the specimen should be sent to the CDC. Only a level 3+ laboratory should attempt to isolate the virus. Blood should be collected and stored locally for an acute (within one week of symptom onset) and convalescent (after three weeks of symptom onset) specimen to test for AI antibodies [38].

Medical practitioners should also be alert to ask all patients with respiratory symptoms and fever if they have traveled to any area in which AI is reported [139].

Increase Detection and Surveillance Systems

Early detection is another way to handle AI so that proper containment procedures can be initiated as soon as possible. As discussed, both the CDC and the WHO are working to increase surveillance in countries around the world [134; 140]. Hopefully, all countries will be able to detect and acknowledge the presence of a disease before it becomes widespread and the death toll escalates [116].

SWINE INFLUENZA

As discussed, pigs represent an important link in the interspecies transmission of influenza and in the creation of new virus types. In addition, swine influenza has the potential to cause significant disease in humans, although it is difficult to predict the potential impact of swine influenza in humans. Because most individuals, with the possible exception of those with regular contact with pigs, do not have immunity to these viruses, the potential for pandemic exists.

Swine influenza is usually caused by the H1N1 subtype, but other swine influenza A viruses do occur, including H1N2, H3N1, and H3N2 [141]. Although swine flu viruses do not normally infect humans, sporadic human infections have occurred. When this occurs, these viruses are called "variant viruses" and are denoted by adding the letter "v" to the virus subtype designation. Human infections with H1N1v, H3N2v, and H1N2v viruses have been detected in the United States [141]. Pigs may become infected with more than one virus subtype simultaneously; in these cases, genes from the viruses may mix and create a new "reassortment" virus [142]. The main swine influenza viruses circulating in U.S. pigs in the past decade include triple reassortant (tr) H1N1, trH3N2, and trH1N2 [141].

Among pigs, swine influenza is a highly contagious acute respiratory disease. In many countries, including the United States, swine populations are routinely vaccinated against the prevalent subtypes. Vaccination of pigs, while not sufficient to produce sterilizing immunity, can reduce the levels of virus shed by the animals and reduce the potential for human exposure and infection [143].

In 2009, an outbreak of H1N1 influenza A (hereafter referred to as 2009 H1N1), popularly referred to as the "swine flu," occurred. Tests showed this virus was similar to influenza viruses normally occurring in pigs in North America. However, with more extensive testing, scientists learned that there were two genes present that typically occur in pigs in Europe and Asia. In addition, there were also avian and human genes. A quadruple reassortment virus was the result [11; 144].

It should be noted that the so-called Spanish Influenza of 1918–1919 was also an H1N1 virus. The hemagglutinin gene in 2009 H1N1 influenza apparently descended from the avian-origin 1918 pandemic influenza virus; however, laboratory testing showed that 2009 H1N1 did not have any 1918-like markers that had been associated with increased risk of severe disease, nor did it have genetic markers that were previously associated with high death rates in people infected with the avian influenza A (H5N1) virus in other countries [144].

The 2009 H1N1 virus was first detected in the United States in April 2009. Laboratory testing at the CDC confirmed infection with the virus in two patients, 8 and 10 years of age, who lived 130 miles apart, who had no contact with pigs, and who had no known connection to one another. Sporadic reports of human infection with North American-lineage swine influenza virus in the United States had been reported from December 2005 to January 2009, but the detection of infection in the two children raised concern that a novel swine-origin influenza virus had made its way into the human population and that human-to-human transmission of the virus had occurred. By September 2009, more than 99% of the circulating viruses were 2009 H1N1 [144].

The 2009 H1N1 virus was not a new subtype, but many humans had no pre-existing antibody to it (especially those younger than 65 years of age). The virus quickly spread worldwide, and on June 11, 2009, the WHO declared it a worldwide pandemic [144]. The 2009 H1N1 virus remained the predominant circulating virus for the entire 2009–2010 influenza season [11; 145]. On June 23, 2010, the public health emergency for 2009 H1N1 expired in the United States, and the WHO declared the pandemic over on August 10, 2010 [146].

Data from past pandemics show that influenza activity occurs in waves. A second wave of 2009 H1N1 occurred in the fall of 2010 and peaked in the first three weeks of October [8]. Experts believe that 2009 H1N1 will continue to circulate for some time as a typical winter flu, as it did extensively in 2012–2013 and 2015–2016. It is included in the formulation of the 2023–2024 vaccine [8].

TRANSMISSION

Like all flu viruses, 2009 H1N1 is mainly spread among people by coughing, sneezing, talking, and occasionally via fomites. It is not spread by food or by eating pork or pork products. There have been no cases acquired from influenza-contaminated drinking water. Chlorine treatment of drinking water has been shown to inactivate the highly pathogenic H5N1 virus, and H1N1 would be similarly affected. A documented case of influenza from any water exposure (drinking or recreational) has not occurred.

Pets, such as dogs, cats, and ferrets, can be infected with H1N1 from close contact with a sick human. All available information indicates that H1N1-infected dogs, cats, and ferrets do not transmit the illness to humans. So far, there is no H1N1 vaccine for animals. Most recover with supportive care [11].

When a swine influenza virus does become a source of widespread human illness, the transmission patterns change. Instead of being mainly limited to swine contact, the virus will spread by human-to-human contact. According to the CDC, available data indicate that the 2009 H1N1 virus is transmitted in ways similar to other influenza viruses, primarily via large-particle respiratory droplet transmission [92]. Because humans have little to no immunity to influenza viruses of swine origin, transmission may be common.

H1N1 survives on surfaces, including kitchen counters, door knobs, desk tops, and other fomites, for two to eight hours. Individuals can pick up the virus when they touch contaminated objects and unconsciously then touch their eyes, mouth, or nose. Thus it is vital for people to learn to keep their hands away from their mouths, eyes, and nose and to frequently wash their hands well with soap and water or use an alcohol-based hand sanitizer. An alcohol-based product, bleach solution, or hot, soapy water can be used to clean surfaces [148]. One positive result of the H1N1 pandemic, as indicated in a study conducted in Hong Kong, was that people were washing their hands more frequently and wearing face masks when having ILI or in public areas [149].

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A major transmission concern with 2009 H1N1 was regarding newborns whose mothers had the virus. The CDC and State Health Departments strongly recommended vaccination for this population because of demonstrated risks to both infants and pregnant women. However, many disregarded the recommendation. It was then decided that infant and mother should be separated until the mother had been on antivirals for at least 48 hours, was afebrile for 24 hours without antipyretics, and could control her cough and respiratory secretions. Before visiting the infant, the mother was instructed to clean her hands well with soap and water or an alcohol-based hand sanitizer, wear a face mask, and observe respiratory/cough etiquette. If her gown had been contaminated with byproducts of coughing or sneezing, she was instructed to change to a fresh gown. Following these guidelines, the mother was then allowed to hold, feed, and care for the infant [8].

PREVENTION

Like seasonal influenza, vaccination is the most important preventive measure. Other common sense preventive steps (e.g., appropriate cough cover, correct disposal of used tissues, adequate rest, good fluid intake, staying home when ill) should also be practiced.

Vaccine

The CDC identified five groups who were given first priority vaccination [144; 150]:

- Pregnant women
- Persons who live with or provide care for infants younger than 6 months of age
- Healthcare and emergency medical services personnel
- Children and young adults 6 months to 24 years of age
- Persons 25 to 64 years of age at higher risk for influenza-related complications

The ACIP also recommended that local public health authorities and healthcare practitioners have flexibility to determine how quickly and when to expand vaccination to other groups [144]. The priority patients were vaccinated as soon as the vaccine was available. The CDC recommended that children younger than 10 years receive two doses of influenza vaccine [144]. For the 2018–2019 flu season, the ACIP recommends that children 6 months through 8 years of age who are receiving influenza vaccine for the first time be given two doses at least four weeks apart [8].

SYMPTOMS

Similar to seasonal flu, H1N1 symptoms include chills, fever, myalgia, fatigue, headache, cough, sore throat, and rhinitis. But unlike seasonal flu, there may be vomiting and diarrhea in some people. Others may have respiratory symptoms without fever [11; 152].

DIAGNOSIS

Unless it becomes a pandemic, swine influenza infection in humans generally goes undistinguished from typical human influenza as a result of the overlapping flu seasons and the relatively mild clinical presentation. The disease is diagnosed by analysis of a sputum sample collected in the first four to five days of illness, when an individual is most likely to be shedding the virus [153]. In June 2010, the FDA authorized the CDC Influenza 2009 A (H1N1)pdm Real-Time RT-PCR panel (IVD) to detect human infections with 2009 H1N1. This test replaced the previous real-time RT-PCR diagnostic test authorized by the FDA in April 2009, just as the WHO declared that a pandemic was imminent [144; 154]. There are now several RT-PCT and other molecular assays available to differentiate 2009 H1N1 [155].

In the case of the 2009 H1N1 virus, the CDC recommended that clinicians not routinely test for the virus when it was known to occur in the community, but that testing be prioritized in people who were hospitalized with suspected flu and in people for whom a diagnosis of flu would help their physician make decisions about their care [155]. As the 2009–2010 H1N1 epidemic progressed, it became apparent that those younger than 65 years of age were at greatest risk [8].

TREATMENT

While most swine influenza cases were sufficiently mild to resolve spontaneously, antiviral medications were used if treatment was indicated. The specifically recommended agents were determined based on clinical and epidemiologic assessment of the virus. For example, in the case of the 2009 H1N1 outbreak in North America, the virus's susceptibility profile indicated that the preferred antivirals would be oseltamivir or zanamivir [97; 156].

During the 2009–2010 H1N1 pandemic, the CDC recommended antiviral treatment for all persons with suspected or confirmed influenza requiring hospitalization [145]. In addition, early empiric treatment with oseltamivir or zanamivir was considered for persons with suspected or confirmed influenza who were at higher risk for complications, including [145]:

- Children younger than 2 years of age
- Persons 65 years of age or older
- Pregnant women and women up to two weeks postpartum (including following pregnancy loss)
- Persons of any age with certain chronic medical or immunosuppressive conditions
- Persons younger than 19 years of age who are receiving long-term aspirin therapy

The recommended treatment for adult and adolescent patients is either 75 mg oseltamivir twice per day or 10 mg (two 5-mg inhalations) of zanamivir twice daily [45; 145]. Children 7 years of age and older may be treated with the adult dose of zanamivir. However, calculating oseltamivir doses for children is more complicated and has been the source of medical errors [157]. It is important to note that while healthcare providers in the United States generally write prescriptions for liquid medications in milliliters, oseltamivir is dosed in milligrams [157]. For infants 2 weeks of age or older, the oseltamivir dosage is 3 mg/kg twice daily [45]. For children between 1 and 12 years of age, dosage is based on weight [45; 145; 158; 160]:

- <15 kg (<33 lbs.): 30 mg twice daily
- >15 kg to 23 kg (>34 lbs. to 51 lbs.): 45 mg twice daily
- >23 kg to 40 kg (>51 lbs. to 88 lbs.): 60 mg twice daily
- >40 kg (>88 lbs.): 75 mg twice daily

Treatment should continue for five days [45]. Pregnancy is not considered a contraindication to the use of oseltamivir or zanamivir.

As of 2015, 2009 H1N1 was susceptible to both oseltamivir and zanamivir, with a few exceptions [96; 103]. Those resistant to oseltamivir have been sensitive to zanamivir. Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified, but the public health impact has been limited [103]. As of 2015, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide [103]. A study published in 2022 found that from 2017 to 2019 there were very few oseltamivir-resistant H1N1 viruses circulating in Brazil [188]. Australian research during their 2020–2021 flu season found 2 out of 1,538 samples that were resistant to oseltamivir [138].

INFLUENZA PANDEMIC

The threat of an influenza pandemic has been overshadowed by the onset of the COVID-19 pandemic and resulting years of surveillance and response. However, some experts predict that an influenza pandemic has the potential to be even more deadly than the COVID-19 pandemic [41]. The risk of an influenza pandemic remains, and lessons should be learned from the challenges and failures of the COVID-19 response.

Should methods for containment of a new avian or swine influenza virus fail, a worldwide pandemic could follow. Because the population has no immunity to the new strain, as was the case with COVID-19, billions of people could be infected and several million could die. The 1918 pandemic afflicted 20% to 40% of the world's population and caused 50 million deaths, at least 675,000 of which were in the United States [161]. As a comparison, "seasonal" flu generally affects less than 20% of the population [162]. The WHO estimates that there could be 233 million outpatient visits, 5.2 million hospitalizations, and 7.4 million deaths globally within a very short period of time were an influenza pandemic to occur [163]. Waves of the outbreak could occur in any given community for approximately six to eight weeks, then reoccur months later, affecting the global population for at least one to two years [161]. The resulting strain on resources (possibly exceeding that of the COVID-19 pandemic) would be far more severe than a terrorist attack that is localized to one or a few areas and lasting from a few minutes to hours. However, planning for a bioterror attack and an influenza pandemic have many similarities, and each can enhance the other [164].

Medical practitioners, emergency departments, and clinics, especially walk-in facilities, will be the first contacts in a pandemic. Having a high index of suspicion and using rapid testing is vital to help slow the spread of the disease. Checking the CDC weekly influenza reports will help to clarify suspicions, but obviously, COVID-19 complicates diagnosis [166].

The WHO has defined phases for a pandemic that reflect a global risk assessment of each influenza virus with pandemic potential [168]:

- Interpandemic phase: The period between influenza pandemics
- Alert phase: Influenza caused by a new subtype has been identified in humans, and the population has little or no immunity to the virus. This may be a precursor to a pandemic.
- Pandemic phase: A period of global spread of human influenza caused by a new subtype with sustained person-to-person transmission. Multiple cases occur in the same geographic area.
- Transition phase: As assessed global risk reduces, de-escalation of global actions may occur, and reduction in response activities may be appropriate.

The CDC has developed guidelines for public response in a pandemic situation. These stress that people should stay away from crowds, avoid close contact with anyone at work or school, stay home if they or anyone in the household is sick, wash hands frequently, practice covering all coughs and sneezes, and dispose of tissues safely. Industrial masks/N95 respirators should be worn by caregivers. N95 masks must fit closely (no air leaks) to be effective. Proper disposal of a mask is imperative, as it has the potential to become a source of infection rather than protection [106; 169].

PLANNING FOR A PANDEMIC

In planning for the inevitable pandemic, five areas should be covered. These include: surveillance and laboratory issues, communication, community services, medical care, and vaccines and drugs. In 2006, the California Department of Health Services developed the *Pandemic Influenza Preparedness and Response Plan* [170]. The plan was then revised in 2007.

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The 2007 plan includes sections on pandemic influenza surveillance and epidemiology, laboratory testing capacity, healthcare planning, infection control in the healthcare setting, case management, vaccine programs, antiviral drug programs, community disease control and prevention, and risk communication. These sections cover the responsibilities of the medical community (health practitioners, hospitals, and clinics) and public health departments and include prevention and mitigation plans [170].

SURVEILLANCE AND LABORATORY ISSUES

This area includes establishing global and local data collection systems in order to determine expected disease rates in humans and animals so that an increase is recognized as quickly as possible. It also includes developing laboratory infrastructure and expertise to handle specimens correctly and accurately. The CDC is a WHO Collaborating Center that plays a major role in identifying antigenically drifted seasonal and novel influenza A viruses that possibly have pandemic potential [171]. The CDC's Influenza Division conducts surveillance throughout the year and collects and analyzes influenza viruses from around the world for antigenic (immune response), antiviral susceptibility, epidemiology, and genetic characterizations.

COMMUNICATION

The second planning area is communication among all those who will be involved in a response on local, state, and federal levels. The Federal Emergency Management Agency requires that all planning for various hazards/disasters/terrorist acts follow the Incident Command System (ICS) [172]. This system provides a structure for the flow of information to the participants providing the response and back to those in authority. An influenza pandemic would require multiple agencies, organizations, and community groups to effectively respond, so in many areas, they would be under the local ICS.

In addition, communication includes relaying accurate, frequent, concise, and timely information to the public by a primary spokesperson. Health experts should use interactions with media personnel to provide educational points about the transmission, prevention, and symptoms of influenza. Such points, referred to as "sound bites," are brief, accurate, in common language, and important.

Another area of communication is between individual healthcare providers and patients. Having patient educational materials prepared before the flu season will assist patients to remember what they have been told and increase their participation in preventing the flu, as well as caring for themselves or someone else with the flu. The U.S. Chamber of Commerce has also developed guidance for business owners that lists steps that can be taken to protect employees and to help keep businesses operating in the case of an outbreak [173].

COMMUNITY SERVICES

One of the facets of a pandemic is the social disruption caused by the illness of so many employees. Therefore, the third area in any preparedness plan is maintenance of community services from healthcare providers, ambulance personnel, police, fire fighters, utility workers, and truck drivers—all the services that are called on daily to maintain life in our communities. This may involve providing vaccine first to healthcare professionals and those responsible for essential services in the community. Some services and work may be done via telecommuting so that more people can stay at home and lessen their exposure to the influenza virus.

MEDICAL CARE

Medical care is the fourth area that will be heavily impacted in a pandemic. The local health officer in most jurisdictions has the legal authority to isolate those with symptoms and quarantine those who have been exposed, as needed, to slow the spread of the disease. Equipment and care may have to be prioritized. In a pandemic, multiple geographic areas are impacted, so obtaining help from another area probably will not be possible. Some hospitals, health departments, and other medical facilities are developing lists of physicians and nurses who are either retired or no longer practicing but who would be available to assist during a crisis if needed [174].

If all available hospital beds in the area are in use, it may be necessary to set up a shelter for medically fragile people. Local health departments have plans and agreements with the American Red Cross and other organizations to establish shelters. Normally, these shelters are for people who have been displaced/evacuated because of a natural event (e.g., fire, flood, earthquake). A shelter for medically fragile people has additional equipment and staffing needs. Such a shelter would be for people who require help with medical treatment, such as wound care, medications, and IVs. People who are too sick to care for themselves and who have no one to care for them would be appropriate referrals for a medically fragile shelter [175].

VACCINES AND DRUGS

The final area to be addressed is the supply and delivery of vaccines and drugs. The objectives of planning are to reduce morbidity and mortality, make sure essential services are available, reduce the economic impact, and equitably distribute the resources [164]. Those with high risk of complications from the flu are generally the first to receive the vaccine if a shortage is anticipated or production is slow. In a pandemic, the decision may be made that healthcare professionals and others providing essential services would be the first recipients of vaccine. Because the vaccine would be completely new to a person's immune system, two doses 30 days apart may be needed to produce immunity, as is the current practice for children 6 months through 8 years of age receiving influenza vaccine for the first time [8].

ASSESSMENT OF A PATIENT WITH INFLUENZA-LIKE ILLNESS
1. Is this the time of year when influenza is expected? 2. Has the patient done any traveling in the last 10 days? If yes, find out where so the practitioner can relate to any known SARS, avian flu, or other outbreaks in the area. Did the patient travel in an airplane or on a cruise ship? 3. Can the patient pinpoint an exact time when the illness began? 4. Has the patient had any recent contact with any farm animals, such as pigs, cows, chickens, turkeys, ducks, or other birds? 5. In the last few days, has the patient been around anyone who is sick? If yes, find out who was sick, type of contact, when it was, and symptoms of the person who was sick. 6. Is the patient getting sicker or feeling just as bad as when he or she first became ill? Or perhaps feeling a bit better? 7. Has the patient been in any place in the mountains? Did he or she notice any signs warning about plague? What did the patient do there—camp, hike, etc.? 8. Has the patient consumed any raw/unpasteurized milk in the last month? 9. If ricin toxin is suspected, find out the patient's activities in the last 24 hours. When asking a patient or family member when a symptom began, or other information that depends on recalling one's activities, it is helpful to have a calendar and to refer any symptom to some event that would be easily remembered; for example, "Your sister visited on Tuesday. Did you have the fever then?"
Source: Author — *Table 4*

NONPHARMACOLOGIC INTERVENTIONS

During the influenza pandemic in 1918, large public gatherings continued to be permitted in some areas, most notably in Philadelphia, which served to spread the epidemic and led to a death rate of 719 per 100,000. Cities that had enforced a shutdown of schools, churches, and other gatherings slowed the spread and experienced a death rate of 347 per 100,000. Quarantine, school closings, and public meeting bans cut peak death rates 30% to 50% [176].

In 2007, the federal government established that, in the case of a severe influenza outbreak, schools should be closed for up to three months; sports events, movies, church, and other public gatherings and events should be canceled; working hours should be staggered to decrease the number of commuters using public transportation at any one time; and the use of public transport should be discouraged [177]. Sick people and their families, even healthy members, should stay home 7 to 10 days. Issues of other gathering places, such as daycare centers and malls, will also need to be addressed. Parents should prevent their children from gathering. Measures of isolation (isolating ill patients) and quarantine (isolating exposed persons) should be used to slow the spread of influenza [178]. State borders and airports would not be closed because of the need to transport food and other supplies [177; 178].

In New York City, the plan emphasizes the importance of early detection. A monitoring system that tracks 60,000 pieces of information (e.g., ambulance runs, emergency room visits, pharmacy sales) has been developed [179].

A cooperative research project between Azusa Pacific University in California and National Chung Sing University in Taiwan is researching traditional Chinese herbal treatments and their effects on influenza virus subunits to develop alternative treatments, especially for countries in which vaccines or pharmaceutical treatments will be unavailable in a pandemic [180].

CHALLENGES OF A PANDEMIC

For medical care providers, an influenza epidemic presents many challenges. These would be compounded by the increased number of cases in a pandemic. A group in Los Angeles studied the impact on emergency departments and outpatient facilities during seven influenza epidemics. Some of the lessons learned in order to better cope with an increased number of patients were that [147]:

- Elective surgery should be reduced or eliminated.
- Facilities should work with licensing agencies, fire marshals, and other regulators to relax staff-patient ratios and/or bed capacity limitations.
- Additional staff resources for epidemics should be developed.
- Walk-in influenza clinics should be established to triage and treat patients at lower cost.
- Methods to identify additional needed equipment should be developed.

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During the SARS outbreak, nurses at Stanford University Medical Center set up receiving areas to prescreen hundreds of patients before they entered the emergency department. Those with ILI were diverted to negative pressure rooms for further testing. Screening questions were used to triage the patients [147]. ***Table 4*** provides a list of questions that could be asked of patients to elicit extra information that may assist in a more rapid diagnosis. These questions should be asked in the receiving area of the hospital, clinic, or office in order to minimize the introduction of highly contagious organisms.

This receiving area would also be a place where educational materials could be provided for the "worried well." In an office situation, it might be possible to set up a small table outside the office door to screen patients and distribute masks and educational materials. Some public health department plans include supplying public health staff to emergency rooms to help answer questions and educate the worried well, allowing the hospital staff to assist in the care of those critically ill.

LESSONS FROM THE COVID-19 PANDEMIC

Although the COVID-19 pandemic is ongoing and the learning process is ongoing, the Lancet COVID-19 Commission highlighted several areas of failure that must be improved in order to prevent the magnitude of death witnessed globally, but particularly in the United States, in the event of another pandemic [42]:

- Most governments failed to acknowledge the threat and reacted too slowly.
- Coordination between governments to slow the spread of the virus and keep economies functioning was inadequate (e.g., commodity supply chains, travel protocols, testing strategies, public health and social measures,) despite high interdependence of nations.
- Routine public health and social measures (e.g., mask usage, gathering in crowds) were ignored by large portions of the population.
- The virus was far more prevalent among essential workers, people living in congregate settings, people with chronic conditions, and people without access to quality health care.
- Countries with strong public health systems (versus only strong clinical systems) fared much better. Low-income countries, with previous epidemic experience and strong public health infrastructure, fared much better than high-income countries.
- Vaccines, although developed relativelyquickly, were hindered by a lack of pre-existing regulations regarding intellectual property rights, technology sharing, and allocation of vaccines to low-income nations.
- Economic recovery was hindered by a lack of vaccine availability and uptake, and the virus continued to circulate and mutate due to a lack of significant ("herd") immunity.
- Extreme levels of systematic misinformation and politization were not effectively countered.

CONCLUSION

Influenza, with its complication, pneumonia, is an infectious disease that remains one of the top 10 killers in the United States. An effective vaccine to prevent influenza has been available for decades but is underused by both the general public and healthcare professionals. As a result, the economic burden of influenza is billions of dollars, including the inefficient use of healthcare resources.

The threat of biologic weapons has made the control of influenza imperative as many of the possible biologic agents initially may be misdiagnosed as influenza because of similar symptoms. Added to the perils facing the world is the expected pandemic of influenza as the result of the introduction of an avian or swine influenza virus to which humans have no immunity.

GLOSSARY OF TERMS

Antigenic drift: Change in an influenza virus that allows it to resist the immunity developed against it. Antigenic drift is a factor behind the need for an annual influenza vaccine.

Antigenic shift: Reassortment of RNA segments involving hemagglutinin and neuraminidase antigens from two different influenza A types in one host cell to create a new influenza type.

Antiviral: A medication that will kill or weaken a virus.

Avian, or bird, influenza (AI): Influenza caused by viruses that occur naturally among wild birds. The low pathogenic variety is common in birds and causes few problems. High pathogenic AI is deadly to domestic fowl and may be transmitted to humans, resulting in high morbidity and mortality rates due to lack of immunity.

Case definition: A standardized precise description of a disease to assist in accurate data collection. Generally, there are three levels in a case definition: suspect, probable, and confirmed. Description for each level is particular to the disease being defined based on clinical symptoms and laboratory findings.

Epidemic: An increase in the expected number of cases of a particular disease. The amount of increase needed to declare an epidemic depends upon the disease involved.

Hemagglutinin: A surface antigen on the influenza A virus indicated in the name of the virus by a capital H followed by the subtype number.

Influenza: Respiratory illness with fever.

Isolation: Separation of a person with a contagious disease from the public.

Neuraminidase: A surface antigen on the influenza A virus indicated in the name of the virus by a capital N followed by the subtype number.

Quarantine: Restriction of a well person who has been exposed to a known infectious organism.

Pandemic: Epidemic of a disease that is worldwide.

Split virus: Chemical alteration of a virus for use in a vaccine. All influenza vaccine in the United States is split virus.

RESOURCES

Association for Professionals in Infection Control and Epidemiology
https://apic.org

Association of State and Territorial Health Officials
http://www.astho.org

Centers for Disease Control and Prevention
https://www.cdc.gov/flu
https://www.cdc.gov/vaccines
https://www.cdc.gov/flu/weekly/fluactivitysurv.htm

National Institute of Allergy and Infectious Diseases
https://www.niaid.nih.gov/diseases-conditions/influenza

U.S. Food and Drug Administration
https://www.fda.gov

U.S. Food and Drug Administration MedWatch
https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

Vaccine Adverse Event Reporting System
https://vaers.hhs.gov

World Health Organization Global Influenza Programme
https://www.who.int/teams/global-influenza-programme

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APPENDIX 1

HOME CARE OF A PATIENT WITH INFLUENZA

1. Monitor the patient for improvement or worsening of symptoms. Write down the date and time of all observations: temperature, coughing, sneezing, amount the patient has had to drink and eat.
2. Supportive care
   - Over-the-counter medicines that bring fever down (no aspirin in anyone younger than 18 years of age)
   - Pain relievers (e.g., medications, carefully monitored heating pads)
   - Back or leg rubs
   - Cough medications, as ordered and needed
   - Cool cloth to the head
   - Limited light in the room
   - An encouraging, positive, but not overly exuberant attitude
3. Maintain the patient's fluid intake with water, juices, popsicles, ice cubes, tea, coffee, or broths. Milk may be appealing to some patients.
4. Provide any foods that are appealing to the patient. However, fluid intake is more critical than solid food intake.
5. Provide tissues and a disposal place that the patient can reach, such as a wastebasket or paper bag pinned to the bed.
6. Assist the patient to the bathroom, if needed.
7. Continue any routine medications, if possible. Check with the physician if the patient cannot take or vomits the medications or if the medication needs to be taken with food and the patient is not eating.
8. Persons on insulin should have their blood sugar carefully monitored. Blood sugar may go up because of the disease process or go down because of poor food intake.
9. Keep the patient oriented as to time of day and date by telling him/her the time (and day, if needed) whenever they awake. Napping can lead to disorientation, especially in the elderly patient.
   Some patients may also need to be reminded where they are.
10. Provide a way for the patient to summon help, such as a bell, whistle, or some other method.

Source: Author

APPENDIX 2

CARING FOR YOURSELF TO PREVENT THE FLU

1. Get the flu shot.
2. Wash your hands frequently. Use soap, make a good lather, rub lather all over your hands for 15 seconds, rinse well, and dry with a paper towel or with your own towel at home. The process should take at least 20 seconds and should be completed:
    - After shaking hands
    - After being around someone who is coughing/sneezing
    - After caring for someone who is sick
    - As soon as you get home
3. Avoid touching your mouth, nose, or eyes.
4. Wear a mask when you take care of someone with the flu.
5. Get 7 to 8 hours rest in 24 hours.
6. Drink at least six to eight glasses of water each day. Sodas do not count. If one is tiring of water, putting it in a colored glass may help. Also, room temperature water is easier to drink in quantities than cold water.
7. Eat at least five or more servings of fruits and vegetables each day.
8. If caring for someone, get away from the house for a period of time each day, even just to go to the store or take a walk.
9. Avoid alcohol and tobacco.

Source: Author

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APPENDIX 3

WHEN TO CALL THE DOCTOR

Phone Number _____

Usually the person with the flu gets very sick suddenly, stays very sick for a few days, and then starts to feel better. The flu can cause other problems. Below is a list of symptoms and signs that indicate that a person needs help from a physician.

As you take care of the person, write down the date and time when you take the temperature or notice a new sign or symptom. If you are having trouble getting the patient to drink fluids, write down the time the person had a drink and how much they drank. The following signs should be reported to a physician immediately.

Fever

The temperature stays above 102 degrees F in spite of the person taking medicine to bring the fever down. (Never give aspirin to anyone younger than 18 years of age.)

Breathing

The person says or looks like he or she is having trouble breathing. The person is short of breath. The child is breathing very fast. The chest between the ribs or above the collar bone retracts when the child takes a breath. The person, especially if a child, looks a little blue.

Fluids

The person will not drink water, juice, or any fluid or suck popsicles or ice. The infant has less than 6 wet diapers in 24 hours. The urine is very dark and there is not much of it. If the skin on the forearm is pinched up, it slowly returns to normal. The eyes are sunken in and the mouth is dry. The person keeps vomiting or retching.

Changes in Mental State

The person is hard to wake up. No matter what you try, the child/infant cannot be comforted. The person is confused or seeing things. The person has fainted or nearly fainted. The person has a convulsion.

Change in Condition

Any worsening of the flu symptoms, as individuals with the flu will start to feel better after 3 to 5 days. Any worsening of any health problem (e.g., chest pain, swelling of the feet).

Rash

May indicate an allergy to a medicine or a disease other than the flu.

Source: Author

Customer Information/Evaluation insert located between pages 32–33.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 32–33.
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BREAST CANCER
#30613 • 15 ANCC / 6 Pharm Hours
Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and allied health professionals with the information necessary to accurately diagnose and effectively treat patients with breast cancer according to established guidelines, with the ultimate goal of improving patient care and quality of life.
Faculty: Jacqueline Houtman, RN, MA, CDP
Audience: This course is designed for nurses and allied healthcare professionals invested in the care, delivery of treatment, and relevant education of patients with breast cancer.
Additional Approval: AACN Synergy CERP Category A, CCMC

TREATMENT OF HEART FAILURE: AN UPDATE
#30934 • 10 ANCC / 3 Pharm Hours
Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide nurses and ancillary nursing personnel with current information about the scientific advances in the treatment of acute heart failure.
Faculty: Patricia Lea, RN, DNP, MSEd, CCRN
Audience: This course is designed for nurses and ancillary nurse personnel involved in the treatment and continued assessment of patients with heart failure.
Additional Approval: AACN Synergy CERP Category A, CCMC

COMMUNICATION AND SOFT SKILLS IN NURSING PRACTICE
NEW!
#31350 • 3 ANCC Hours
Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide nurses with strategies to support the soft skills needed to provide optimal patient care and enhance professionalism in health care.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for nurses in all practice settings.
Additional Approval: AACN Synergy CERP Category C

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CHILDHOOD OBESITY: IMPACT ON HEALTH CARE
UPDATE
#32014 • 5 ANCC / 1 Pharm Hour
Book By Mail – $38 • ONLINE – $30

Purpose: The impact of childhood obesity on an already stressed healthcare system is high and is estimated to rise as the diagnoses of comorbid conditions continue to occur at a younger age. The purpose of this course is to provide nurses with the information necessary to improve the care of children and adolescents who are overweight or obese.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings with a desire to better understand the issues facing obese children and their families and the impact of childhood obesity on national and global health care.
Additional Approval: AACN Synergy CERP Category A, CCMC

ETHICAL DECISION MAKING
#37074 • 15 ANCC Hours
Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course of treatment, or refusal of such, for and with those for whom they care.
Faculty: Michele Nichols, RN, BSN, MA
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approval: AACN Synergy CERP Category B, CCMC

FORENSIC NURSING: AN OVERVIEW
KY Mandate
#37104 • 2 ANCC Hours
Book By Mail – $23 • ONLINE – $15

Purpose: Forensic nurses are an important link between the medical and legal worlds. The purpose of this course is to inform nursing professionals about forensic evidence collection and documentation, being mindful of preserving evidence while managing critically injured patients, and making referrals to or requesting the assistance of forensic specialists.
Faculty: Michelle Booth, RN, BSN
Audience: This course is designed for all nurses involved in the assessment and care victims, including sexual assault nurse examiners and other forensic nursing specialists.
Additional Approval: AACN Synergy CERP Category A
Special Approvals: This course meets the Kentucky requirement for sexual assault education for SANE credential holders.

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Course Availability List *(Cont'd)*

HIPAA PRIVACY AND SECURITY

NEW!

#91140 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.
Faculty: Carol Shenold, RN, ICP
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B, CCMC

MATERNAL HEALTH DISPARITIES

NEW!

#93010 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.
Additional Approval: AACN Synergy CERP Category B

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES

UPDATE

#94194 • 15 ANCC / 7 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.
Faculty: Susan Semb, MSN, CDCES
Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.
Additional Approval: AACN Synergy CERP Category A

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

Opioids/ Pain Mgmt

#95152 • 3 ANCC / 3 Pharm Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approvals: This course meets the requirements for opioid/ controlled substances and pain management education.

FRONTOTEMPORAL DEMENTIA

MA Mandate

#96102 • 2 ANCC / 1 Pharm Hour

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals with current information on frontotemporal dementia (FTD). Understanding the epidemiology, pathology, clinical features, diagnostic process, genetics, symptom treatment/management, role of brain autopsy, and current research provides a foundation for the care of patients with FTD and support for their families.
Faculty: Ellen Steinbart, RN, MA; Lauren E. Evans, MSW
Audience: This course is designed for physicians, nurses, and allied health and mental health professionals who may intervene to support patients with frontotemporal dementia and their families.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approvals: This course meets the one-time Massachusetts requirement for dementia education.

SUICIDE ASSESSMENT AND PREVENTION

KY Mandate

#96442 • 6 ANCC Hours

Book By Mail – $44 • ONLINE – $36

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approvals: This course meets the one-time Kentucky requirement for suicide education.

ELDER ABUSE: CULTURAL CONTEXTS AND IMPLICATIONS

KY Mandate

#97824 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to increase the knowledge base of nurses, physicians, and other allied health professionals about elder abuse, assessment, and intervention. This curriculum will focus on abuse against elders in domestic settings perpetrated by family members.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is targeted to physicians, nurses, and other allied health professionals who may identify and intervene in cases of elder abuse.
Additional Approval: AACN Synergy CERP Category B, CCMC
Special Approvals: This course meets the one-time Kentucky requirement for domestic violence/elder abuse education.

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

CANNABINOID OVERVIEW

NEW!

#98010 • 3 ANCC / 3 Pharm Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.
Additional Approval: AACN Synergy CERP Category A

COMMONLY ABUSED SUPPLEMENTS

NEW!

#98020 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking dietary supplements.
Additional Approval: AACN Synergy CERP Category A

PARKINSON DISEASE

UPDATE

#98772 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.
Additional Approval: AACN Synergy CERP Category A, CCMC

FOOD ALLERGIES

#98793 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to encourage healthcare professionals in the primary care setting to raise the issue of reactions to food during patient encounters, especially with parents of young patients, and to educate patients about the importance of protecting themselves or their children from allergic reactions.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for pediatricians, other physicians, physician assistants, nurses, nurse practitioners, and members of the interdisciplinary team involved in the care of patients with food allergies who would benefit from a better understanding of the natural history, diagnosis, and treatment of food allergies.
Additional Approval: AACN Synergy CERP Category A

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

#98813 • 10 ANCC / 8 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare professionals a current review of pathogenesis, diagnosis, assessment, and treatment of chronic obstructive pulmonary disease (COPD), emphasizing strategies for prevention and best practice clinical guidelines for managing the stable patient and COPD exacerbations.
Faculty: John M. Leonard, MD
Audience: This course is designed for physicians, primary care providers, nurses, respiratory therapists, and medical assistants involved in the care of patients with COPD.
Additional Approval: AACN Synergy CERP Category A, CCMC

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	91660	Falls and Fall Prevention / 3 Contact Hours	$15
	94424	Influenza: A Comprehensive Review / 10 Contact Hours	$60

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☐	30934	Treatment of Heart Failure: An Update / 10	$68	☐	96102	Frontotemporal Dementia / 2	$23
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☐	37104	Forensic Nursing: An Overview / 2	$23	☐	98020	Commonly Abused Supplements / 2	$23
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1. Was the course content new or review?
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3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
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6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
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10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#90120
Pulmonary Embolism
2 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#91660
Falls and Fall Prevention
3 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#94424
Influenza
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90120 Pulmonary Embolism — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

#91660 Falls and Fall Prevention — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____

_____

_____

#94424 Influenza: A Comprehensive Review — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

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