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Influenza

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Influenza viruses are constantly altering their antigenic structure, and every year the World Health Organization recommends which strains of influenza should be included in vaccines.

- During the autumn and winter months, influenza circulates more often (influenza seasons), causing a greater proportion of influenza-like illness and sometimes serious seasonal epidemics.
- The incidence of symptoms depends on the underlying immunity of the population.

When a significantly different form of influenza occurs by mutation, it can greatly increase infection rates, as well as morbidity and mortality (a pandemic).

Influenza and influenza-like illness (caused by a range of other viruses) are clinically indistinguishable.

- Trials of vaccines assess how to prevent the symptoms and consequences of both, as well as assessing infection rates.
- Many of the studies we found were industry sponsored or written by employees of vaccine companies.

Vaccines are effective in reducing symptoms and school absences in children older than two years, but we found no evidence that they reduce hospitalizations, pneumonia, or death.

Influenza vaccines have a modest effect in reducing influenza symptoms and working days lost in healthy adults. We found no evidence that they affect complications such as pneumonia or hospitalizations. However, vaccines may be associated with adverse effects.

Owing to the poor quality of the evidence, we cannot draw conclusions about the effects of influenza vaccines in persons 65 years and older.

Single studies reporting data for one or two seasons are difficult to interpret and generalize because of the marked variability of viral circulation.

Definition

Influenza is an acute respiratory illness caused by infection with influenza A and B viruses. The illness can affect both the upper and lower respiratory tract, and is often accompanied by systemic signs and symptoms, such as abrupt onset of fever, chills, nonproductive cough, myalgias, headache, nasal congestion, sore throat, and fatigue.

Not everyone infected with influenza virus will become symptomatic, and not everyone with the associated symptoms will have influenza. This is because different viral and bacterial circulating agents cause an influenza-like illness with a clinical picture each year that is indistinguishable from influenza. Between 40 and 85 percent of influenza infections result in clinical illness, depending on age and preexisting immunity.

One systematic review (search date 2004, consisting of six randomized controlled trials in Europe, North America, and the Southern Hemisphere, and totaling 7,164 persons) of influenza symptoms found that, in all age groups, the likelihood of influenza was decreased by the absence of fever (odds ratio [OR] = 0.40; 95% confidence interval [CI], 0.25 to 0.66), cough (OR = 0.42; 95% CI, 0.31 to 0.57), or nasal congestion (OR = 0.49; 95% CI, 0.42 to 0.59). It found that, in persons 60 years or older, the probability of influenza was increased by the combination of fever, cough, and acute onset (OR = 5.4; 95% CI, 3.8 to 7.7), fever and cough (OR = 5.0; 95% CI, 3.5 to 6.9), fever alone (OR = 3.8; 95% CI, 2.8 to 5.0), malaise (OR = 2.6; 95% CI, 2.2 to 3.1), or chills (OR = 2.6; 95% CI, 2.0 to 3.2). The review also found that influenza was less likely if sneezing was present (OR = 0.47; 95% CI, 0.24 to 0.92).

Although influenza is usually diagnosed clinically, genuine influenza infection can be diagnosed only with laboratory confirmation, by culture, by serological responses, or by bedside testing. The rapid bedside diagnostic tests available on the market are mainly antigen detection immunoassays, and (unlike laboratory tests, such as culture or reverse transcription–polymerase chain reaction) can be carried out within 30 minutes. However, the results must be interpreted with caution. During times of low influenza viral circulation, the positive predictive value is low, leading to an increased proportion of false-positive results. In times of high viral circulation, the negative predictive value is low, leading to an increased proportion of false-negative results. It is also impractical to test all potential influenza cases. If a good surveillance system is in place, with quick feedback, the positive predictive value of clinical diagnosis alone (based on high fever and a cough) will be similar to the bedside test (between 79 and 87 percent).

For the purpose of this review, we have included trials that assessed both influenza-like illness and influenza, which are clinically indistinguishable, in persons with no comorbid conditions. Where appropriate, the applicability of data to influenza pandemics has been discussed.

Incidence and Prevalence

SEASONAL INFLUENZA

Circulation of seasonal influenza viruses can vary among years, seasons, and even settings. In temperate areas, seasonal influenza activity typically peaks between late December and early March in the Northern Hemisphere, and between May and September in the Southern Hemisphere. In tropical areas, there is no temporal peak in influenza activity throughout the year. The annual incidence of influenza varies, and depends partly on the underlying level of population immunity to circulating influenza viruses. The incidence statistic for influenza is commonly estimated from virologic testing of symptomatic persons (so-called viral circulation). Patients presenting to a physician typically have a syndrome (influenza-like illness) that can be caused by various agents, and only a proportion of these syndromes is caused by influenza A and B viruses.

One way to determine (not estimate) the incidence of influenza is represented by virologic testing of a truly random sample of persons with influenza-like illness, together with the testing for all other major causal agents. This is not typically done because it is not known how many persons have influenza-like illness at a given time. For this reason, the only method to determine influenza incidence with a high level of accuracy is to use the control arms of influenza vaccine and antiviral studies. Based on studies in The Cochrane Library, incidence of influenza is estimated at around 7 percent. However, the control arms of the 95 studies identified evaluated persons with influenza-like illness. Therefore, 7 percent is not the absolute incidence of influenza in the general population, but rather the portion of influenza-like illness that is caused by influenza, making the incidence of influenza itself in the general population much smaller (approximately 0.5 percent).

PANDEMIC INFLUENZA

The incidence of symptomatic influenza depends on, among other factors, the susceptibility of the host. Occasionally, a new type of influenza virus appears, generated either by direct mutation or by reassortment of the viral genome. Because immunity to this new virus is low, it is able to behave in an aggressive way, causing morbidity and mortality on a global scale, mainly because of the body's inability to prevent the creation of a high viral load, the cytopathic effect of the new virus, and the complications in target organs, such as the lungs and airways. Widespread epidemics are known as pandemics. In the 20th century, three pandemics were caused by different influenza A viral subtypes: in 1918 to 1919 (H1N1), 1957 (H2N2), and 1968 (H3N2).

AVIAN INFLUENZA

Influenza virus infection may also appear as a zoonotic infection, with direct spread of the avian virus to humans. In April 2003, 87 persons in the Netherlands were infected with avian virus H7N7. In most cases, the only symptom was conjunctivitis. However, a 57-year-old veterinarian dealing with veterinary public health interventions died of acute respiratory distress. An avian virus (H5N1) has been transmitted from birds to humans (and occasionally from human to human) sporadically since 1997. Such transmission has usually taken place in situations of poor hygiene and close proximity between birds and humans.

Etiology and Risk Factors

The influenza virus is composed of a protein envelope around an RNA core. On the surface of the envelope are

Clinical Question

What are the effects of vaccines to prevent influenza?

Likely to be beneficial	Vaccines in adults (prevention of cases)
	Vaccines in children (prevention of symptoms and/or infection)
Unknown effectiveness	Vaccines in older persons

two antigens: neuraminidase (N antigen) and hemagglutinin (H antigen). The influenza virus has a marked propensity to mutate its external antigenic composition to escape the host's immune defenses. Given this extreme mutability, a classification of viral subtype A based on H and N typing has been introduced.

Influenza viruses are transmitted primarily from person to person through respiratory droplets disseminated during sneezing, coughing, and talking, and through contact with contaminated surfaces. The incubation period of influenza is one to four days, and infected adults are usually contagious from the day before symptom onset until five days after symptom onset.

Pandemics are thought to originate mostly in southern China, where ducks (the animal reservoir and breeding ground for new strains), pigs (thought to be the biological intermediate host, or "mixing vessel"), and humans live in close proximity. Pigs are considered plausible intermediate hosts because their respiratory epithelial cells have receptors for both avian (i.e., duck) and human viral hemagglutinins. Minor changes in viral antigenic configurations, known as "drift," cause local or more circumscribed epidemics.

Prognosis

The symptoms of uncomplicated influenza usually resolve within one week, although cough and fatigue may persist. Complications include otitis media, bacterial sinusitis, secondary bacterial pneumonia, and (less commonly) viral pneumonia, respiratory failure, and exacerbations of underlying disease. In the United Kingdom, 1.3 percent of persons with influenza-like illness are hospitalized each year (95% CI, 0.6 to 2.6 percent). It is estimated that 300 to 400 deaths each year are attributable to influenza, rising to more than 29,000 during an epidemic. The risk of hospitalization is highest in persons 65 years or older, in young children, and in persons with chronic medical conditions. More than 90 percent of influenza-related deaths during recent seasonal epidemics in the United States have been in those 65 years or older. During influenza pandemics, morbidity and mortality may be high in younger age groups. Severe illness is more common with influenza A infections than with influenza B infections.

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Author disclosure: Tom Jefferson is a coauthor of several reviews cited in this review.

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