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DOCUMENTO DE CONSENSO

Diagnosis, treatment and prophylaxis of influenza virus infection – Consensus statement of the Spanish Society of Infectious Diseases and Clinical Microbiology (*SEIMC*), the Spanish Society of Pediatric Infectious Diseases (*SEIP*), the Spanish Association of Vaccinology (*AEV*), the Spanish Society of Family and Community Medicine (*SEMFYC*) and the Spanish Society of Preventive Medicine, Public Health and Health Management (*SEMPSPGS*)

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Conflicto de intereses:

Francisco López-Medrano, Diego van Esso-Arbolave, Santiago Alfayate, Manuel García Cenoz, Santiago Melón, Judith Chamorro-Camazón, Alfredo Tagarro, Marta Cruz, Diego Viasus, Jordi Carratalà, Elisa Cordero, Germán Schwarz-Chávarri, M Ángeles Marcos and Nemesio Moreno-Millán declare no conflict of interests. María Fernández-Prada has been a member of advisory boards and has given talks for continuing medical education for Pfizer, GSK, Seqirus, MSD, Sanofi, and Sanofi-Genzyme. Jaime Pérez-Martín has given talks for continuing medical education for Seqirus and Sanofi. Tomàs Pumarola has been a member of advisory boards for Seqirus and Sanofi. Juan Rodríguez García has been a member of advisory boards or has given talks for continuing medical education for Pfizer, GSK and Sanofi

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Abstract:

The influenza virus has accompanied humans since time immemorial, in the form of annual epidemics and occasional pandemics. It is a respiratory infection with multiple repercussions on people's lives at an individual and social level, as well as representing a significant burden on the health system. This Consensus Document arises from the collaboration of various Spanish scientific societies involved in influenza virus infection. The conclusions drawn are based on the highest quality evidence available in the scientific literature and, failing that, on the opinion of the experts convened. The Consensus Document addresses the clinical, microbiological, therapeutic, and preventive aspects (with respect to the prevention of transmission and in relation to vaccination) of influenza, for both adult and pediatric populations. This Consensus Document aims to help facilitate the clinical, microbiological, and preventive approach to influenza virus infection and, consequently, to reduce its important consequences on the morbidity and mortality of the population.

Resumen:

El virus de la gripe ha acompañado al ser humano desde tiempo inmemorial, en forma de epidemias anuales y pandemias ocasionales. Se trata de una infección respiratoria con múltiples repercusiones sobre la vida de las personas a nivel individual y social, así como una importante sobrecarga para el sistema sanitario. El presente documento de consenso surge de la colaboración de diversas sociedades científicas españolas implicadas en la atención de la infección por virus de la gripe. Las conclusiones extraídas se han fundamentado en las evidencias de mayor calidad disponibles en la literatura científica y, en su defecto, en la opinión de los expertos convocados. En el documento de consenso se abordan los aspectos clínicos, microbiológicos, terapéuticos y preventivos (respecto de la prevención de la transmisión y en relación con la vacunación) de la gripe, tanto para población pediátrica como para adultos. Este documento de consenso pretende ayudar a facilitar el abordaje clínico, microbiológico y preventivo de la infección por virus de la gripe y, consecuentemente, a disminuir sus importantes consecuencias sobre la morbimortalidad de la población.

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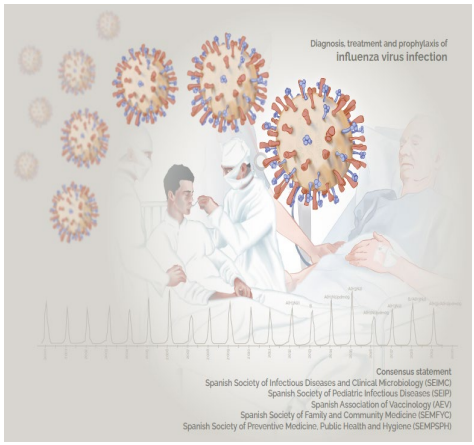
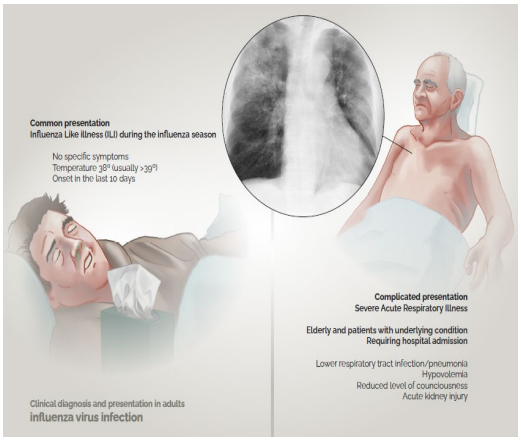
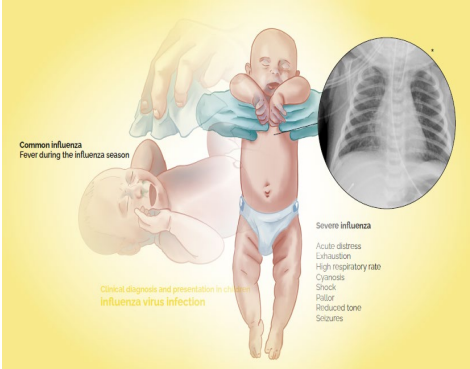
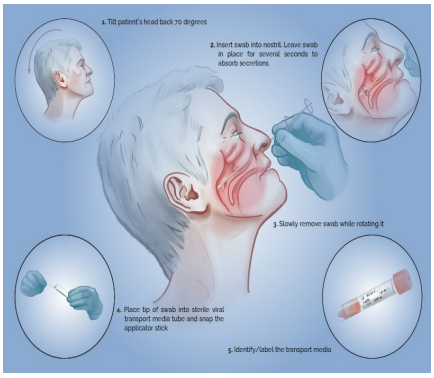
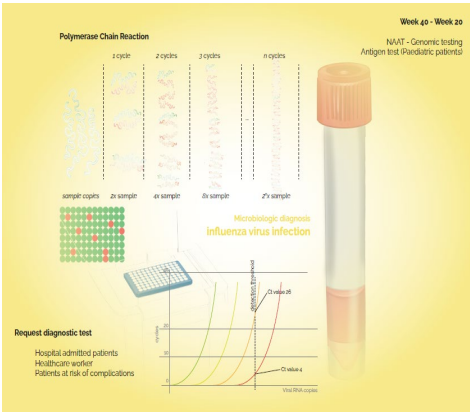
Visual abstract

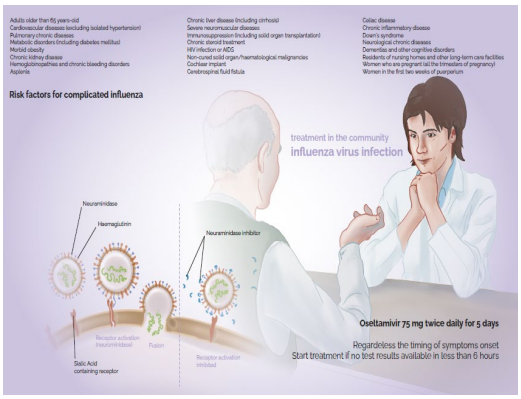


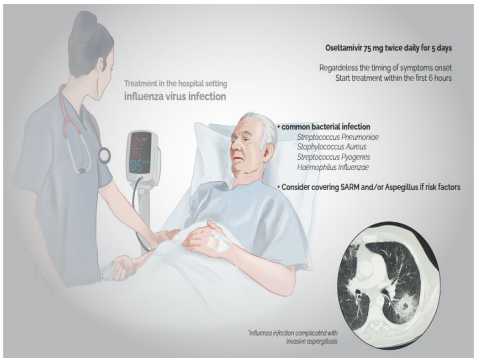


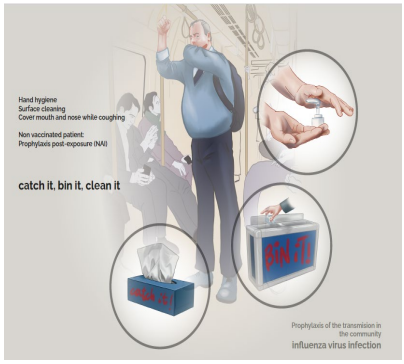


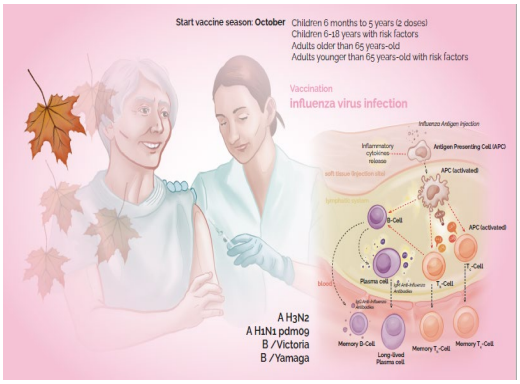












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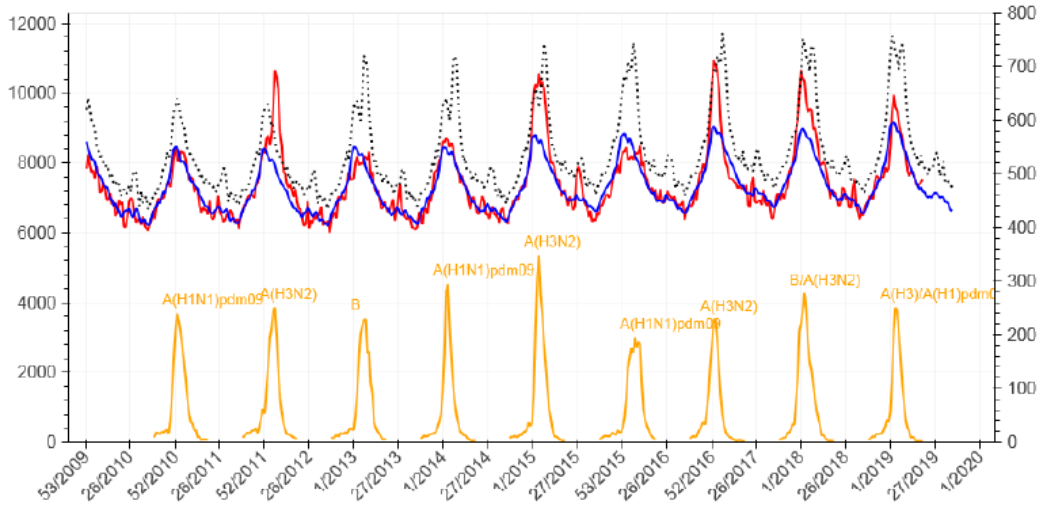
1- Introduction: justification and aims

Infection by influenza virus has accompanied humanity from time immemorial, producing annual epidemics that can cause severe infection, mainly in the elderly, pregnant women, or in those with previous comorbidities. Moreover, from time to time, it produces periodic pandemics related to genomic mutations that can give rise to a devastating disease, mostly in young people without previous exposure to that type of virus. There is probably no other infectious disease that better correlates with population mortality as influenza virus infection does. As shown in **Figure 1**, there is a tiny correlation between the daily oscillation of mortality for the general population and the weekly rate of influenza virus infection (1). Only the recent pandemic of COVID-19 by coronavirus SARS-Cov-2 has presented a comparable effect on the mortality of the general population in modern times.

Figure 1 – Daily global mortality by any cause in Spain (2010-2019) and weekly incidence of influenza virus infection. Source: National Center of Epidemiology, Health Institute Carlos III, Ministry of Science, Spain (1).



Footnote: red line: detected mortality; blue line: expected mortality; yellow line: incidence of influenza; x-axis: week/year; left y-axis: absolute number of deaths; right y-axis: number of cases of influenza infection per 100,000 inhabitants

Despite these facts, influenza virus infection is still considered a benign unimportant infection by a large proportion of citizens and, even more worrisome, by physicians.

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In the last few decades, we have witnessed a huge development in the diagnostic, preventive, and therapeutic tools for influenza virus infection that have demonstrated their usefulness in reducing the incidence, morbidity, and mortality of this infection. Meanwhile, a powerful media movement has made a big fuss based on non-scientific statements, provoking mass rejection to the application of these tools that could benefit public health. A recent study estimated that seasonal influenza produces between 300,000 and 600,000 deaths annually worldwide (2).

This Consensus Statement arose as an initiative of the Spanish Society of Medical Microbiology and Infectious Diseases (*SEIMC*) and was enthusiastically taken on by the following scientific societies: the Spanish Society of Pediatric Infectious Diseases (*SEIP*), the Spanish Association of Vaccinology (*AEV*), the Spanish Society of Family and Community Medicine (*SEMFYC*), and the Spanish Society of Preventive Medicine, Public Health and Health Management (*SEMPSPGS*). The result is this Consensus Document that jointly approaches influenza virus infection from different complementary perspectives.

In the opinion of the authors of this Consensus Statement and their supporting Scientific Societies, this document represents a great opportunity for the diffusion of systematized scientific knowledge to the medical community, in order to improve the approach towards influenza virus infection in the twenty-first century.

2- Methods:

The development of this Consensus Statement was an initiative of the Executive Committee of *SEIMC*. They appointed an Infectious Diseases expert (FLM) and a Microbiology specialist (TP) as coordinators of the working group for the drafting of the manuscript in April 2018. Moreover, the Executive Committee of *SEIMC* contacted other Scientific Societies in order to develop a unified document approaching influenza virus infection from a holistic point of view. The following Scientific Societies were contacted: the Spanish Society of Pediatric Infectious Diseases (*SEIP*), the Spanish Association of Vaccinology (*AEV*), the Spanish Society of Family and Community Medicine (*SEMFYC*) and the Spanish Society of Preventive Medicine, Public Health and Health Management (*SEMPSPGS*). The Executive Committee of each of these societies appointed experts who were

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contacted and agreed to join the working group. The coordinators appointed by *SEIMC* prepared the index of the Consensus Statement and wrote out the queries to be answered by the panel of experts. Each group of experts worked in their field of expertise and a unified draft was constructed. The multidisciplinary panel of experts held a teleconference (May 2019) and a face-to-face meeting (June 2019) to discuss the aspects of the document in which consensus had not been achieved. Apart from the literature evidence (up to June 2022), the clinical experience and personal expertise of the members of the panel were taken into consideration when high quality evidence could not be found in the literature. In case of discrepancy, the criteria of the coordinators were applied.

The panel experts were asked to perform a systematic review of the scientific literature, with no time limit, in order to answer the assigned queries according to the best evidence available. PubMed, Embase, and the Cochrane Database for Systematic Reviews were consulted. The literature search was updated up to February 2020. The strength of the recommendations and the quality of evidence were graded based on the US Public Health Service Grading System (**Table 1**). Apart from the method for grading the recommendations, the document was written following the Appraisal of Guidelines Research and Evaluation (AGREE II) tutorial.

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Table 1 – Strength of the recommendations and quality of the evidence

Category/Grade	Definition
Strength of recommendations	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from one or more properly randomized controlled trial
II	Evidence from one or more well-designed clinical trial without randomization; from cohort or case-controlled analytical studies (preferably from more than one center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees

The target of the Consensus Statement is the diagnosis, treatment, and prevention of seasonal influenza virus infection. It was not designed to address the management of pandemic outbreaks by non-previously circulating influenza virus or the management of exceptional infections by strains of influenza virus of animal origin ("avian flu").

All the members of the panel participated in the building of the Consensus Statement and approved the final version. The document was sent for audit by external peer reviewers. All the members of the Scientific Societies involved in the preparation of the manuscript had the opportunity to review the draft and make comments before publication. The final version was revised and approved by the Executive Committee of *SEIMC* and the other societies involved in the consensus (*SEIP, AEV, SEMFYC* and *SEMPSPGS*) prior to publication and adoption as an official document by the respective societies.

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3- Clinical Diagnosis and Management of Influenza Virus Infection in Adults:

3.1 When should influenza virus infection be suspected in an adult?

Recommendations

1- Influenza infection does not have specific clinical symptoms and its clinical picture might be undistinguishable from that produced by another respiratory virus. From an epidemiological point of view, the World Health Organization (WHO) case definition of influenza-like illness (ILI) for influenza sentinel surveillance refers to an acute respiratory infection with a temperature greater than or equal to 38°C and cough, with sudden onset within the previous 10 days (**Table 2**) (A-II).

2- The symptoms that most accurately predict an influenza infection are cough and a temperature greater than or equal to 39 °C. Nevertheless, a lower temperature or even the absence of fever does not exclude the possibility of influenza virus infection (A-II).

3- During influenza season, influenza infection can be considered in people with fever and acute exacerbation of underlying chronic lung disease, in elderly people with new or worsening respiratory symptoms (including exacerbation of congestive heart failure or altered mental status, with or without fever), in severely ill people with fever or hypothermia, and hospitalized adults who develop febrile respiratory illness after hospital admission (A-II).

4- At any time of the year, in people with acute febrile respiratory symptoms who are epidemiologically linked to an influenza outbreak (healthcare workers, household and close contacts of people with suspected influenza, travelers returning from countries where influenza viruses may be circulating, participants in international mass gatherings, and cruise ship passengers) (A-II).

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Rationale

The non-specificity of influenza signs and symptoms requires laboratory confirmation to be certain of the role of influenza virus in either ILI or severe acute respiratory infections (SARI) (3).
The first ILI case definition criterion for Influenza that WHO recommended appeared in 1999; the sensitivity of the definition was generally only about 60% and its specificity ranged from 0% – e.g., when there was little circulation of influenza virus – to 60-90% – e.g., during each main influenza season and the 2009-2010 influenza pandemic. It was revised in 2001 in order to improve the sensitivity and specificity of the influenza case definition, and to avoid ambiguities in the interpretation of the initially proposed criteria (4-9).

The comparisons subsequently made with other ILI case definition criteria support the use of the WHO definition due to its higher specificity and better performance in all age groups. In the 15-65-year-old age group, 93.7% sensitivity and 19.9% specificity have been described, and also 96.0% sensitivity and 13.9% specificity in the ≥ 65-year-old age group (5).

The performance of a case definition is influenced by multiple demographic and clinical variables of the population, and by circumstances such as the epidemic context of influenza or the influenza virus subtype. Furthermore, influenza infections commonly present a wide variety of clinical manifestations, ranging from asymptomatic infection to critical or fatal illness. Commonly, it presents with fever, cough, sore throat, nasal congestion or rhinorrhea, headache, muscle pain, and malaise. Severe cases can also present shortness of breath and dyspnea. Gastrointestinal illness such as diarrhea and/or vomiting may also be present.
Some patients with uncomplicated illness may experience atypical symptoms and may not have fever (e.g., elderly or immunosuppressed patients). In people with chronic medical conditions, influenza may be an unrecognized cause of exacerbation of that condition (4, 10).

The WHO case definition is designed for epidemiological surveillance and does not aim to identify each and every case of influenza infection that may present

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with symptoms that are less typical or mild, or even asymptomatic. However, studies that report rates of clinical outcomes, such as medically attended influenza or hospitalization without laboratory confirmation of influenza, can be difficult to interpret because of coincident circulation of other respiratory pathogens (11, 12).

Influenza illness can be suspected in the presence of respiratory symptoms among household contacts after a case of previously diagnosed influenza virus infection. A large proportion of community disease transmission of influenza has been estimated to take place in the household setting. In some studies, conducted using viral genetic sequences to demonstrate influenza infection transmission, more than 95% of infections among household contacts did occur within the household (13, 14).

Finally, asymptomatic influenza infections can be detected but, obviously, they cannot be suspected on the basis of clinical symptoms. Studies on influenza outbreaks detected a pooled mean of 16% (95% confidence interval [CI] 13%-19%) of asymptomatic subjects (15).

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Table 2 - WHO case definitions for influenza sentinel surveillance

Case	Definition criteria
Influenza like illness (ILI)	• An acute respiratory infection with temperature ≥ 38°C • AND cough • With sudden onset within the last 10 days
Severe acute respiratory infections (SARI)	• An acute respiratory infection with history of fever or measured temperature ≥ 38°C • AND cough • With onset within the last 10 days, • AND that requires hospitalization

Source: http://www.who.int/influenza/resources/documents/influenza_surveillance_manual/en/index.html

3.2 Can influenza virus infection be clinically distinguished from another respiratory virus in an adult?

Recommendations

1. Among adult patients with influenza-like illness, clinical findings are not particularly useful to differentiate influenza virus infection from another respiratory virus infection (B-II).

Rationale

Respiratory virus infection may present with sudden onset of symptoms, fever, cough, sore throat, coryza, headache, weakness/malaise, myalgia, arthralgia, and sometimes gastrointestinal symptoms. Studies document that the clinical presentation of influenza infection overlaps substantially with that described in

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other respiratory virus infections. No single symptom or set of symptoms are sufficient to enable conclusive differentiation between influenza and other viral causes of acute respiratory infection. In this context, the importance of microbiological diagnosis must be highlighted. Among patients with influenza-like illness, in which influenza virus infection may account for a variable number of such cases, studies compared the clinical presentation of influenza infection to other individual respiratory virus infections or a group of respiratory virus infections, including respiratory syncytial virus (RSV), rhinovirus, adenovirus, parainfluenza virus, coronavirus, and/or metapneumovirus (16). Cinemre et al. (17) found no significant differences in clinical features of influenza virus infection from other respiratory virus infections among adult patients (18-55 years old) with acute respiratory infections. Similarly, Loubet et al. (18) performed a study comparing clinical findings in adult patients with influenza infection and respiratory syncytial virus infection. Although there were differences in comorbidities between study groups (solid neoplasia and immunosuppression were more frequently found in patients with respiratory syncytial virus infection, while pneumonia and contact with children at home were more frequent in the influenza group), no significant differences in clinical features were documented. Other studies found that some clinical features were more frequent in patients with influenza than with another respiratory virus. However, results were inconsistent between studies. Fever, sore throat, cough, chills, arthralgia, and myalgia were documented more frequently in patients with influenza infection in some studies. In contrast, fever, cough, coryza, myalgia, and wheezing were found more commonly in patients with another respiratory virus infection (19-22). Finally, Wald et al. (23) found that a set of systemic or gastrointestinal symptoms were more frequent in patients with influenza compared to patients with respiratory syncytial virus. They did not find significant differences in individual symptoms. This study included a low number of adult patients (32 in influenza group versus 9 in respiratory syncytial virus group) from nursing homes. Recently, some studies identified differences in terms of laboratory findings and clinical symptoms between coronavirus disease 2019 (COVID-19) and influenza. In this regard, runny nose, dyspnea, sore throat, and rhinorrhea occurred less frequently in patients with COVID-19 in comparison to those with influenza type A and type B infections (24, 25). Conversely, anosmia, dysgeusia, diarrhea, frontal

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headache, and bilateral crackling sounds were more common among patients with COVID-19 (26).

3.3 When should an adult patient with suspected influenza virus infection be sent to the Emergency Room of a hospital?

Recommendations

1. An adult patient should be sent to the Emergency Department of a hospital if the patient might benefit from hospital admission due to the development of pneumonia as a complication of influenza virus infection (A-II).

2. From a clinical point of view, this possibility should be suspected in the presence of shortness of breath, pain or pressure in the chest, sudden dizziness, confusion, and/or severe or persistent vomiting. It should also be considered in case of influenza virus infection symptoms that improve but then relapse in the form of fever and/or worsening lower respiratory tract symptoms (A-II).

3. A patient with a suspected or diagnosed influenza virus infection with a chest X-ray performed outside the hospital environment showing pneumonia should be sent to the Emergency Room of a hospital to consider the need for hospital admission (A-III).

4. An adult patient with influenza virus infection should be sent to the Emergency Department of a hospital if he/she presents exacerbation of underlying chronic diseases that might require hospital admission (A-II).

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Rationale

Sending a patient to the emergency room will be conditioned by the severity of the symptoms and by the possibility of confirming and treating influenza in patients with chronic diseases with a high risk of complications (27).

The definition of complicated or severe influenza virus infection given by the World Health Organization for the influenza pandemic in 2009-2010 included:

- clinical and/or radiological signs of lower respiratory tract disease, central nervous system involvement, severe dehydration, or presenting secondary complications such as renal or multiorgan failure, and septic shock.
- Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease, chronic hepatic or renal insufficiency, diabetes, or other cardiovascular conditions (28).
- Any other condition or clinical presentation requiring hospital admission for clinical management (including bacterial pneumonia).
- Any of the signs and symptoms of progressive disease, such as:
  - Signs and symptoms suggesting oxygen impairment or cardiopulmonary insufficiency
  - Signs and symptoms suggesting central nervous system complications
  - Evidence of sustained virus replication or invasive secondary bacterial infection based on laboratory testing or clinical signs
  - Severe dehydration, manifested as decreased activity, dizziness, decreased urine output, and lethargy.

3.4 When should pneumonia be suspected in an adult with influenza virus infection?

Recommendations

1. Pneumonia should be considered in every patient with suspected influenza virus presenting with clinical features suggestive of lower

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respiratory tract infection in the context of the annual epidemic period of influenza (A-II).

2. Pneumonia should be considered in every patient with confirmed influenza virus infection presenting with clinical features suggestive of lower respiratory tract infection (A-II).

3. The possibility of influenza virus infection should be considered in everyone with a diagnosis of pneumonia in the context of the annual epidemic period of influenza (A-II).

Rationale

The main complications of influenza are those involving the lower respiratory tract, principally pneumonia (primary influenza pneumonia and concomitant/secondary bacterial or fungal pneumonia) and exacerbations of chronic pulmonary diseases (29). Pneumonia during influenza infection is a fearsome complication due to its frequency and high morbidity and mortality. Nonetheless, information about when influenza virus pneumonia should be suspected in an adult is particularly scarce. Garg et al. (30) described the factors associated with pneumonia among adults hospitalized with influenza during October 2005 through April 2008 in the U.S. In the multivariable analysis, factors associated with pneumonia included: age ≥ 75 years, white race, nursing home residence, chronic lung disease, and immunosuppression. Similarly, Viasus et al. (31) performed an observational analysis of a prospective cohort of adults hospitalized for influenza A(H1N1) 2009 in Spain. Patients with influenza pneumonia were compared to patients with influenza without pneumonia. No significant differences were found between groups in terms of age or sex. Patients with pneumonia were more frequently current smokers and heavy alcohol drinkers. Similarly, patients with pneumonia more frequently had shortness of breath, pleuritic chest pain, diarrhea, hypotension, tachypnea, and

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impaired consciousness. Conversely, asthma was more common in patients without pneumonia. On admission, patients with pneumonia more frequently had leukopenia and hyponatremia, and elevated liver enzymes, lactate dehydrogenase, and C-reactive protein than patients without pneumonia. Respiratory failure was also more frequent in patients with pneumonia. In another retrospective study carried out in South Korea (32), patients with pneumonia were more likely to have suffered from dyspnea, cough, and sputum. Patients with pneumonia also had higher white blood cell counts, erythrocyte sedimentation rate, and C-reactive protein levels, and a greater prevalence of hypoxemia than patients without pneumonia.

3.5 Can influenza virus pneumonia be clinically distinguished from bacterial pneumonia in an adult?

Recommendations

1. Although certain presenting clinical features may enable recognition of influenza pneumonia, no single symptom or scoring system is sufficient to differentiate between influenza and bacterial pneumonia (B-II).

Rationale

A rapid diagnosis on admission of viral or bacterial pneumonia is crucial to early initiation or withdrawal of antibiotic and antiviral treatment. Therefore, researchers in several studies analyzed the predictive value of clinical features and laboratory findings to distinguish influenza virus pneumonia from bacterial pneumonia. Bewick et al. (33) performed a study in which 254 adult patients with influenza-related pneumonia were compared to 648 patients with inter-pandemic community-acquired pneumonia (CAP). Patients in the influenza cohort were more likely to be younger, febrile, tachycardic, have bilateral radiographic abnormalities, and lower leucocyte counts and levels of C-reactive protein. Confusion, comorbidity, and blood urea levels were higher among patients in the CAP cohort. A multivariate logistic regression model was performed to identify

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independent variables associated with influenza pneumonia and a scoring model was generated by assigning one point for each of five clinical criteria: age, mental orientation, temperature, leucocyte count, and bilateral radiographic consolidation. However, a study documented that this score did not differentiate reliably between patients with influenza pneumonia and those with other etiologies (34). Importantly, some authors consider that the most useful finding of the scoring system proposed by Bewick et al. (33) is that antiviral treatment might be avoided in some patients with a score of 0 or 1 (34, 35). Similarly, Cunha et al. (36) developed the Winthrop-University Hospital Infectious Disease Division's diagnostic weighted point score system to identify patients with influenza pneumonia and negative results in the rapid influenza diagnostic tests. This score was based on key features: adults with influenza-like illness with a body temperature higher than 38.8ºC, negative diagnostic tests for other viral CAP pathogens, and a chest X-ray with no focal/segmental lobar infiltrates, plus severe myalgia, relative lymphopenia, elevated creatine-kinase and serum transaminases, and thrombocytopenia. However, this score has not been evaluated extensively. In addition, it is important to note that previous diagnostic prediction models were developed in the context of pandemic 2009 influenza A (H1N1) virus infection. Moreover, a meta-analysis documented that biomarker levels are also unlikely to provide reliable evidence regarding the need for antibiotic treatment in patients with CAP (37).

4- Clinical Diagnosis and Management of Influenza Virus Infection in Children:

4.1 When should influenza virus infection be suspected in a child?

Recommendations

1. Influenza should be suspected in any child that presents acute fever with or without respiratory symptoms during the annual epidemic influenza period (A-II).

2. The definition of influenza-like illness (ILI) has a very low diagnostic yield in children, especially in those younger than 5 years (A-II).

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3. In infants younger than 6 months, influenza may present as a sepsis-like syndrome (A-II).

Rationale

The clinical diagnosis of influenza in pediatrics is difficult, especially in infants and children in their first years of life (38-40). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical diagnosis has been studied and varies according to age, time of year, and definition of ILI (38-43).

Moderate and high-quality studies show that sensitivity varies between 40 and 90%, and specificity between 60-70%, while PPV is much lower, less than 40% in children of all ages and less than 25% in children under 3 years (38-43). Fever is the most prominent sign, present in 95% of patients, and the only one to predict influenza in all studies (38-43). In infants under 6 months, influenza may be confused with a sepsis-like illness (43, 44). The usefulness of symptoms such as cough or sore throat, which are usually used in definitions of ILI, was not demonstrated in many studies (9, 38-44).

The WHO (9) (**Table 2**) and CDC (45) definitions of ILI have a low diagnostic performance. The WHO case definition for ILI has the highest specificity (21.4%), but the yield is much lower in children under 5 years.

4.2 Can influenza virus infection be clinically distinguished from other respiratory viruses in a child?

Recommendations

1. Many of the respiratory viral illnesses in children share similar signs and symptoms and although there are clinical differences that are specific to some viruses, physicians cannot usually confirm or rule out a particular viral infection on clinical grounds alone (A-I).

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2. It is essential to be able to obtain a microbiological diagnosis in patients where a specific diagnosis may modify patient management (specifically, the possibility to initiate antiviral influenza treatment) (A-I).

Rationale

Influenza clinical diagnosis in children is difficult and PPV is very low. The winter seasonal influenza period overlaps with many other respiratory viruses circulating in the community during the same period (38, 39).

A recent study aiming to identify clinical characteristics that may help to differentiate infections with pathogens including influenza, respiratory syncytial virus, adenovirus, metapneumovirus, rhinovirus, bocavirus-1, coronaviruses, or parainfluenza virus used a dual approach. It compared a systematic review and meta-analysis of 47 clinical studies published in Medline (PROSPERO registration number: CRD42017059557) comprising 49,858 individuals with a data-driven analysis of an inception cohort of 6,073 children with ILI (aged 0-18 years) examined at the point-of-care in addition to blinded PCR testing (46).

The significant association of fever and influenza was not present in RSV infection, which in turn was associated with wheezing (a sign that did not appear associated to influenza). Metapneumovirus infection shared many common clinical data with influenza (fever, malaise, headache, cough, and rhinorrhea and diarrhea). Bocavirus was a frequent cause of cough and dyspnea. The cohort study revealed some data that were not observed in the meta-analysis: influenza was positively associated with myalgia and negatively with rash and diarrhea. RSV was positively associated with apnea and feeding difficulties and negatively with fever, headache, myalgia, seizures, and rash. Data for rhinovirus, adenovirus, parainfluenza and bocavirus were very limited (46).

The authors concluded that several viral infections share common signs and symptoms and, although some associations are significant, none of them enable clinicians to confirm an infection by a particular virus. For this reason, diagnostic tests for respiratory viruses are the cornerstone of accurate diagnosis (46).

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4.3 When should a pediatric patient with suspected influenza virus infection be sent to the Emergency Room of a hospital?

Recommendations

1. Infants, children, or adolescent patients should be sent to the Emergency Department of a hospital if they could benefit from inpatient treatment due to the development of pneumonia or any other complication of influenza virus infection (A-II).

2. Infants, children, and adolescent patients with risk factors (immunosuppressed patients, chronic lung disease, hemodynamically significant heart disease, severe neurological pathology, nephropathies and chronic liver diseases) should be microbiologically tested in the Primary Care environment or sent to the Emergency Department for a microbiological confirmation of influenza virus infection if this might modify the management of these patients (admission to hospital, initiation of antiviral treatment, performance of chest X-ray, etc.) (B-II).

3. From a clinical point of view, this possibility should be suspected in the presence of poor general condition, signs of sepsis, altered level of consciousness or seizures, dehydration, shock, respiratory distress (tachypnea, chest retractions, hypoxemia, and episodes of apnea), or any alarming sign in clinical evolution according to medical criteria. It should also be considered in case of influenza virus infection symptoms that improve but then relapse in the form of fever and/or worsening lower respiratory tract symptoms (A-II).

4. A pediatric patient with suspected or X-ray confirmed pneumonia should be sent to the Emergency Room of a hospital to consider the need for hospital admission if he or she is in poor clinical condition (A-II).

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5. Infants younger than 3 months of age with fever of unknown origin should be sent to the Emergency Department as, based on clinical grounds, influenza virus infection might be indistinguishable from other potentially life-threatening conditions (A-II).

Rationale

Influenza is usually a benign, self-limiting disease in children. Nevertheless, as some patients have a higher risk of developing complications, obtaining a definite diagnosis might be relevant in this context.

There are two possible clinical scenarios to be considered. One possibility is that the patient belongs to a group with risk factors for developing severe forms of influenza or complications.

The influenza surveillance system for mortality and hospital admission in the USA shows that more than half of the children that suffer complications in the context of influenza virus infection present at least one risk factor (47). Another possibility involves patients with clinical suspicion of poor outcome and/or complications.

Influenza complications can be stratified according to the anatomical site involved and bacterial coinfection. Lower respiratory tract complications (pneumonia, bronchitis, and bronchopneumonia) are the main reasons to refer a patient to the Hospital Emergency Room (48).

A list of clinical signs and symptoms related to severe forms of influenza virus infection among children can be consulted in **Table 3** (49).

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Table 3 – Signs and symptoms related to severe forms of influenza virus infections among children

Respiratory distress signs (retractions, grunting)
Abnormal respiratory pattern due to exhaustion or episodes of apnea
Breathing rate higher than 60 per minute in those younger than 2 months, higher than 50 per minute in infants between 2-12 months, greater than or equal to 40 in 1-5-year-old children, and greater than or equal to 30 in over 5-year-olds
Oxygen saturation less than or equal to 92%
Cyanosis
Evidence of dehydration or shock
Signs such as hypotension, hypotonia, or extreme pallor
Altered level of consciousness, extreme irritability or agitation, general malaise
Seizures

4.4 When should pneumonia be suspected in a child with influenza virus infection? Can influenza virus pneumonia be clinically distinguished from bacterial pneumonia in a child?

Recommendations

1. Pneumonia should be considered as a possibility in every pediatric patient with suspected influenza virus presenting with clinical features suggestive of lower respiratory tract infection in the context of the annual epidemic period of influenza (A-II).

2. Pneumonia should be considered as a possibility in every patient with confirmed influenza virus infection presenting with clinical features suggestive of lower respiratory tract infection (A-II).

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3. The possibility of influenza virus infection should be considered in every child with the diagnosis of pneumonia in the context of the annual epidemic period of influenza (A-II).

4. Influenza pneumonia and bacterial pneumonia may present overlapping clinical symptoms. Differential diagnosis may require a chest X-ray, and laboratory and microbiological tests, and cannot be defined only on a clinical basis (B-II).

Rationale

The link between lower respiratory tract infections (LRTI) and severe influenza is well described in adult patients, but the recognition of severe outcomes following influenza virus infections in children is more recent (50). Pneumonia has been reported in 12-20% of children hospitalized with influenza (51). Pediatric patients with influenza virus infection may develop LRTI due to influenza virus alone, co-infection with other circulating viruses, or secondary bacterial or fungal infection. Accurately identifying these different LRTIs is difficult. Several studies have tried to identify the risk of LRTI following influenza virus infection using epidemiologic, clinical, radiological, and laboratory data, but microbiological tests are essential in order to confirm or exclude influenza virus infection in the context of LRTI among children.

Based on epidemiologic data, children younger than 3 years of age are those most affected by viral pneumonia (51-54). This possibility should be suspected when increasing tachypnea, shortness of breath, poor feeding, and rales on physical exam appear and in case of worsening of the disease after the initial days of the clinical picture (51).

In general, the frequency of bacterial coinfection in laboratory confirmed influenza patients, according to a systematic review and meta-analysis of studies published since 1982, ranged from 2% to 65% (55). Nevertheless, in most of the studies, bacterial co-infection was microbiologically detected in 11% to 35% of patients (55).

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Streptococcus pneumoniae and *Staphylococcus aureus* are the most commonly detected pathogens according to these studies (53, 55). It can be difficult to clinically identify influenza patients suffering pulmonary bacterial coinfection, given the substantial symptom overlap of influenza and bacterial infection (55). None of the epidemiological, clinical, radiological, or laboratory data enable an accurate distinction between influenza virus pneumonia and bacterial superinfection (56). In this context, microbiological diagnosis constitutes a key tool to making a precise diagnosis.

In a study developed in Finland, the association of an interstitial pattern, atelectasis, and a mixed alveolar-interstitial pattern associated with less than 15,000 leucocytes and/or a PCR lower than 8.0 mg/dl was suggestive of viral pneumonia (51). The association of alveolar pattern together with a count of more than 15,000 leucocytes and/or a PCR higher than 8.0 mg/dl was suggestive of bacterial co-infection (30). In this cohort, 14% (134/936) of children with influenza virus infection developed pneumonia. In the same study, 64% of the children with pneumonia were admitted to hospital for a median of two days. The clinical course of the pneumonia was favorable for most of them, and mortality was low (0.7%). The authors highlight the fact that, unlike what has been described for adults, most children with pneumonia in the context of influenza virus infection recover uneventfully and with reduced associated mortality (51).

Another study analyzed the usefulness of PCR and procalcitonin (PCT) for the early diagnosis of bacterial infections in children with influenza, revealing that both PCR (19.20 mg/dl vs 5.10 mg/dl) and PCT (1.46 ng/ml vs 0.21 ng/ml) were independent diagnostic markers for the diagnosis of bacterial pneumonia (53). The same study (53) showed that a combination of PCR higher than 13 mg/dl and PCT higher than 0.52 ng/ml presented a sensitivity, specificity, positive predictive value, and negative predictive value of 0.83, 0.87, 0.85, and 0.85, respectively, for the diagnosis of bacterial co-infection in children with influenza virus infection and pneumonia.

A prospective study performed in Spain analyzed several variables with the aim of building a score to adequately differentiate bacterial and viral community

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acquired pneumonia, demonstrating that age (older than 3 years) and presence of a consolidation on chest X-ray are the most important variables for a diagnosis of bacterial pneumonia (57). The score has been implemented in a free mobile App (Pneumonia Etiology Predictor).

As previously described, virtually all the information available regarding the diagnosis of influenza virus pneumonia with or without bacterial co-infection is provided by retrospective studies.

5- Microbiological Diagnosis of Influenza Virus Infection:

5.1 When is the microbiological diagnosis of influenza indicated?

Recommendations

1. Microbiological diagnosis is indicated when the result of the test might change the clinical care of the patient or influence the clinical approach to other subjects exposed to the patient tested (A-II).

2. Microbiological diagnosis is indicated in cases of severe clinical course and for people at high risk of developing influenza-related complications (for instance, those with underlying cardiopulmonary diseases or immunocompromised subjects) (A-II).

3. Microbiological diagnosis should be attempted in every case with clinical suspicion of influenza virus infection in subjects admitted to hospital (A-II).

4. Microbiological diagnosis should be attempted in healthcare workers (HCWs) with a clinical suspicion of influenza virus infection when they are taking care of patients with risk factors for developing severe forms of influenza, and when taking care of patients admitted to hospital or to long-term care facilities (B-III).

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5. Microbiological diagnosis is not indicated for non-immunocompromised subjects and subjects not presenting risk factors for the development of severe forms of influenza virus infection when they are not going to be admitted to hospital and/or they do not present a severe clinical condition (A-II).

6. An accurate microbiological diagnosis of influenza virus infection and other respiratory viruses might help to avoid unnecessary antibiotic treatment and might help to accurately prescribe specific antiviral influenza treatment when indicated (A-III).

7. For epidemiological purposes, cases of influenza virus infection should be microbiologically diagnosed, starting at week 40 and ending on week 20 of the following year (for the Northern hemisphere) and by designated reference laboratories, in order to establish the type of virus strain circulating and the moment of initiation of the epidemic period (A-II).

Rationale

Besides epidemiological purposes, microbiological diagnosis of influenza virus infection is indicated when the result of the test (positive or negative) might influence the clinical approach to the patient, the treatment prescribed, or the measures adopted to avoid transmission. Microbiological diagnosis might avoid transmission in hospital or long-term facilities, or inappropriate antibiotic use.

Table 4 includes situations in which a microbiological diagnosis is needed, either because of clinical circumstances or owing to the presence of risk factors for the development of severe forms of influenza virus infection.

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Table 4 – Situations in which a microbiological diagnosis of influenza virus infection is indicated

1- Adults older than 65 years
2- Children younger than 2 years when hospitalized or when the result might trigger treatment or avoidance of antimicrobial prescription
3- Pregnant women
4- Women in the first two weeks of puerperium
5- People living in nursing homes or other types of long-term facilities
6- Asthma
7- Neurological and neurodevelopmental diseases
8- Sickle cell disease
9- Chronic obstructive pulmonary disease (COPD) and cystic fibrosis
10-Congenital heart diseases
11-Congestive heart failure and coronary artery disease
12-Chronic renal failure, including dialysis
13-Chronic liver failure, including cirrhosis
14-Inherited metabolic disorders and mitochondrial disorders
15-Obesity with a body mass index [BMI] of 40 or higher
16-Subjects younger than 19 years of age on long-term aspirin- or salicylate-containing medications
17-People with HIV infection or AIDS
18-People with non-cured malignant tumors
19-People with non-cured leukemia or lymphoma
20-Hematopoietic stem cell transplant recipients
21-Solid organ transplant recipients
22-Subjects receiving chronic treatment with steroids (prednisone in a dose greater than or equal to 20 mg for more than three weeks or an equivalent dose)
23-Subjects with any other type of immunosuppression

5.2 How should specimens be collected, stored, and transported?

Recommendations

1. Nasopharyngeal (NPS) or oropharyngeal (OPS) specimens collected by using sterile polyester swabs with plastic or aluminum shafts (not wooden shafts) are the preferred samples for non-invasive microbiological diagnosis of influenza virus infection in adults (A-I).

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2. NPS aspirate or washing is an alternative specimen that can be used for diagnosis. Collection of this specimen is especially well tolerated by children (A-II).

3. A correct technique for NPS sampling must be highlighted as a factor that directly correlates with the yield of the microbiological diagnosis (A-III) – see **Figure 2**.

4. Alternatively, saliva specimens may be used but they are associated with a lower yield for microbiological diagnosis (A-II).

5. Swabs must be transported to the Microbiology laboratory in sterile transport tubes with virus transport medium. Dry tubes for the transport of samples for bacterial diagnosis are not adequate (A-II).

6. Lower respiratory tract specimens (bronchoalveolar lavage or tracheobronchial aspirate, depending on clinical status of patient) should be collected for viral microbiological diagnosis from hospitalized patients with respiratory failure receiving mechanical ventilation, including subjects presenting a sever clinical condition with a previous negative virus detection in an upper respiratory tract specimen sampled during the ongoing infectious episode (A-II).

7. The yield of the microbiological diagnosis is inversely related to the time elapsed since the beginning of the symptoms. The earlier the sampling, the higher the yield of the microbiological diagnosis (A-II).

8. Blood, plasma, serum, urine, stool, and cerebrospinal fluid are not suitable specimens for routine influenza virus infection diagnosis (A-III).

9. Single or paired serum samples for serological diagnosis are only indicated for epidemiological purposes (A-III).

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Rationale

Successful microbiological diagnosis of influenza virus depends on the early collection of high-quality specimens, rapid and appropriate transportation of specimens to the laboratory, and adequate storage prior to testing (if necessary).

The possibility of obtaining a positive result for a microbiological diagnostic test for influenza virus in respiratory samples is highly impacted by the viral load content in the specimen. This explains the importance of early sample collection after onset of respiratory infection symptoms (58, 59). Viral shedding peaks decline rapidly after the first 48-72 hours (60).

The optimal specimens for influenza testing are nasopharyngeal aspirates, washings, and swabs. Alternatively, nasal and throat swab specimens may be collected (61). A tipped swab previously moistened in virus transportation medium (62) is inserted into the nostril parallel to the palate and left in place while rotating it for a few seconds before being slowly withdrawn (see **Figure 2**). Both tonsils and the posterior pharynx are swabbed vigorously with another swab. Both swabs are placed into the same tube containing virus transport medium. Swabs with metal or plastic shanks are preferable, because wooden ones can inhibit cell culture.

For patients with lower respiratory tract infection or under mechanical ventilation, an endotracheal aspirate or bronchoalveolar lavage (BAL) might be collected. Influenza virus replication in the lower respiratory tract may be detectable for longer periods than in the upper respiratory tract.

All specimens should be kept at 4ºC for no longer than 72 hours before testing. In order to increase the yield of the microbiological diagnosis, they should be analyzed within 24 hours after collection. If clinical specimens need to be stored for more than 72 hours, they should be kept at -80ºC, preferably in liquid nitrogen.

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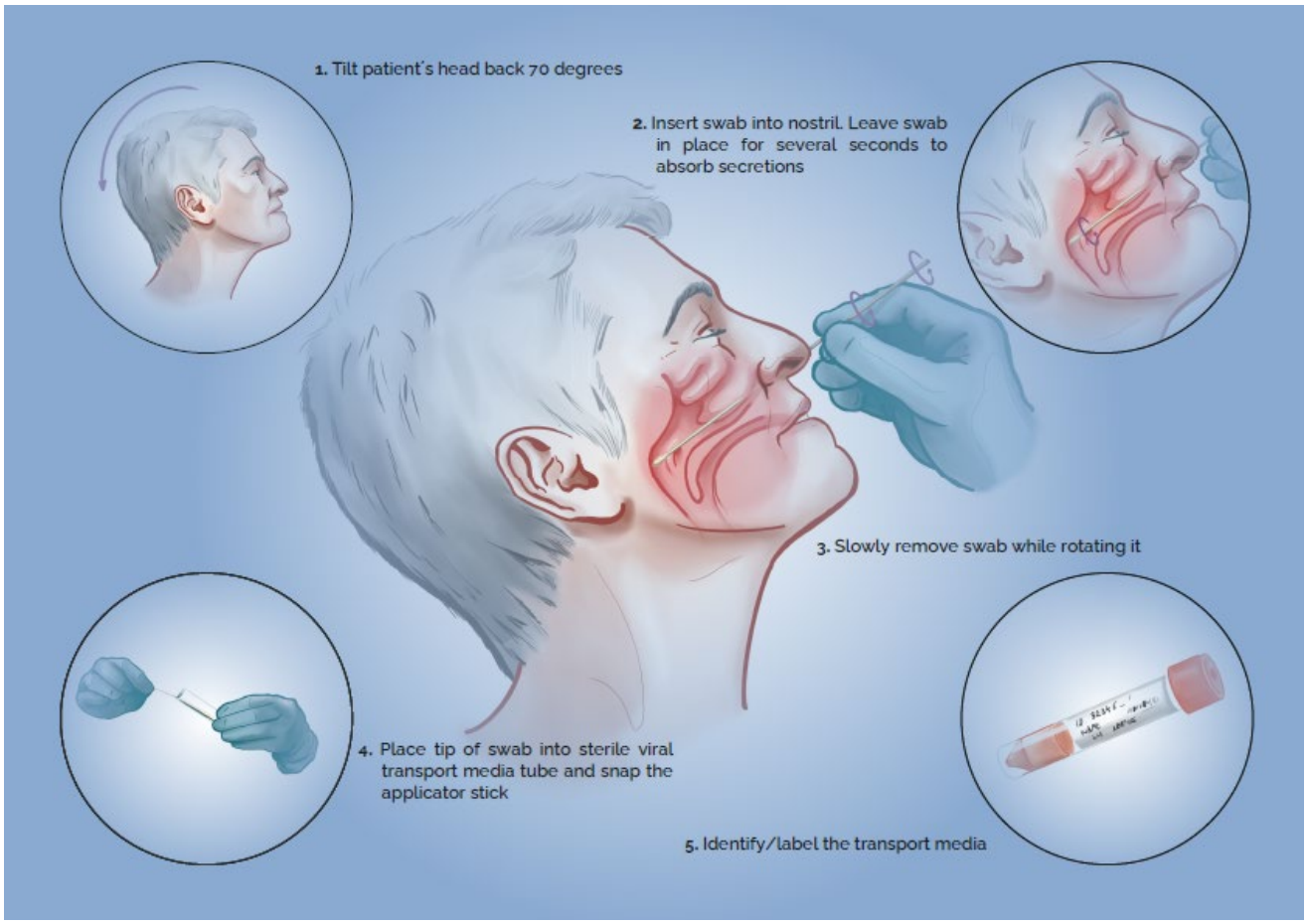
Figure 2 – Nasopharyngeal swab technique for influenza sample collection



5.3 What test should be used for the microbiological diagnosis of influenza virus infection?

Recommendations

1. Nucleic acid amplification test (NAAT) is the method of choice for the microbiological diagnosis of influenza virus infection. It should be able to identify type A and type B influenza virus. It is advisable to use a test that is able to identify type A influenza virus and distinguish subtypes H1 and H3 (A-II).

2. Rapid molecular assays detect influenza virus infection with high sensitivity and specificity. These tests are recommended to be used in hospitalized patients with suspected influenza virus infection and may

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be a better alternative to the other rapid influenza diagnostic tests in outpatient settings (A-II).

3. Antigen detection tests should be restricted to pediatric patients with samples collected within 24-48 hours following the onset of symptoms, when NAAT is not available (A-III).

4. Viral culture should not be used for primary diagnosis in the clinical setting. It should be reserved for cases in which further antigenic or genetic characterization is needed (A-III).

5. Serological testing for influenza is not generally recommended except for research purposes and for Public Health surveillance (A-II).

Rationale

The sensitivity and specificity of any test for the microbiological diagnosis of influenza virus infection might be conditioned by many factors: immunocompetence of the patient; time elapsed since symptom onset; severity of the clinical illness; type of respiratory sample; skill and experience of the person collecting the sample; time and medium for handling, processing, and storing the sample; type of test performed for microbiological diagnosis; and experience of the virology laboratory in the diagnosis of respiratory viruses (59, 63, 64). Carefulness in the performance of each step of this process is of key importance to obtain an accurate microbiological diagnosis.

Genomic assays

Due to its sensitivity and specificity, NAAT is the method of choice for the microbiological diagnosis of influenza virus infection nowadays. A variety of different genomic assays of NAAT are currently used for diagnosis of influenza and other viral respiratory infections in humans (65). These assays can yield results in a time frame that ranges from 20 minutes to several hours, showing higher sensitivity and specificity (both >95%) than tests that detect influenza virus antigens (59, 63, 64).

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Some NAAT can discriminate between infections by influenza A and influenza B virus, as well as seasonal influenza A virus subtypes [A(H1N1) pdm09 and A(H3N2)].

Detection of influenza RNA by these assays, as happens with rapid influence diagnostic tests (RIDTs), does not necessarily indicate detection of viable infectious virus or on-going influenza viral replication.

Techniques developed in-house can also be a good strategy to detect influenza virus. These home-brew tests can be adapted more rapidly than commercial kits to accommodate changes in the nucleic acid sequences of circulating viruses, but they need to be checked regularly for accuracy and reliability.

Rapid molecular assays (RMAs), which produce results in approximately 15-30 minutes, according to FDA rules, are able to detect influenza virus nucleic acids in upper respiratory tract specimens with high sensitivity and specificity (close to 100%) (66). These tests have the limitation that only one or fewer than four samples can be processed simultaneously.

Some of these RMAs include detection of RSV, another important epidemic respiratory virus for the pediatric population that overlaps with influenza circulation and SARS-CoV-2, thus giving the possibility of a specific diagnosis and different patient management.

Antigen assays

Rapid influenza diagnostic tests are immunoassays that can identify influenza A and influenza B viral nucleoprotein antigens from respiratory specimens in approximately 15 minutes. Information about influenza A virus subtypes is not provided by these tests. Most of them show 50-70% sensitivity and more than 90% specificity when compared to NAAT. It should be taken into account that most of the studies that provided these results were performed in a pediatric population with nasal aspirate samples as opposed to an adult population and NPS (see below) (67).

Some RIDTs use an analyzer reader device to standardize results and to improve sensitivity (75-80%) (59, 65).

Immunofluorescence assays can provide diagnostic results in 2-4 hours. They present moderate sensitivity but high specificity. Both direct and indirect

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fluorescent antibody techniques are able to detect influenza A and B viral antigens in respiratory tract specimens. Furthermore, other respiratory viruses can also be detected by this test. Fluorescent based techniques are highly dependent on cell content of the samples.

All these techniques based on the detection of influenza virus antigens are limited by the viral load content of the sample (ideally, they should contain at least 10^5 to 10^6 viral particles). Thus, they are likely to be most reliable early in the course of illness, when viral shedding is at its peak (65).

In general terms, all the above assays perform better in samples recovered from children than adults because of the greater viral load and longer period of excretion in children and are particularly less sensitive for diagnosis in elderly people.

Antigen assays are simple, cheap, fast, and easy to perform, especially those based on capillary immunochromatography. Notwithstanding, due to their higher sensitivity, NAATs are preferred for the microbiological diagnosis of influenza virus infection.

Owing to the sensitivity of these assays, a negative antigen detection test result should be interpreted with caution, given the potential for false negative results. False positive results are less likely. The Panel of the Consensus Statement considers this type of test should be restricted, for the pediatric population, to samples collected in the first 24-48 hours after the onset of symptoms and only when NAAT is not available.

Viral culture

Influenza virus infection can be microbiologically diagnosed by inoculation of pretreated respiratory samples in permissive cell lines (MDCK, MDCK SIAT1, etc.) for 7-10 days or embryonated hen eggs (10-11 days of life) for 72 hours. Confirmation of influenza virus infection and characterization is made by hemagglutination or hemadsorption using erythrocytes, with specific antibody staining immunofluorescence microscopy and/or ELISA. Virus isolation is highly sensitive (except for some clades of A [H3N2] subtypes) but not as high as the sensitivity of NAAT. Virus culture is the only method to confirm the presence of viable virus in the sample. This could be particularly needed in long viral excreting

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treated patients, as NAAT could be detecting genetic material from non-viable virus (68). Major limitations of viral culture are the need for specifically trained personnel and its expensiveness. The shell-vial culture approach is relatively straightforward and more sensitive compared to traditional viral culture method, with viral detection possible in 24-48 hours (64).

Viral culture is considered the gold standard. It is used to confirm viral infectivity and for extensive antigenic and genetic characterization of influenza viruses and is essential for the surveillance and antigenic characterization of new emerging seasonal influenza A and influenza B virus strains or mismatched viruses that may need to be considered for inclusion in the next year's influenza vaccine.

The Panel of the Consensus Statement considers that viral culture for the diagnosis of influenza virus infection should be available only in reference laboratories of virology for those cases in which further antigenic or genetic characterization is needed.

Serology

Hemagglutination inhibition, neutralization, and enzyme-linked lecithin assay (ELLA) for neuraminidase antibodies are serological tests for influenza virus that are not generally recommended for diagnosis in clinical practice. Requirement of acute and convalescent sera does not provide timely results to help with clinical decision-making. It is only recommended for a limited number of Public Health or research laboratories, with its use reserved for seroepidemiology and for the determination of humoral response and vaccine efficacy studies.

5.4 When should resistance to neuraminidase inhibitors be sought?

Recommendations

1. Resistance to neuraminidase inhibitors should be considered when a microbiological diagnostic test continues to be positive more than 8-10 days after initiation of treatment with this type of antivirals (particularly when the antiviral dose is suboptimal) (B-III).

2. Resistance to neuraminidase inhibitors should also be considered when a microbiological diagnostic test is positive while on or immediately after prophylaxis with this type of antivirals (C-III).

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3. Resistance to antivirals should be especially considered in the immunocompromised population with evidence of persistent viral replication (e.g., 7-10 days after initiation of treatment) (B-III).

4. Periodic tests to detect resistance in influenza virus from random samples from community circulating virus should be performed. This surveillance should be limited to the reference laboratories designated by regional or national government authorities or by international Public Health organizations (C-III).

5. Antiviral resistance testing can be performed by specific gene sequencing, real-time single-nucleotide polymorphism (SNP) detection, polymerase chain reaction, or by genome-wide genotyping (C-III).

Rationale

Nowadays, the percentage of resistance to neuraminidase inhibitors among seasonal circulating influenza virus remains low (69). However, prompt and correct identification of these infrequent strains is of key importance for adequate treatment of this subgroup of patients and for the implementation of the measures necessary to avoid their dissemination (70-72).

Up to 100% of the globally circulating Influenza A virus H1N1 subtypes were resistant to oseltamivir until 2009. However, pandemic 2009 Influenza A H1N1 replaced the pre-pandemic oseltamivir-resistant H1N1 lineage and remains largely sensitive to neuraminidase inhibitors. Nevertheless, high transmission (15-29%) of oseltamivir-resistant pandemic 2009 influenza virus type A H1N1 has been observed in some local communities and in immunocompromised subjects (70).

Genotypic methods, especially gene sequencing (Sanger or next generation sequencing, depending on the availability in each laboratory) are recommended for screening for amino acid substitutions known to be associated with resistance, reduced inhibition (RI), or highly reduced inhibition (HRI) by NAIs. Single nucleotide polymorphism (SNP) assays can be an easy alternative to sequencing

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methods for well-established single mutations associated with viral resistance (64, 73, 74).

The amino acid substitution H275Y is considered clinically relevant due to its frequency and the evidence of clinical data to demonstrate reduced treatment efficacy (72, 75). The remaining substitutions have been observed infrequently and cause reduced susceptibility in vitro but their clinical significance is less clear.

Phenotypic characterization is considered the gold standard for determining susceptibility of influenza virus isolates to NAIs but is only available in reference laboratories. To assist in the establishment of NAI assays and standardization of IC50 values within a laboratory, the Neuraminidase Inhibitor Surveillance Network (NISN) and the Center for Disease Control and Prevention (CDC) in Atlanta, Georgia – which is a WHO collaborating center (CC) – have assembled panels of reference viruses (75).

The WHO Global Influenza Surveillance and Response System (GISRS) laboratories and GISRS experts in the WHO Antiviral Working Group (WHO-AVWG) perform surveillance of influenza antiviral susceptibility ensuring appropriate monitoring, and publish data on these regularly reviewed amino acid substitutions (76). Surveillance for resistant strains should be limited to the reference laboratories designated by regional or national government authorities or by international Public Health organizations.

5.5 What is the role of rapid diagnostic tests *at point-of-care* in primary care medicine and emergency rooms of hospitals?

Recommendations

1. Genomic assays are preferred over antigen detection assays as rapid diagnostic tests when used for microbiological diagnosis of influenza virus infection *at* point-of-care (A-III).

2. Rapid diagnostic tests performed by clinicians *at* point-of-care must be implemented and used under the quality control of a reference laboratory of virology, in both the primary care setting and emergency facilities (B-III).

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Rationale

In the most recent years, some NAATs have been developed to be used by clinicians at the bedside, in the office, or emergency room (point-of-care tests) (59). This test can provide an accurate diagnosis for influenza virus infection or another type of respiratory virus in less than 15 minutes. It also presents the advantage of being able to be used 24 hours a day, seven days a week. Some retrospective comparative studies have demonstrated that patients, in whom a point-of-care influenza A and B diagnostic test was used, were administered oseltamivir significantly more rapidly (9 hours vs 23 hours). They also spent less time in the emergency department and had lower rates of antibiotic prescription and hospitalization (77).

Other studies demonstrated better assignment to isolation measures during hospitalization when the point-of-care NAAT was performed in the emergency room (78) and a reduction in the prescription of antibiotics (79).

These tests have also been used in the pediatric outpatient setting, demonstrating greater accuracy than rapid tests for antigen detection and resulting in a significant reduction in appointment duration time (80,81).

However, there are some drawbacks to these tests that need highlighting. For example, as they are used at point-of-care, there are usually many healthcare workers performing the tests. Lack of experience, as a factor influencing the accuracy of the test, has not yet been studied with precision. Another detail to take into consideration before its generalization in clinical routine is cost. It has been estimated that each test performed at point-of-care may be two to five times more expensive than traditional NAATs or a rapid test based on detection of antigens (77).

A pragmatic prospective randomized open-label clinical trial demonstrated the usefulness of a point-of-care molecular diagnosis test performed in the emergency room for the diagnosis of influenza virus infection in adults presenting respiratory symptoms. Patients with a microbiological diagnosis at point-of-care

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presented 100% accuracy in the microbiological diagnosis, a shorter time from hospital admission to the initiation of antiviral treatment, and a higher percentage of single-room accommodation than patients included in the routine-diagnosis arm of the study (82).

Notwithstanding these promising results, the Panel of this Consensus Statement considers that a higher level of evidence regarding the accuracy, reproducibility, clinical impact, and cost of point-of-care NAATs is necessary before they can be recommended for implementation in the clinical routine.

5.6 Capacity of microbiology laboratories for influenza virus diagnosis and characterization. How far should they go?

Recommendations

1. Detection of influenza virus by genomic tests (at the type and subtype level) for seasonal strains should be available for laboratories performing microbiological diagnosis (A-II).

2. SNP assays for well-established single mutations associated with viral resistance should be implemented in large regional hospitals.

3. Deep genetic and antigenic characterization (clades and subclades or minor antigenic variants) as well as specific serological assays should be limited to the reference laboratories designated by regional or national government authorities or by international Public Health organizations (A-II).

Rationale

Influenza viruses are constantly evolving. Actually, all influenza viruses undergo genetic changes over time but not all of these changes are translated into antigenic changes. It is worth making in-depth antigenic and genetic characterization available for reference laboratories designated by regional or national government authorities or by international Public Health organizations. Characterization of influenza viruses through antigenic and genetic tests is used

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to monitor circulating influenza viruses and to compare them to antigens included in the seasonal vaccine. This information is useful to identify the strains that should be included in the vaccines to be developed for forthcoming seasons (64).

5.7 Virological surveillance of influenza

Recommendations

1. Active viral surveillance of influenza virus is the cornerstone for detecting emerging influenza virus strains with pandemic potential (A-I).

2. Viral surveillance is the backbone for the selection of candidate viruses for the next-season vaccine (A-III), and also provides relevant and crucial information for interpreting vaccine effectiveness.

3. Seasonal influenza virus surveillance is necessary in order to establish when the epidemic annual period starts. It can also determine the proportions of type, subtype, and lineage of circulating viruses and assess antigen or genetic mismatch of circulating viruses with those included in the seasonal vaccine (A-I).

4. Virologic surveillance should be limited to the reference laboratories designated by regional or national government authorities or by international Public Health organizations (A-II).

Rationale

Close, systematic, and continuous surveillance of seasonal influenza viruses at the community and national level is required so as to better assess the burden of influenza and its potential impact on Public Health.

The GISRS was established in 1952, with more than 144 laboratories now collaborating and monitoring influenza virus circulation worldwide.

Laboratory-based surveillance for influenza virus by viral culture is critical to achieving a reliable antigenic and genetic characterization of circulating influenza strains. Isolates are also needed to obtain information on the emergence and prevalence of antiviral resistant strains, and the identification of human infection with novel influenza A virus that may present pandemic potential. Fast and easy communication between healthcare centers and tertiary institutions is key to cost-

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effective influenza surveillance. The Panel of the Consensus Statement considers virological surveillance should be limited to the reference laboratories designated by regional or national government authorities or by international Public Health organizations.

6- Treatment of influenza virus infection in the community

6.1 Which adult patients with influenza virus infection should be treated with antivirals in the community?

Recommendations

1. Adults diagnosed with non-complicated influenza virus infection within the community should start specific antiviral treatment as outpatients if they present risk factors for the development of a complicated infection (A-II).

2. Neuraminidase inhibitors are the first line drugs to be prescribed for those in whom treatment is indicated as outpatients (A-I).

3. Oral oseltamivir is preferred over inhaled zanamivir for adults who can take oral drugs (A-III).

4. The earlier the initiation of treatment with neuraminidase inhibitors, the greater the beneficial effect (A-II).

5. Treatment with neuraminidase inhibitors should ideally be started within the first 48 hours after the onset of symptoms but a clinical benefit might be obtained even if started later than 48 hours after the onset of symptoms (A-II).

6. Competent health authorities should adopt the measures to ensure access to these drugs for those in whom treatment is indicated, in the context of the National Health System (A-III).

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Rationale

The drugs of choice for antiviral treatment of influenza virus infection are neuraminidase inhibitors. An alternative option will be amantadine or rimantadine, but these drugs are not active against influenza type B and have important adverse effects; additionally, current circulating strains of the influenza virus A (H1N1 and H3N2 subtypes) are naturally resistant (H1pdm) and mutational (H3) (83). Treatment of previously healthy adults with neuraminidase inhibitors has demonstrated a mean reduction of 0.5-1 days in the duration of clinical symptoms of influenza virus infection (84). The Panel of this Consensus Statement considers that this benefit does not justify the recommendation of an indiscriminate use of these drugs in the general population, as population-based studies demonstrating their beneficial effect in terms of reduction of complicated infection, hospitalization, or mortality have not been published (85, 86). Another reason would be the absence of a microbiological diagnosis for most of the upper respiratory infections in the outpatient setting for otherwise healthy adults. Treatment with neuraminidase inhibitors should be reserved for those presenting a higher risk of the development of a complicated infection (85-88). These clinical situations are detailed in **Table 5** and are in accordance with situations in which a microbiological diagnosis is recommended (**Table 4**) and in which vaccination is indicated (**Table 13** and **Table 14**).

The Panel of the Consensus Statement favors the prescription of oral oseltamivir over inhaled zanamivir for adults in whom treatment is indicated (providing they can tolerate oral capsules or an oral suspension). This recommendation is based on the greater possibility of a correct administration of oral drugs over inhaled drugs (more dependent on the patient´s skill for the inhalation technique). The recommended dose of oral oseltamivir for adults is 75 mg every 12 hours for 5 days (if body weight is under 40 kg, follow recommendations for the pediatric population detailed in **Table 8**). **Table 6** includes the recommended dose for adults presenting impaired renal function. Oral oseltamivir is available in capsules containing 75 mg, 45 mg, or 30 mg. It is also available as an oral suspension containing 6 mg/ml. The recommended dose of zanamivir for adults is 10 mg (2 inhalations of 5 mg) twice a day (total dose of 20 mg per day). It is not necessary to adjust the dose of zanamivir in case of impaired renal function.

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Baloxavir-marboxil is another oral drug commercialized in some countries for the treatment of outpatients with influenza virus infection, but it is not yet available in Spain (89, 90). Its therapeutic virus target is the endonuclease cap. The combination of neuraminidase inhibitors plus baloxavir-marboxil has not been demonstrated to be superior to treatment with neuraminidase inhibitors alone (91).

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Table 5 – Situations in which treatment of adults presenting non-complicated influenza virus infection is indicated as outpatients

1- Adults older than 65 years
2- Chronic cardiovascular diseases (excluding isolated hypertension)
3- Chronic pulmonary diseases (including asthma and COPD)
4- Metabolic disorders (including diabetes mellitus)
5- Morbid obesity (body mass index equal to or greater than 35)
6- Chronic kidney disease and nephrotic syndrome (including dialysis)
7- Hemoglobinopathies and other anemias
8- Hemophilia and chronic bleeding disorders
9- Asplenia or previous splenectomy
10- Chronic liver disease (including cirrhosis)
11- Severe neuromuscular diseases
12- Immunosuppression (including solid organ transplantation)
13- Subjects receiving chronic treatment with steroids (prednisone in a dose greater than or equal to 20 mg for more than three weeks or an equivalent dose)
14- People with HIV infection or AIDS
15- Non-cured solid organ cancer and non-cured hematological malignancies
16- Cochlear implant
17- Cerebrospinal fluid fistula
18- Celiac disease
19- Chronic inflammatory disease
20- Down´s syndrome
21- Chronic neurological diseases
22- Dementias and other cognitive disorders
23- Residents of nursing homes and other long-term care facilities
24- Women who are pregnant (all trimesters of pregnancy)
25- Women in the first two weeks of puerperium
26- Adults who can transmit the influenza virus infection to those who present a high risk of developing severe forms of influenza virus infection: healthcare workers; those working in geriatric institutions or in centers for the care of chronically ill subjects; students in practices in healthcare centers; adults who provide home care to high-risk or elderly subjects; adults living with others belonging to some of these high-risk groups
27- Adults who work in essential public services: policemen; firefighters; people working in emergencies services; personnel working in penitentiary institutions and other detention centers

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Table 6 – Recommended dosage of oral oseltamivir for the treatment of active influenza infection in adults according to renal function (88)

Creatinine clearance (ml/min)	**Dose**
	75 mg loading dose in all cases and then:
> 60 ml/min	75 mg BID
> 30 to 60 ml/min	75 mg BID
> 15 to 30 ml/min	45 mg QD
≤ 15 ml/min	75 mg single dose
Patients under hemodialysis	30 mg after every other hemodialysis session
Patients under peritoneal dialysis	30 mg weekly

Note: BID – twice a day; QD – once daily

Available in hard capsules (75 mg) and as powder for oral suspension (6mg/ml).

6.2 Is there an indication for antiviral treatment without microbiological diagnosis in adults?

Recommendation

1. Adults fulfilling the criteria for outpatient treatment of the influenza virus infection (see 6.1) should start antiviral treatment as soon as possible when they are evaluated throughout the period of annual influenza epidemic, providing a microbiological diagnosis to confirm or exclude the infection is not available in less than 6 hours (A-III).

Rationale

Some studies have demonstrated that treatment of influenza virus infection with neuraminidase inhibitors is of greater benefit (in terms of time to resolution of clinical symptoms and in development of complications) if it is started as soon as possible after the onset of symptoms. Some studies have demonstrated a significant benefit when started in the first 48 hours (92).

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According to these results, the Panel of this Consensus Statement considers that initiation of empirical treatment is justified if all the following conditions are fulfilled: 1) the patient presents a clinical picture compatible with influenza virus infection (see description in 3.1); 2) the infection is detected during the annual period of epidemic influenza activity according to the reports of the national or autonomic competent health authorities; 3) a result of a microbiological diagnosis to confirm or exclude the infection by influenza virus is not available in less than 6 hours.

6.3 Apart from antivirals, what other therapeutic measures should be offered to an adult patient with influenza virus infection in the community or in long-term facilities?

Recommendation

1. Symptomatic treatment is recommended to alleviate the symptoms of influenza (C-II).
2. Symptomatic treatment of influenza for fever, headache, and myalgia is appropriate with paracetamol, ibuprofen, or dipyrone (B-II).
3. Cough can be relieved with honey and dextromethorphan, but the use of over-the-counter medications should be carefully weighed against the risk of adverse effects (B-II).
4. Treatment with antibiotics is not indicated unless bacterial superinfection is suspected (A-III).

Rationale

Common symptoms of influenza include high fever, chills, myalgia, headache, cough, nasal congestion, and fatigue. Most healthy people present mild symptoms when infected by influenza virus and do not warrant specific treatment for their symptoms. Paracetamol or ibuprofen may alleviate symptoms, although some studies have found no effect in terms of symptom relief for paracetamol (93).

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Supportive interventions (administration of nebulized saline solution alone or with mucolytic; saline nasal drops, spray, or irrigation; adequate hydration; cool mist humidifier) are usually safe and relieve congestion. In randomized trials, and as stated in systematic reviews and meta-analyses, mucolytics have not been proven to be better than placebo (94, 95).

6.4 Which pediatric patients with influenza virus infection should be treated with antivirals in the community?

Recommendations

1. Selected previously healthy patients with a confirmed early diagnosis of seasonal influenza during the epidemic period may start specific antiviral treatment as outpatients in the first 24 hours after the start of the clinical picture. It must be considered that expected benefit is limited to the reduction of time of illness or the development of acute otitis media and not to a reduced rate of hospitalization or other complications. Parents must be informed of the benefit-risk balance obtained with the treatment. The Panel of this Consensus Statement considers this benefit does not justify the recommendation for the indiscriminate use of antiviral treatment in the general pediatric population (A-II).

2. Selected children diagnosed with non-complicated influenza virus infection within the community may start specific antiviral treatment as outpatients if they present significant risk factors for the development of a complicated infection (immunosuppressed patients, chronic lung disease, hemodynamically significant heart disease, severe neurological pathology, nephropathies, and chronic liver diseases) (A-II).

3. Neuraminidase inhibitors are the first line drugs to be prescribed for those in whom treatment is indicated as outpatients (A-I).

4. Oral oseltamivir (capsules or oral suspension) is preferred over inhaled zanamivir (not indicated in any case for those under 5 years of age) for children who can take oral drugs (A-III).

5. The earlier the initiation of treatment with neuraminidase inhibitors, the greater the beneficial effect (A-II).

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6. Treatment with neuraminidase inhibitors should ideally be started in the first 48 hours after the onset of symptoms but a clinical benefit might be obtained even if started later than 48 hours after symptom onset (A-II).

7. Competent health authorities should adopt the measures to ensure access to these drugs for children in whom treatment is indicated, in the context of the National Health System (C-III).

Rationale:

There are high quality studies reporting that oseltamivir initiated in the first 24 hours of illness in children presenting with influenza virus infection may afford a beneficial effect in terms of reduction of days of illness (mean of 3.5 days if started within the first 24 hours in children one to three years old and 12-47 hours if started in the first 48 hours after the onset of symptoms) (96-98). It is important to highlight that this benefit in terms of symptom reduction was not demonstrated in a study targeting children with asthma (96).
Some trials of moderate-high quality suggest a decrease in the incidence of otitis media in children one to three years of age when treatment with oseltamivir is started in the first 12-24 hours of illness. However, a meta-analysis did not confirm this benefit and suggested that the diagnosis of otitis in these studies might not be sufficiently reliable.
A meta-analysis that analyzed three studies including 1,359 children treated or not with neuraminidase inhibitors did not demonstrate a significant difference in hospitalization rates (RR 1.92, 95% CI 0.70 to 5.23) (60). The economic cost of treating the entire population with influenza or with suspected influenza would be high.

For children with preexisting diseases, especially neurological and respiratory ones (99), the evidence is limited and recommendations for treatment are based on clinical experience (arguing that there is no other treatment available). There is no strong evidence that treatment with neuraminidase inhibitors in risk groups vaccinated or not represents a benefit in terms of mortality or hospitalization. Although positive effects have been described in the treatment of asthmatic

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children with influenza (reduction of flu-like symptoms in hours, decrease in asthmatic exacerbations in the following week (51% vs 68%, p=0.03), subsequent systematic reviews found no benefit in the treatment of asthmatic children with laboratory-confirmed influenza (100, 101). There are few studies conducted only in children, data are often offered jointly with the adult population, and are not stratified into a healthy population and at-risk population. Therefore, recommendation is provided to assess situations individually, considering the underlying disease, potential severity, and evolution.

The Panel of this Consensus Statement considers that this benefit does not justify the recommendation for the indiscriminate use of these drugs in the general population, as studies demonstrating its beneficial effect in terms of reduction of complicated infection, hospitalization, or mortality have not been published. Another reason would be the absence of a microbiological diagnosis for most upper respiratory infections in the outpatient setting for otherwise healthy children. Treatment with neuraminidase inhibitors should be reserved for those presenting a higher risk for the development of a complicated infection, but it is unclear what specific diseases constitute high risk situations (the following could be considered: immunosuppressed patients, chronic lung disease, hemodynamically significant heart disease, severe neurological pathology, nephropathies, and chronic liver diseases).

The Panel of the Consensus Statement favors the prescription of oral oseltamivir over inhaled zanamivir for children in whom treatment is indicated (providing they can tolerate oral capsules or an oral suspension). Treatment with inhaled zanamivir is not indicated for children under five years of age. This recommendation is based on the greater possibility of correct administration of oral drugs over inhaled drugs (more dependent on the patient´s skill for the inhalation technique). The recommended dose of oral oseltamivir for children is detailed in **Table 7**. Oral oseltamivir is available in capsules containing 75 mg, 45 mg, or 30 mg. It is also available as an oral suspension containing 6 mg/ml. The recommended dose of zanamivir for children older than five years is 10 mg (2 inhalations of 5 mg) twice a day (total dose of 20 mg per day). It is not necessary

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to adjust the dose of zanamivir in case of impaired renal function. Baloxavir-marboxil is another oral drug commercialized in some countries for the treatment of outpatients with influenza virus infection, but it is not yet available in Spain (89,90). Its therapeutic viral target is the endonuclease cap.

Table 7 – Posology of oseltamivir (capsules or oral suspension) for the treatment of influenza virus infection among children according to their weight

Children younger than 1 year	3 mg/kg BID for 5 days
Children older than 1 year	
Weight (kg)	Daily dose for 5 days
10 to 15 kg	30 mg BID
>15 to 23 kg	45 mg BID
> 23 to 40 kg	60 mg BID
> 40 kg	75 mg BID

Note: BID – twice a day

6.5 Is there an indication for antiviral treatment without microbiological diagnosis in children?

Recommendation

1. It is not indicated for the general pediatric population (C-III).
2. It is indicated in exceptional cases where pediatric patients present risk factors for an adverse outcome in the context of a strong clinical suspicion of influenza virus infection while simultaneously presenting an impossibility of performing diagnostic tests (C-III).

Rationale

There are no clinical trials evaluating pediatric patients without microbiological confirmation, so the evidence is poor. The diagnosis of influenza is difficult in the

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pediatric age, especially in infants and young children. Studies of moderate-high quality show that the sensitivity and positive predictive value of the clinical diagnosis are low (less than 40% in children overall and less than 25% in children under three years of age) (38).

The definitions of "influenza-like illness" have a very low diagnostic yield. The WHO case definition of "flu-like illness" has the highest specificity (21.4%) while that of the ECDC has the highest sensitivity (96.1%) (9, 38). Performance is even lower in children under five years of age.

The discrete benefit found in healthy pediatric patients, and the low sensitivity and specificity of the clinical diagnosis suggest that treatment without microbiological confirmation is not indicated for the general population. Seldom, in the case of patients with high risk of complications (immunosuppressed patients, chronic lung disease, hemodynamically significant heart disease, severe neurological pathology, nephropathies, and chronic liver diseases), strong clinical suspicion, and the impossibility of performing diagnostic tests, there could be a favorable benefit-risk balance for early treatment.

6.6 Apart from antivirals, what other therapeutic measures should be offered to a pediatric patient with influenza virus infection in the community?

Recommendations

1. Symptomatic treatment of influenza for fever, headache, and myalgia is appropriate with paracetamol, ibuprofen, or dipyrone (B-II).
2. Cough can be relieved with honey and dextromethorphan, but the use of over-the-counter medications should be carefully weighed against the risk of overdose (B-III).
3. The use of salicylates and codeine should be avoided in patients younger than 18 years of age because of risk of fatal outcomes (C-III).
4. Treatment with antibiotics is not indicated unless bacterial superinfection is suspected (A-III).

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Rationale

Symptoms should be treated when they bother the child or other family members (e.g., interrupting sleep, interfering with drinking, causing discomfort). Discomfort due to fever and pain can be treated with paracetamol or ibuprofen (102).

Supportive interventions (nebulization with saline alone or with mucolytics; nasal suction; saline nasal drops, spray, or irrigation; adequate hydration; cool mist humidifier) are usually safe and relieve congestion. In randomized trials, and as stated in systematic reviews and meta-analyses, mucolytics have not been proven to be better than placebo in children whereas they can present serious side effects (94, 95).

Honey (0.5 to 1 teaspoon) has a modest beneficial effect on nocturnal cough and is unlikely to be harmful in children older than one year of age. A systematic review and meta-analysis of randomized trials confirmed that honey can reduce cough frequency when compared to placebo (103). Honey also reduced cough frequency compared with no treatment and diphenhydramine, but not compared with dextromethorphan (103). The WHO suggest that dextromethorphan may be warranted when severe prolonged coughing interferes with feeding or sleeping (104). Other over-the-counter medications have been associated with a fatal overdose in young children (94). Therefore, if used, the benefit must be carefully weighed against the risk.

The FDA and WHO recommend against the use of codeine preparations for cough in children, due to fatal cases of patients with a very fast metabolism of codeine into morphine, especially black people and those with North-East African ascendency (105).

The use of salicylates should be avoided in children younger than 18 years of age because of the association with Reye’s syndrome (106).

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7- Treatment of influenza virus infection in hospital

7.1 Which adult patients admitted to hospital due to influenza virus infection should be treated with antivirals?

Recommendations

1. Prompt use of antivirals is recommended for adult patients admitted to hospital with suspected or confirmed influenza virus infection (A-II).

2. Neuraminidase inhibitors are the first-line drugs to be prescribed for those in whom treatment is indicated when admitted to hospital (A-I).

3. Oral oseltamivir is preferred over inhaled zanamivir for adults who can take oral drugs (A-III).

4. Oseltamivir can be administered as an oral solution through a nasogastric tube for those unable to swallow the capsules or to inhale zanamivir (A-II).

5. The earlier the initiation of treatment with neuraminidase inhibitors, the greater the beneficial effect. Neuraminidase inhibitors should be started as soon as possible, preferably within the first 6 hours after arrival at the Emergency Room (A-II).

6. Treatment with neuraminidase inhibitors should ideally be started in the first 48 hours after the onset of symptoms but, for those admitted to hospital, treatment must be started regardless of duration of symptoms (A-II).

7. Adults fulfilling the criteria for treatment of influenza virus infection when admitted to hospital should start antiviral treatment as soon as possible when they are evaluated during the period of annual influenza epidemic (A-III).

8. Competent health authorities should adopt the measures to ensure access to these drugs for those in whom treatment is indicated, in the context of the National Health System (A-III).

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Rationale

The efficacy of oseltamivir has not been evaluated in randomized clinical trials (RCTs) in hospitalized patients. Therefore, evidence of the impact of antiviral therapy in hospitalized and critically ill patients is limited to observational reports and meta-analyses. Several meta-analyses have shown that the use of antivirals improves the outcome of hospitalized patients with influenza virus infection (85, 107, 108).

In a meta-analysis of 29,234 hospitalized patients with influenza virus infection, 64% of whom were treated with antivirals, treatment with neuraminidase inhibitors reduced the risk of death (107). A recently published meta-analysis, confirmed that the odds of mortality were consistently lower among hospitalized individuals receiving antiviral treatment versus no treatment in all but one of the study populations (108).

Time from onset of symptoms to oseltamivir administration in patients hospitalized with influenza A H1N1, after adjustment for confounding factors, is associated with a prolonged duration of fever, length of stay, and higher mortality (109). Hence, antiviral therapy should be started as soon as possible, as it is most likely to provide benefit when initiated within the first 48 hours of illness in patients hospitalized in conventional wards and the intensive care unit (108, 110-118).

Although the benefit of antiviral treatment is better if given within 48 hours of symptom onset, treatment up to 5 days after symptom onset may reduce morbidity and mortality in hospitalized patients (115, 119). In hospitalized patients greater than or equal to 65 years of age, antiviral treatment within 4 days of illness onset was associated with a shorter hospital stay and reduced need for extended care after discharge (120).

Early therapy, defined as initiation of antiviral therapy within two days of symptoms, might be difficult to achieve, as only 28-40% of patients are admitted within 48 hours of the onset of symptoms (107, 109, 121). Rapid instauration of antiviral therapy once the patient is admitted to hospital, within the first six hours, is recommended, as it decreased length of hospital stay and mortality (121).

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Even though early treatment is better than late treatment, the latter (more than 48 hours after symptom onset) was independently associated with a reduction of mortality compared to no treatment in adult critical care patients, wherefore it should be initiated even in patients who have had symptoms for more than 48 hours (107, 109, 122).

A special benefit of the prompt use of neuraminidase inhibitors has been demonstrated for some populations, such as the elderly, obese patients, pregnant women, patients taking immunosuppressing drugs, or patients under mechanical ventilation. This benefit has been demonstrated in terms of a reduction in hospitalization, admission to the intensive care unit, the need for mechanical ventilation, and mortality (110, 123-126).

The Panel of this Consensus Statement considers the initiation of antiviral therapy should not be delayed, especially in severe cases, during the period of annual influenza epidemic while awaiting the results of diagnostic testing. Empiric antiviral therapy has been associated with a lower risk of in-hospital mortality (127). A cohort of hospitalized patients who received empiric therapy died less frequently than those who waited for confirmed microbiological diagnosis (1% vs 5.7%), turning out to be an independent risk factor of mortality in the multivariate analyses (121).

The Panel of the Consensus Statement favors the prescription of oral oseltamivir over inhaled zanamivir for adults admitted to hospital in whom treatment is indicated (providing they can tolerate oral capsules or an oral suspension). This recommendation is based on the greater likelihood of a correct administration of oral drugs over inhaled drugs (more dependent on the patient´s skill for the inhalation technique). Oseltamivir can be administered as an oral solution through a nasogastric tube for those unable to swallow the capsules or to inhale zanamivir (for example those under mechanical ventilation and/or presenting neurological impairment).

The recommended dose of oral oseltamivir for adults admitted to hospital is 75 mg every 12 hours for 5 days (if body weight is under 40 kg, follow recommendations for the pediatric population detailed in **Table 7**). **Table 6** includes the recommended dose for adults presenting impaired renal function. Oral oseltamivir is available in capsules containing 75 mg, 45 mg, or 30 mg. It is

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also available as an oral suspension containing 6 mg/ml. The recommended dose of zanamivir for adults is 10 mg (2 inhalations of 5 mg) twice a day (total dose of 20 mg per day). It is not necessary to adjust the dose of zanamivir in case of impaired renal function. Baloxavir-marboxil is another oral drug commercialized in some countries for the treatment of outpatients with influenza virus infection, but it is not yet available in Spain (89, 90).

7.2 Apart from antivirals, what other therapeutic measures should be offered to an adult patient with influenza virus infection admitted to hospital?

Recommendations

1. Corticosteroids should not be added to influenza treatment in hospitalized patients, unless indicated for other reasons (A-III).

2. Adding macrolides and naproxen to oseltamivir might be of benefit in patients with simultaneous pneumonia and influenza virus infection (C-I).

3. Passive immunotherapy and sirolimus need further studies to be recommended in cases of severe influenza virus infection (B.II).

4. Other therapeutic measures studied in humans, such as statins, nitazoxanide and herbal medicines, have not been consistently proven to improve prognosis in hospitalized adults with influenza infection, and therefore are not routinely recommended (C-III).

5. Cough can be relieved with dextromethorphan, but the use of over-the-counter medications should be carefully weighed against the risk of adverse effects (B-II).

Rationale

The use of corticosteroids in influenza infected patients has been associated with increased risk of mortality, nosocomial infection, duration of mechanical

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ventilation, and length of stay in the intensive care unit, in both observational studies (114, 128-132) and systematic reviews (133, 134). As clinical trials are lacking and the evidence available from observational studies is of low quality, the Panel of this Consensus Statement recommends not to use corticosteroids for the treatment of influenza virus infection in hospitalized adults.

Statins present anti-inflammatory and immunomodulatory effects and their role in cases of severe influenza have been argued for, but there are currently no published randomized control trials on the use of statins in the management of severe influenza. Statin use has been associated with reduced mortality in some observational studies (135-137) but not others (138). The protective effect of statins was less certain among new users and those with concomitant chronic illness predisposing to influenza virus infection complications, such as respiratory and cardiac disease. The data suggest that the beneficial effects of statins on influenza-related adverse outcomes may be due to a healthy-user bias (139).

The anti-inflammatory effects of macrolides have been associated with lower duration of cough and lower grade fever in mild influenza infection (140, 141). In critically ill patients with primary influenza pneumonia, macrolides reduced mortality in univariate analyses, but did not do so in a propensity score analysis (142). In a randomized, non-blind clinical trial carried out in hospitalized adult patients with pneumonia and influenza virus A (H3N2) infection, treatment with clarithromycin plus naproxen plus oseltamivir for two days followed by oseltamivir for three days compared to oseltamivir for five days, significantly reduced mortality (0.9% vs. 8.2%) and hospital stay. Reduction of viral load was earlier in the combination therapy group. The possible individual contributions of naproxen or clarithromycin could not be assessed due to the study design (143). Other studies have shown a reduction in plasma cytokine/chemokine concentration over time when azithromycin was added to oseltamivir in adults with severe influenza infection (144). Although further studies are needed to recommend its use in severe influenza virus infection, adding macrolides and naproxen to oseltamivir might be of benefit in patients with pneumonia and influenza infection.

Regarding passive immunotherapy, the use of convalescent plasma in cases of severe influenza infection has been reported to reduce mortality in some case

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reports, case series, and a case-control study (145). A randomized clinical trial reported a potential efficacy of immune plasma for the treatment of severe influenza. However, the study was not able to conclusively demonstrate efficacy based upon the primary endpoint (resolution of tachypnea/hypoxia), but a trend towards resolution of tachypnea/hypoxia and mortality was observed (146). In a phase 3 randomized double-blind placebo-controlled trial, a benefit of this intervention was not demonstrated (147). A randomized control trial of hyper-immune anti-influenza immunoglobulin did not show any benefit in terms of mortality, ICU stay, or hospital stay. In patients treated within five days of the onset of symptoms, hyper-immune anti-influenza immunoglobulin reduced mortality (148).

The use of sirolimus in addition to oseltamivir and prednisolone was evaluated in a randomized clinical trial including patients under mechanical ventilation with influenza virus infection. This study reported a reduction in the length of invasive mechanical ventilation but no reduction in mortality (149).

Nitazoxanide is an antiparasitic drug that presents antiviral and immuno-modulatory effects. In uncomplicated mild influenza virus infection, it demonstrated shorter symptom duration (150). In hospitalized patients, adding nitazoxanide to the standard of care did not reduce length of hospital stay (151).

Several Chinese medicinal herbs have been used to improve recovery from influenza. These herbs include Antiwei capsule, Ganmao capsule, and Lianhua Qingwen capsule. However, most studies are methodologically poor and include non-severe cases of influenza virus infection. Therefore, no recommendation can be made with regard to these herbs (152).

Supportive interventions (administration of nebulized saline solution alone or with mucolytic; saline nasal drops, spray, or irrigation; adequate hydration; cool mist humidifier) are usually safe and relieve congestion. In randomized trials, and as stated in systematic reviews and meta-analyses, mucolytics have not been demonstrated to be better than placebo (94, 95).

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7.3 Which adult patients admitted to hospital due to influenza virus infection should be treated with other antimicrobials?

Recommendations

1. Adults presenting a clinical picture of a severe respiratory infection (extensive pneumonia, respiratory failure, hypotension) while infected by influenza virus should receive early antibiotic treatment in addition to antiviral therapy.

2. In adults with influenza virus infection whose respiratory symptoms deteriorate after an initial improvement, antibiotic therapy should be considered (A-III).

3. Microbiological diagnostic tests to confirm bacterial coinfection or superinfection must be performed in these situations in patients admitted to hospital (A-III).

4. If started when indicated, antibiotic treatment of adults with influenza virus infection should be active against commonly influenza-associated bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes,* and *Haemophilus influenzae* (A-II).

5. In case of nosocomial superinfection, the possibility of methicillin-resistant *Staphylococcus aureus* should be considered (A-II).

6. *Aspergillus* spp. coinfection should also be considered, especially in immunosuppressed patients and those admitted to an intensive care unit (A-II).

Rationale

Bacterial coinfection or superinfection increases mortality of influenza virus infection (114, 153-161). Studies have shown that up to 65% of confirmed cases

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of influenza infection in hospitalized adults exhibited bacterial coinfection or superinfection (55).

Patients with influenza infection and bacterial coinfection cannot be clinically distinguished from those with influenza infection. Diagnosis of influenza-associated bacterial pneumonia remains difficult, and is often based upon a combination of clinical, laboratory, and radiographic data. However, bacterial co-infected patients are more likely to present with shock, require mechanical ventilation at the time of admission to the intensive care unit, and present higher APACHE II scores, particularly in at-risk groups such as the immunocompromised (153, 157). As early therapy improves the outcome in community-acquired pneumonia (162), patients with severe influenza virus infection should receive early antibiotics in addition to antiviral therapy. Treatment should be active against the influenza virus infection it is most commonly associated with, for example *Streptococcus pneuomoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes,* and *Haemophilus influenzae*. In case of nosocomial superinfection (especially in patients admitted to the ICU), the possibility of methicillin-resistant *Staphylococcus aureus* should be considered (163).

Bacterial superinfection can occur days after the onset of influenza disease. It must be suspected in patients with influenza infection who deteriorate after initial improvement. At this point, antibiotic therapy should be started.

In recent years, an increasing number of cases of influenza-associated aspergillosis has been reported. Although most of these adults presented at least one underlying medical condition, mainly immunosuppression, up to 28% were previously healthy. In intensive care units, patients with *Aspergillus*-influenza coinfection presented a higher mortality than patients not coinfected (51% vs 28%, 5·19; 95% CI 2·63–10·26; p<0·0001)(164). Therefore, a low threshold for the suspicion of pulmonary aspergillosis and initiation of its diagnostic work-up should be maintained among adults admitted to hospital presenting a severe non-improving influenza virus infection.

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7.4 Which pediatric patients admitted to hospital due to influenza virus infection should be treated with antivirals?

Recommendations

1. Antiviral treatment is recommended for children presenting risk factors for a complicated course (immunosuppressed, chronic lung disease other than asthma, hemodynamically significant heart disease, severe neurological pathology, nephropathies, and chronic liver diseases) when admitted to hospital due to influenza virus infection (B-III).

2. Antiviral treatment may also be considered for children admitted to hospital due to influenza virus infection but not fulfilling the risk factors for a complicated course when presenting pneumonia or respiratory failure or at the time of admission into the critical care unit (B-III).

3. Neuraminidase inhibitors are the first line drugs to be prescribed for those in whom treatment is indicated when admitted to hospital (A-I).

4. Oral oseltamivir is preferred over inhaled zanamivir for children who can take oral drugs (C-III).

5. Oseltamivir as an oral solution might be a better option than capsules for the pediatric population (C-III).

6. Zanamivir is not indicated, under any circumstances, for children younger than five years of age (A-III).

7. Oseltamivir can be administered as an oral solution through a nasogastric tube for those unable to swallow the capsules or to inhale zanamivir (A-II).

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8. The earlier the initiation of treatment with neuraminidase inhibitors, the greater the beneficial effect. When indicated, neuraminidase inhibitors should be started as soon as possible, preferably within the first six hours after arrival at the Emergency Room (A-II).

9. When indicated, treatment with neuraminidase inhibitors should ideally be started within the first 48 hours after the onset of symptoms but, for severely ill children, treatment might be started regardless of duration of symptoms (A-II).

10. Microbiologically confirmed influenza diagnoses should ideally be made before antiviral indication, due to the lack of specificity of symptoms. Etiological diagnosis also enables patient isolation in seasonal influenza period, which overlaps with other viruses, such as Respiratory Syncytial Virus (A-I).

11. Exceptionally in patients who are critically ill and/or have risk factors, a strong clinical suspicion of influenza, and impossibility of performing a diagnostic test, antivirals could be prescribed without microbiological confirmation (C-III).

12. Competent health authorities should adopt the measures to ensure access to these drugs for those in whom treatment is indicated, in the context of the National Health System (C-III).

Rationale

Children with a risk factor for influenza-related complications (immunosuppressed patients, chronic lung disease, hemodynamically significant heart disease, severe neurological pathology, nephropathies, and chronic liver diseases) should receive antiviral treatment as soon as possible. Even though

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the level of evidence for this recommendation in the pediatric population is not as high as for adults, the Panel of this Consensus Statement considers that the risk of the development of severe complications in this population justifies this endorsement (165). A prospective Australian study included 722 children under 15 years old admitted to hospital when presenting at least one severe complication of influenza virus infection (60% were previously healthy children) and reported that having an underlying medical condition is an independent predictor of ICU admission, mechanical ventilation, and fatal outcome (99). In a retrospective cohort study of children and young adults (aged 0 to 21 years), 39% of patients with one or more complex chronic conditions who were admitted to the intensive care unit and treated with oseltamivir within 24 hours of hospitalization were associated with a shorter duration of hospital stay, whereas intensive care unit stay, in-hospital mortality, and readmission rates did not differ (166).

While maximum influenza virus infection incidence rate has fallen in the pediatric population, the proportion of severe cases requiring hospitalization is small (7% of the total of influenza virus infection hospitalizations in Spain in the 2017-2018 season) (167). This fact could explain, at least partially, the lack of evidence on this issue. Oseltamivir is recommended for previously healthy pediatric inpatients with pneumonia, respiratory failure, or admittance to the critical care unit. The indication of specific antiviral treatment is not clear for previously healthy pediatric inpatients not fulfilling previously detailed criteria, such as bronchiolitis/wheezing infection without respiratory insufficiency, and infants hospitalized for acute fever and influenza diagnostic confirmation during the stay in hospital (168).

Clinical trials have not shown usefulness to prevent mortality or major complications in this group of children (108, 169, 170). A multicenter retrospective study including 287 children did not find any proven benefits of treatment with oseltamivir in hospitalized pediatric patients without underlying diseases or risk factors for developing a serious illness (including those with asthma) (171). There have been moderate-low quality studies published that suggest that critically ill patients with mechanical ventilation may have a lower mortality when treated with oseltamivir, especially if started in the first 24 hours (165). There have been low quality studies at risk of bias published that suggest a lower mortality in patients

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– adults and children under 16 years of age [data from children were not provided separately] with influenza virus infection who developed pneumonia – when treated in the first 48 hours after symptom onset (172).

A microbiological confirmation of influenza virus infection should be achieved whenever possible due to the non-specificity of the clinical picture (see **Section 4**) (165). In a prospective study conducted over seven consecutive seasons in hospitalized children under 14 years of age with criteria of suspected influenza virus infection (febrile syndrome, upper respiratory tract infection, bronchiolitis, wheezing episodes, or pneumonia), influenza virus was detected in 5.6-12% of cases, depending on the season. A high proportion of children would have received specific influenza antiviral treatment without presenting that infection if they had been treated empirically (165, 173).

For children fulfilling the criteria for treatment of influenza virus infection when admitted to hospital, empirical antiviral treatment should be started as soon as possible when they are evaluated during the period of annual influenza epidemic only if a microbiological diagnosis to confirm or exclude the infection is not available.

7.5 Apart from antivirals, what other therapeutic measures should (and should not) be offered to a pediatric patient with influenza virus infection admitted to hospital?

Recommendations

1. Symptomatic treatment of influenza for fever, headache, and myalgia is appropriate with paracetamol, ibuprofen or dipyrone (B-II).
2. The use of salicylates should be avoided in children younger than 18 years of age because of the risk of developing Reye's syndrome (C-III).
3. Supported sitting position and gentle suction of the nares when secretions block them can be useful (B-II).
4. Intravenous fluid therapy is indicated if adequate oral intake is not possible, and oxygen therapy or mechanical ventilation as indicated (B-II).

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5. Other drugs such as antihistamines, nasal decongestants, antitussives, expectorants, or mucolytics are not generally recommended (B-II).
6. Corticosteroids should not be added to influenza treatment in hospitalized patients, unless indicated for other reasons (A-III).

Rationale

Acetaminofen or ibuprofen can be used to treat fever and pain in order to keep the child comfortable. There is no evidence that fever or antipyretic treatment affects illness course or protects against neurological complications (96, 174).

Children hospitalized with influenza virus infection should receive mechanical ventilatory support as indicated by their clinical condition. A supported sitting position may help to expand the lungs and improve respiratory symptoms. Gentle bulb suction of the nares may be helpful in infants and children whose nares are blocked with secretions. Oxygen supplementation is recommended for patients with oxygen saturation less than or equal to 92% when breathing room air. Oxygen can be delivered by nasal cannula or high-flow delivery devices (175). Children who cannot maintain adequate fluid intake because of breathlessness, respiratory fatigue, or risk of aspiration may require intravenous fluid therapy (176).

Over-the-counter products for symptomatic treatment include antihistamines, decongestants, antitussives, expectorants, mucolytics, antipyretics/analgesics, and combinations of these medications. Except for antipyretics/analgesics, they are not generally recommended. In randomized trials, and as stated in systematic reviews and meta-analyses, these drugs have not been demonstrated to be better than placebo in children whereas they can present serious side effects (94, 95).

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7.6 Which pediatric patients admitted to hospital due to influenza virus infection should be treated with antibiotics?

Recommendations

1. Antibiotic treatment is indicated in proven or strongly suspected secondary bacterial infections cases (including bacterial otitis media, sinusitis, and pneumonia). Empiric antibiotics should generally be directed at the most common bacterial pathogens following influenza: *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Streptococcus pyogenes* (A-I).

2. There is no indication for prescribing antibiotics in order to prevent secondary bacterial complication (A-I).

3. In hospitalized children with influenza infection when bacterial pneumonia is suspected, complementary tests are recommended, as symptoms and signs of virus and bacteria often overlap. No complementary test on its own is enough to define bacterial coinfection (B-II).

4. The best performing clinical decision rule for the diagnosis of bacterial coinfection or superinfection combines C-reactive protein (CRP) higher than 13 mg/dl, procalcitonin higher than 0.52 ng/ml, and/or alveolar consolidation in chest X-ray (B-II).

5. In children with influenza virus infection whose respiratory symptoms deteriorate after an initial improvement, antibiotic therapy should be considered (A-III).

6. Microbiological diagnostic tests to confirm bacterial coinfection or superinfection must be performed in these situations, in patients admitted to hospital (A-III).

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Rationale

The use of antibiotics is only recommended in proven or strongly suspected bacterial complications of acute influenza, such as bacterial pneumonia, otitis media, and sinusitis. Antibiotics do not alter the course of influenza virus infection and do not prevent secondary complications but may cause significant side effects and contribute to increasing bacterial antimicrobial resistance. In children with a positive test for influenza virus in the absence of clinical, laboratory, or radiographic findings suggesting bacterial coinfection, antibacterial therapy is not indicated. Further, testing is usually not indicated in children in whom no complication is suspected. On the other hand, bacterial coinfection in children with influenza is known to involve severe outcomes: it increases the rate of admission to the intensive care unit and is associated with higher mortality, longer hospital stays, and greater costs (177).

There is an overlap between signs of bacterial and viral infections, and no single clinical feature is sufficient to diagnose bacterial pneumonia (178,179). Neither is a single complementary test enough to define bacterial superinfection. So, when bacterial pneumonia is suspected, it will be necessary to combine tests in order to increase diagnostic accuracy (180). Some tools are available to guide the diagnosis of bacterial or viral pneumonia and may help to make the decision of whether to give antibiotics or not. For example, the mobile app Pneumonia Etiology Predictor was developed after a thorough study of pneumonia in children and is endorsed by the Spanish Society of Pediatric Infectology and the Spanish Society of Pediatric Emergencies (57).

In a prospective study including 401 children with pneumonia, bacterial infections presented a C-reactive protein higher than 8 mg/dL more frequently than viral ones (OR 3.6, 95% CI 1.65–8.07, p = 0.001), but levels lower than 2 mg/dL did not distinguish bacterial infections from viral ones (p = 0.254) (181). In another study, a C-reactive protein higher than 8 mg/dL presented good specificity (0.72) but poor sensitivity (0.52) for the diagnosis of bacterial pneumonia (56).

Procalcitonin seems to be a better biomarker for the diagnosis of bacterial infection than C-reactive protein or erythrocyte sedimentation rate (182-185). The use of C-reactive protein is associated with a reduction in antibiotic exposure without increases in all-cause mortality or treatment failure in children (186).

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A study on the combination of biomarkers found that a C-reactive protein level over 8 mg/dL together with a procalcitonin level greater than or equal to 2 ng/ml presents a significant positive likelihood ratio on ruling in systemic bacterial infection, whereas values lower than 2 mg/dL and lower than 0.5 ng/ml, respectively, are likely to rule out bacterial infection (187). A well-designed study that included 126 children found significantly higher procalcitonin values in bacterial pneumonia cases than in viral pneumonia ones (median procalcitonin value 2.09 ng/ml *vs.* 0.56 ng/ml, p = 0.019). The C-reactive protein values were also significantly higher in patients with bacterial pneumonia (median value 9.6 mg/dL *vs.* 5.4 mg/dL, *P* = 0.008) (188).

In a retrospective cohort study including 3,180 children younger than five years of age, hospitalized and outpatient patients with influenza A (H1N1) microbiologically-confirmed infection, C-reactive protein and procalcitonin were found to be significant diagnostic biomarkers. The combination of C-reactive protein higher than 13.55 mg/dl and procalcitonin higher than 0.52 ng/ml presented a sensitivity of 0.75 and a specificity of 0.86 for the diagnosis of bacterial pneumonia (53)White blood cell count, neutrophil counts, and erythrocyte sedimentation rate are suboptimal or differentiation between bacterial and viral pneumonia (189).

Concerning chest X-rays, a significant alveolar consolidation (a dense or fluffy opacity that occupies a portion or whole lobe, or the entire lung, which may or may not contain air-bronchograms) is considered the most specific radiographic predictor of bacterial pneumonia (190). Interstitial infiltrates are seen in both viral and bacterial pneumonias.

The Panel of this Consensus Statement considers that none of the proposed biomarkers or their combinations can substitute clinical judgment when deciding whether to start antibiotic treatment based on the possibility of bacterial coinfection or superinfection in a child admitted to hospital and presenting pneumonia in the context of influenza virus infection.

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8- Prophylaxis of Influenza Transmission in the Community:

8.1 What measures should be taken to avoid the transmission of influenza virus in the community?

Recommendations

- Annual influenza vaccination of people in high-risk groups is recommended (A-I) – **see Section 10**.

- It is recommended to perform hand hygiene after contact with respiratory secretions by means of hand washing with soap and water (or alcohol-based hand sanitizers containing at least 60% ethanol or isopropanol when soap and water are not available) (A-II).

- People should cover their nose and mouth when coughing or sneezing using tissues or flexed elbow (if a tissue is not available) in order to contain respiratory secretions, followed by hand hygiene. Touching eyes, nose, or mouth should be avoided where possible (B-II).

- Routine cleaning of frequently touched surfaces and objects that might be contaminated with respiratory secretions (at home, schools, childcare facilities, and workplaces) is recommended (B-II).

- Post-exposure chemoprophylaxis could be considered in asymptomatic people at high risk of developing complications from influenza and for those in whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., people who are significantly immunocompromised) (C-II).

- Clinicians can also consider post-exposure chemoprophylaxis for people who are unvaccinated and are household contacts of a patient at very high risk of complications from influenza (e.g., severely immunocompromised patients) (C-II).

- A 10-day regimen with a neuraminidase inhibitor is recommended as post-exposure chemoprophylaxis. It should be initiated as soon as possible (within 48 hours of exposure for oral oseltamivir or within 36 hours for inhaled zanamivir) (A-III).

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Rationale

Influenza vaccination is the most effective way to prevent infection by influenza virus and its complications (consult **Section 10** for details on indications).

Susceptibility to influenza virus infection is considered to be universal in the general population. Age-specific attack rates in seasonal epidemics reflect the persistence of immunity in relation to previous circulating viruses, so the incidence of influenza is higher in children who have had fewer previous infections and lower antibody response (191).

Hand hygiene is a measure of proven efficacy in reducing the transmission of infections. Hand hygiene has shown efficacy in reducing the transmission of influenza, reaching in some studies a reduction of 47% (192-194). It should be performed on a regular basis by using soap and water or alcohol-based solutions (containing at least 60% ethanol or isopropanol). It is especially relevant to perform hand hygiene after contact of the fingers with respiratory secretions. It is important to install dispensers of hydro-alcoholic solutions in visible and accessible places in public spaces, as well as display posters on how to correctly perform hand hygiene (195). It has been shown that in schools where health-education on hand hygiene was carried out, there was less school absenteeism during the influenza season (196). A correct technique for hand hygiene is as important as using the right products (193, 197).

The influenza virus is transmitted by drops generated when speaking or sneezing. It is important to educate the population so that, when coughing and/or sneezing, they cover their nose and mouth with a tissue or their elbow to minimize the dispersion of droplets that may contain the virus; then they should remove the tissue and perform hand hygiene (195). Multivariate models have shown significant association between covering the mouth and nose when coughing and/or sneezing and a decrease in the transmission of infection (198). Public Health campaigns – such as the one promoted by the Centre for Diseases Control in the United States, "Cover your Cough" – call for adequate respiratory hygiene and safe cough management to avoid the spread of respiratory viruses. Posters

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warning about cough etiquette should be available in public spaces to inform the population of how to handle their cough and sneezes (192, 199).

It is advisable for infected patients to wear a surgical mask when they cannot avoid being in crowds or in close contact with other people. The mask should cover the nose and mouth correctly and should be changed when wet. There are few studies that evaluate, outside health institutions, the effectiveness of this measure, including use, but it can be a risk factor if they are not used well or are handled incorrectly (195). Research conducted during the 2009 H1N1 influenza pandemic found that wearing a surgical mask along with proper hand hygiene was effective in controlling the transmissibility of the virus (192, 200).

People with influenza infection should not go to work or to public places where transmission to susceptible persons is favored.

An inanimate environment can be a source of infection. Surfaces and objects that are frequently handled (at home, schools, or workplaces) may be contaminated with the influenza virus. Hands can transmit these viruses from contaminated objects to the eyes, nose, and mouth. To avoid transmission, it is necessary to properly clean and disinfect these surfaces and objects with detergents (192) registered as effective against influenza virus.

Several studies have evaluated the efficacy of post-exposure antiviral chemoprophylaxis for household members after influenza diagnosis in a household member (201-205). All showed statistically significant protection; the pooled estimate of efficacy against laboratory-confirmed symptomatic influenza for the three trials was 79% (95% CI, 67%-87%) (206). Antiviral medication can be considered after exposure to a person with influenza in some circumstances, such as people at high risk of developing complications from influenza infection and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness. Further, clinicians should recommend post-exposure chemoprophylaxis for those who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (i.e., severely immunocompromised patients). People with indication for post-exposure prophylaxis are the same as those with indication for vaccination (see **Table 12**

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and **Table 13** in **Section 10**). Neuraminidase inhibitors (zanamivir and oseltamivir) can offer individual protection against influenza that can range from 67-89%. The protective effect is only maintained while the prophylaxis is ongoing (195, 207, 208). The sooner the prophylaxis is started after exposure, the greater the benefit. Time from exposure to the first dose should not be longer than 36 hours for inhaled zanamivir or more than 48 hours for oral oseltamivir. The established dose of zanamivir for prophylaxis is one puff (10 mg) per day for ten days (204). It should not be used in children younger than five years of age. Doses of oseltamivir for prophylaxis in adults according to renal function are shown in **Table 8**. Doses of oseltamivir for prophylaxis in children according to weight are shown in **Table 9.** Length of prophylaxis for oseltamivir has also been set at ten days. Antiviral treatment in this context might play an important role in the reduction of influenza transmission in the community (209).

Baloxavir-marboxil has demonstrated its role in the prophylaxis of the transmission of influenza infection in the community setting but is not yet available in Spain (210).

Table 8 – Recommended dosage of oral oseltamivir for the prophylaxis of influenza infection in adults according to renal function (88)

Creatinine clearance (ml/min)	**Dose**
> 60 ml/min	75 mg QD
> 30 to 60 ml/min	75 mg QD
> 15 to 30 ml/min	45 mg q2d
≤ 15 ml/min	75 mg single dose
Patients under hemodialysis	30 mg after every other hemodialysis session
Patients under peritoneal dialysis	30 mg weekly

Note: QD – once daily; q2d – every other day

Available in hard capsules (75 mg) and as powder for oral suspension (6mg/ml).

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Table 9 - Recommended dosage of oral oseltamivir for the prophylaxis of influenza infection in children

Preterm infants (less than 37 weeks of pregnancy)	0 to 12 months	>1-12 years: Dose according to weight			
		≤15kg	>15-23kg	>23-40kg	>40kg
See below[1]	3 mg/kg QD	30 mg QD	45 mg QD	60 mg QD	75 mg QD

Note: QD – once daily.

Available in hard capsules (75 mg) and as powder for oral suspension (6mg/ml).

[1]Although it may be possible to provide half the treatment frequency, there is currently no available dosage information for oseltamivir prophylaxis in preterm infants.

9- Prophylaxis of Nosocomial Transmission of Influenza:

9.1. What measures should be taken to avoid the transmission of influenza virus in healthcare settings?

Recommendations

Vaccination

- Annual influenza vaccination of healthcare workers and people in high-risk groups is recommended (A-I) – **see Section 10.**
- Annual influenza vaccination and pneumococcal vaccine of residents in long term care facilities is recommended (A-II) – **see Section 10.**

Chemoprophylaxis

- Post-exposure antiviral chemoprophylaxis should not be used routinely (B-III). Antiviral prophylaxis can be considered after exposure (**Table 10**) to a person with influenza in some circumstances, such as asymptomatic patients, healthcare workers at high risk of developing complications from influenza, or for those in whom influenza vaccination is contraindicated, unavailable, or

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expected to have low effectiveness (e.g., people who are significantly immunocompromised) (A-II).

- A 10-day regimen with a neuraminidase inhibitor is recommended as post-exposure chemoprophylaxis. It should be initiated as soon as possible (within 48 hours of exposure for oral oseltamivir or within 36 hours for inhaled zanamivir) (A-I) – **see Table 8 and Table 9).**

Standard precautions, hand hygiene, and respiratory hygiene/cough etiquette

- Reinforce effective hand hygiene and *cough etiquette* when in contact with patients, visitors, and staff (*Catch it, Bin it, Kill it*) (B-II).
- Provide disposable tissues, no-touch receptacles for disposal of tissues, and alcohol-based hand rubs (B-II).
- Provide instructions to cover mouths/noses when coughing or sneezing, use disposable tissues, and perform hand hygiene (i.e., by posting signs at entrances and in strategic places) (B-II).
- Standard cleaning and disinfection procedures as well as food handling, laundry, and waste management are adequate when attending patients with suspected or confirmed influenza (B-II).

Triage for rapid identification of patients with influenza-like illness (ILI)

- Instruct people to inform healthcare professionals upon arrival if they present symptoms of respiratory infection so that preventive actions can be taken (B-III).
- Offer masks to coughing persons upon entry to hospital (B-II).
- Enable differentiated spaces in waiting rooms for patients with symptoms of respiratory infection (B-III).
- It is recommended that patients be separated one or more meters from each other and by physical barriers (B-III).

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Infection prevention and control precautions when caring for patients with ILI or confirmed influenza infection

- Droplet precautions are required for all cases of ILI that are known or suspected to be influenza virus infection until influenza has been excluded or the patient is no longer deemed contagious (A-II).

- Place patients with suspected or confirmed influenza in individual rooms or specific areas. If an individual room is not available, consult the Infection Prevention and Control Team for assessing isolation by cohort (B-III). In long-term care and other residential settings, make decisions regarding patient placement on a case-by-case basis after considering infection risks of other patients in the room and available alternatives (C-III).

- Patients with suspected or proven influenza who require non-invasive ventilation should have priority for negative-pressure rooms (if available) and/or rooms with 100% exhaust capability (B-II).

- For aerosol generating procedures, use of FFP2 face mask or a respirator, fluid repellent gown, disposable gloves, and eye protection (B-III).

- Closed-ventilation suction circuits should be used where available, with bacterial and viral filters placed over the expiratory port (B-III).

Peri- and postpartum care

- A pregnant woman with suspected or confirmed influenza virus infection admitted to hospital should be attended according to the recommendations for the general population before, during, and after delivery. These measures include standard and droplet precautions (B-II).

- After delivery, due to the risk of serious complications were the newborn to become infected by influenza, temporary separation from the baby should be considered, in accordance with the mother´s wishes. The baby should be cared for by a healthy caregiver whenever possible (B-III).

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- Mothers with the intention to breastfeed should express their milk in order to establish and maintain the milk supply. This breastmilk can be fed to the newborn by the healthy caregiver (B-III).

- In case the baby remains in the same room (due to the mother´s wishes or for logistic reasons), standard and droplet precautions should be established in order to minimize transmission (B-III). The hospital must implement measures to reduce viral exposure of the newborn including physical barriers (i.e., a curtain between the mother and the newborn), maintaining at least 2 meters between the mother and the newborn, and ensuring another adult is present to care for the newborn.

- If breastfeeding is maintained while the mother presents influenza virus infection, she should wear a surgical face mask and practice hand hygiene before each feeding or contact with her newborn (B-III).

Containment measures

- During periods of increased influenza activity, minimize visits by patients seeking care for mild influenza-like illness who are not at increased risk of complications (B-III).

- Limit visitors with acute respiratory symptoms and/or with high risk of influenza complications (B-III).

- Healthcare workers presenting symptoms that suggest influenza virus infection should stop patient care activities, don a facemask, and immediately notify their supervisor (and infection control personnel) to determine appropriateness of contact with patients, temporary reassignment, or exclusion from work until criteria for a non-infectious status are met (B-III).

Training and education of healthcare workers (HCWs)

- Educate healthcare workers on the importance of source control measures to contain respiratory secretions so as to prevent droplet and fomite transmission of respiratory pathogens (B-II).

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- Staff education and training on infection control methods, policies, and procedures should be delivered to all staff members (B-II).
- Healthcare settings must establish mechanisms to find out about influenza virus activity in the community as well as for the prompt detection of outbreaks in healthcare settings (B-III).

Rationale

Vaccination

Achieving high influenza vaccination rates of HCWs and patients is a critical step in preventing healthcare transmission of influenza from HCWs to patients and from patients to HCWs (211-214). Strategies employed by some institutions to improve HCW vaccination rates include providing vaccine at no cost, or improving access (211). A systematic review and meta-analysis reinforced influenza vaccine effects in reducing infection incidence and length of absenteeism in HCWs (215).

Pneumococcal infection secondary to influenza is associated with a particularly poor outcome in the elderly and is a major cause of death. Data from observational studies suggest that dual seasonal influenza and pneumococcal vaccination may have an additive effect resulting in greater reductions in hospitalization for pneumonia and deaths in the elderly than either of the vaccines alone (216). A reduction in hospitalization rates will theoretically reduce the nosocomial transmission of influenza. Administration of the pneumococcal vaccine should follow the recommendations established by Public Health authorities.

Chemoprophylaxis

Routine use of antiviral medication for chemoprophylaxis is not recommended (213, 217). The use of oseltamivir has been shown to increase the risk of headaches, nausea, and psychiatric events in trial participants, who are often healthy adults (218). Antiviral medications can be considered for chemoprophylaxis in order to prevent transmission of influenza virus in healthcare settings in certain situations (after exposure to a person with influenza)

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in people at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g., people who are significantly immunocompromised).

Prophylaxis with neuraminidase inhibitors was shown to be more effective than placebo at preventing symptomatic influenza in individuals and household contacts in a randomized control trial (218) and this was supported by additional data from observational studies (208). The use of antivirals for prophylaxis is recommended for people with a high risk of complications, especially for those who are unvaccinated or in whom vaccination is contraindicated, and immunocompromised people without an immunological response to vaccination (219). This recommendation is also considered for HCWs with a high risk of influenza complications and who present significant unprotected exposure to a person with influenza (**Table 10)** (213).

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Table 10. Description of significant exposure for patients and healthcare workers after contact with a person with influenza virus infection (213)

For patients	For HCWs
- More than 15 minutes of face-to-face contact with anyone with influenza - More than 24 hours spent in the same room as the index patient when the index patient is not bedridden - More than 24 hours spent in the same room as the index patient, when the index patient is bedridden, but beds are placed less than a meter apart and a curtain has not been drawn between them - Care by a HCW with influenza for more than 15 minutes while the HCW is contagious (from 1 day before symptom onset to 7 days after (if the HCW has not received antiviral treatment) or 3 days after if the HCW has received antiviral treatment)	- Unprotected exposure to a patient with influenza during aerosol-generating procedures (high-risk contact) - During patient care for longer than 15 minutes without using a surgical mask within 1 meter of distance from the patient (moderate-risk contact)

Note – HCWs – healthcare workers

When secondary chemoprophylaxis is indicated, neuraminidase inhibitor medication should be started as early as possible after contact with an influenza infected patient (preferably within the first 48h after contact) in order to reduce the risk of developing symptomatic disease. Zanamivir and oseltamivir are the drugs of choice when initiating influenza chemoprophylaxis. If oseltamivir resistance is suspected, it is recommended to administer zanamivir. Given the high incidence of resistance to amantadine and rimantadine among circulating strains of influenza A and the intrinsic resistance of influenza B, they are not recommended for initiating chemoprophylaxis (220). The established dose of zanamivir for prophylaxis is one puff (10 mg) per day for 10 days (204). Doses of

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oseltamivir for prophylaxis according to renal function and in the pediatric population are shown in **Table 9** and **Table 10**. Length of prophylaxis for oseltamivir has also been set at 10 days.

Standard precautions, hand hygiene, and respiratory hygiene/cough etiquette

Standard precautions are a basic set of precautions or routine measures that should be practiced at all times by all staff in contact with patients. The key components of standard precautions are hand hygiene, respiratory hygiene, use of personal protective equipment (PPE), environmental control (cleaning and disinfection), waste management, packing and transporting of patient care equipment, linen and laundry and waste from isolation areas, and the prevention of needlestick or sharp injuries (221). Influenza virus can survive in the environment for variable periods of time (up to 48 hours) (222). Direct and indirect contact are potential routes of transmission for influenza (223, 224). Cleaning reduces the bio-burden of microorganisms on contaminated surfaces and standard disinfectants inactivate them (221).

Droplet precautions

Droplet precautions are intended to prevent transmission of pathogens through close respiratory or mucous membrane contact with respiratory secretions and should be practiced in addition to standard precautions. These include patient placement, use of a medical mask when working within 2 meters of infected patients, and use of a medical mask by patients when being transported.

Physical separation of patients infected with influenza in the same unit or zone and minimizing staff movement between areas can reduce transmission of virus to other patients and staff and facilitate the application of infection prevention and control measures. HCWs and other staff members can become infected through exposure to infected patients, and once infected they become a source of transmission to other staff and uninfected patients (221). When there is no single

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room available, patients may be placed in the same room (cohort) providing they are infected by the same pathogen. Ideally, only patients infected by the same subtype of influenza A virus should be placed in the same room (211). Therefore, isolation by cohorts of unconfirmed influenza cases should be avoided, if possible.

The infective period for influenza is thought to be from one day before the onset of symptoms up to seven days after the onset of symptoms. Droplet precautions should be implemented for patients with suspected or confirmed influenza for seven days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms without the use of antipyretics, whichever is longer. Children, immunocompromised people, and seriously ill patients may remain contagious for a longer period. Children under two years of age may shed virus for more than seven days, therefore, longer isolation should be considered (e.g., until ten days after illness onset) (211, 213).

Aerosol-generating procedures

An aerosol-generating procedure is defined as any medical procedure that can induce the production of aerosols of various sizes, including small (< 5μ) particles. Aerosol-generating procedures that may be associated with an increased risk of infection transmission include elective procedures such as bronchoscopy, gastroscopy, sputum induction, aerosolized or nebulized medication administration, elective endotracheal intubation and weaning, as well as emergency procedures such as cardiopulmonary resuscitation, emergency intubation, open suctioning of airways, manual ventilation before intubation, and initiation of non-invasive ventilation (e.g., continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BPAP]) (213). Measures recommended in this situation involve wearing an FFP3 face mask or respirator, wearing gloves, gown, and either a face shield that fully covers the front and sides of the face or goggles. The procedure should be performed in an airborne infection isolation room (negative-pressure rooms), when feasible, or in a room with 100% exhaust capacity (211, 221).

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Peri- and postpartum

Since influenza infection in newborns is associated with an elevated risk of complications, hospitalization, and death, it seems reasonable to establish recommendations to minimize the transmission risk from ill mother to the newborn in acute care hospitals (225). However, in addition to high evidence-based measures to decrease risk of influenza infection in the newborn, – such as mother vaccination (226, 227) – the optimal method for caring for newborns of mothers with influenza has not been clearly established. Some experts recommend complete separation of the mother from the newborn until the end of the mother's infection or at least until the mother has completed 48 hours of antiviral treatment (228) based on the principle of "minimum risk assumption". Other experts advocate to allow rooming and direct contact including breastfeeding, but while maximizing hygienic and barrier measures (213). These measures include the use of curtains between mother and baby and keeping the baby at least 2 meters away. If a healthy adult cannot care for the newborn and the mother decides to carry out skin-to-skin breastfeeding, she must use a surgical mask and perform hand hygiene before breastfeeding or any other close contact with the newborn.

The risk and benefits of each strategy should be discussed with the mother by the healthcare team and decisions should be made in accordance with the mother's wishes (228).

Close monitoring of the newborn must be maintained in order to adjust (remove or maintain) the transmission precautions and, in case of developing symptoms of influenza infection, to notify clinicians so as to consider prompt starting on antiviral treatment (228).

Containment measures

Staff members with fever or symptoms of influenza should be excluded from work for at least seven days after symptom onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer. If a residual cough persists, a mask should be used and strict adherence to hand hygiene must be observed (211).

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Training and education of healthcare workers

Management of healthcare settings should ensure that all staff receive training to include vaccination policy, infection control methods, and information about influenza (including its impact, recognition of suspected cases, communication channels, measures to be instigated in a potential outbreak situation, and staff exclusion policies) (221, 229).

9.2. What is the definition of a nosocomial outbreak of influenza virus infection?

A nosocomial outbreak is defined by the diagnosis of healthcare-associated influenza infection (at least one of the cases with microbiological confirmation) in two or more patients admitted to the same ward in a period of less than 48 hours (A-II).

Rationale

Considering the high attack of influenza virus infection, it is prudent to consider a single case of laboratory-confirmed disease in the context of two or more cases of influenza-like illness occurring within 48 hours as an outbreak, leading to the prompt implementation of control measures (207, 221, 230-233).

9.3. What measures should be adopted to control an influenza outbreak?

A bundle of measures, rather than one measure alone, must be implemented when a nosocomial influenza outbreak is detected in an institution (A-II). This includes administrative, pharmacological, and non-pharmacological measures (A-II).

Rationale

A bundle of measures must be established in order to control an outbreak detected in a hospital ward (207, 212, 221, 230-234). **Table 11** summarizes the

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set of measures to be applied in different scenarios. Grade A corresponds to measures that must be implemented immediately after an outbreak has been declared. Grade B corresponds to measures to be incorporated when an outbreak cannot be resolved after application of the Grade A measures. **Table 10** shows the criteria for close contact when exposed to influenza virus infection.

9.3.1. Acute Care Hospitals

Recommendations

- Non-pharmacological measures must be used to prevent virus dissemination (B-II).
- Administer post-exposure prophylaxis as soon as possible to patients in close contact with a confirmed or suspected case of influenza and risk factors for developing serious complications in case of infection (A-II).
- Post-exposure prophylaxis should be used in healthcare workers with comorbidities who are prone to complications in case of influenza infection (A-II).
- Routine pre-exposure prophylaxis for all patients or staff is not recommended, not even in an outbreak situation, but could be considered in wards admitting immunocompromised patients or when staff members are suspected of being involved in maintaining an outbreak (B-II).

Rationale

Table 11 includes a bundle of measures that has demonstrated its usefulness in the control of nosocomial influenza outbreaks (212, 221, 233). Pre- and post-exposure prophylaxis have demonstrated their effectiveness in the context of a bundle of measures to control nosocomial influenza outbreaks (208, 235, 236).

Antiviral drugs, doses, and length of treatment for post-exposure prophylaxis are shown in **Table 8** and **Table 9**.

Post-exposure prophylaxis for healthcare workers is recommended when they are unvaccinated or immunosuppressed, when their household members are

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immunosuppressed, or when they are considered to be the main route for keeping the outbreak going (**Table 11**) (108, 208).

9.3.2. Neonatal or pediatric intensive care units and pediatric wards

Recommendations

- Patients admitted to neonatal or pediatric intensive care units should be placed in individual rooms whenever they develop influenza virus infection (B-II).

- Mask, gown, and gloves should be worn when taking care of patients with influenza virus infection admitted to neonatal or pediatric intensive care units (B-II).

- Post-exposure prophylaxis should be administered as soon as possible to unvaccinated exposed neonates or infants admitted to pediatric intensive care units (A-III).

- Post-exposure prophylaxis should be used in healthcare workers whose comorbidities for high-risk influenza complications are present in themselves or in their household members (A-III).

- Administer antiviral prophylaxis to unvaccinated healthcare workers and family members including those vaccinated in the previous two weeks or if vaccine failure is suspected (A-III).

- Massive prophylaxis for all neonates or infants admitted to pediatric intensive care units and their staff should be considered in case of a persistent outbreak despite other more restrictive measures or in case the staff are suspected to be involved in maintaining the outbreak (C-III).

- Entry to the ward must be restricted to people presenting respiratory symptoms (A-III).

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Rationale

Furthermore, although the use of gloves and gowns has not been evaluated independently – and neither has that of masks or respirators used to control influenza outbreaks in pediatric wards or neonatal ICU – since, during nosocomial outbreaks of influenza, the virus frequently coexists with other respiratory viruses that can be transmitted by contact mechanisms – such as respiratory syncytial virus or adenovirus – it would be prudent to wear gloves and gowns as well as use droplet precautions for handling infants in Neonatal Units. The use of masks, gloves and gowns has demonstrated its usefulness (in combination with other measures) in controlling influenza outbreaks in neonatal units (194, 212, 221, 233, 237). **Table 10** includes the criteria for close contact when exposed to influenza virus.

Post-exposure prophylaxis for patients has been successfully used to control influenza outbreaks in pediatric wards and neonatal intensive units (in combination with other measures) according to the results of observational studies and case reports (208, 236, 238).

Post-exposure prophylaxis for healthcare workers is recommended when they are unvaccinated or immunosuppressed, when their household members are immunosuppressed, or when they are considered to be the main route for maintaining the ongoing outbreak (**Table 11**) (108, 208, 239).

Antiviral drugs, doses, and length of treatment for post-exposure prophylaxis are shown in **Table 8** and **Table 9**.

9.3.3. Long-Term Care Facilities and Nursing Homes

Recommendations

- Whenever a case of influenza virus infection is detected in a resident of a long-term care facility or nursing home, the rest of the residents should receive antiviral prophylaxis, regardless of their vaccination status (A-I).

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- Post-exposure prophylaxis should be administered to healthcare workers with comorbidities who are prone to complications in case of influenza infection (A-II).

- Routine pre-exposure prophylaxis for all staff is not recommended, not even in an outbreak situation, but could be considered when staff members are suspected to be involved in maintaining an outbreak (B-II).

- Reinforce hand hygiene and the use of face masks among staff (B-II).

- Vaccination of staff and residents when the first cases of influenza virus infection are detected should not be considered an adequate control measure (A-I).

- Implementation of other non-pharmacological measures such as social distancing and cohorting could be considered (B-III).

Rationale

Universal antiviral prophylaxis has demonstrated its usefulness among residents admitted to long-term care facilities and nursing homes after a single case is detected (207, 212, 221, 230, 232, 233). It should be started as soon as possible and independently of vaccination status.

Antiviral drugs and doses for post-exposure prophylaxis are shown in **Table 8** and **Table 9**. Antiviral chemoprophylaxis should be administered for 14 days and continued for at least 7 days after the onset of symptoms in the last person infected (207, 233, 240).

Post-exposure prophylaxis for healthcare workers is recommended when they are unvaccinated or immunosuppressed, when their household members are immunosuppressed, or when they are considered to be the main route for maintaining the ongoing outbreak (**Table 11**) (108, 198, 208, 239).

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Vaccination of staff and residents when the first cases of influenza virus infection are detected should not be considered an adequate control measure as it may take approximately 14 days for those vaccinated to develop an adequate immunological response (197, 232).

Reinforcement of standard and droplet precautions is another important tool for the control of an outbreak in a long-term care facility or nursing home (194, 221, 232).

Implementation of other non-pharmacological measures such as social distancing and isolation requires careful consideration since they may have a negative psychosocial impact on residents, resulting in impaired quality of life and deterioration of functional status. These measures have been used and recommended for outbreak control but have not been evaluated individually. Some of these measures consist of accommodating cohorted symptomatic patients into separate floors or wings, specific staff to care for infected residents, restriction of communal activities, limitation of external social activities or non-urgent medical appointments, extension of mealtimes to avoid crowding, and meals served in residents' rooms (221, 230, 233).

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Table 11 - Measures applicable for the control of an influenza outbreak in different scenarios

Grade*	Acute Care Adult Ward	Neonatal ICU or Pediatric Ward	Long-Term Care Facilities
Grade A measures	Reinforce standard precautions Reinforce droplet precautions Individual room Patients placed into cohorts Visitors limited Symptomatic visitors not allowed Symptomatic healthcare workers not allowed Promote patients' discharge when possible Antiviral prophylaxis for unvaccinated close contact patients when indicated Antiviral prophylaxis to healthcare workers when indicated	Reinforce standard precautions Add mask, gloves, and gown for care Patients placed into cohorts Visits restricted Symptomatic healthcare workers not allowed Promote patients' discharge when possible Antiviral prophylaxis for unvaccinated close contact neonates or infants when indicated Antiviral prophylaxis for healthcare workers when indicated	Reinforce standard precautions Reinforce droplet precautions Restrict movements of ill patients Room, unit, or ward cohorting when possible Visitors limited Symptomatic visitors not allowed Symptomatic healthcare workers not allowed Promote residents' discharge when possible Antiviral prophylaxis for residents on the same ward or floor regardless of influenza vaccination status Antiviral prophylaxis for healthcare workers when indicated
Grade B measures	Antiviral prophylaxis for all patients in wards admitting an immunocompromised patient	Antiviral prophylaxis for unvaccinated/breakthrough suspected healthcare workers in neonatal or immunocompromised infants' wards	Antiviral prophylaxis for all residents regardless of influenza vaccination status Antiviral prophylaxis for all unvaccinated healthcare workers

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	Antiviral prophylaxis for unvaccinated/ breakthrough suspected healthcare workers working in wards admitting immunocompromised patients Reverse isolation for all patients admitted to wards of immunocompromised patients Limit inter-ward transfers Exclusive staff for ill patients' care Limit elective new admissions	Exclusive staff for ill patients' care Limit elective new admissions	Room quarantine Delay non-urgent medical appointments Exclusive staff for ill residents' care Limit elective new admissions
(*) Grade A measures: for immediate application after the outbreak is declared; Grade B measures: to be incorporated when the outbreak cannot be resolved after application of Grade A measures			

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10- Vaccination against influenza virus

10.1 Among children, who should receive the influenza vaccine?

Recommendations

1. Vaccination is recommended for children between 6 months and 18 years of age in certain circumstances (see **Table 12)** (A-III).

2. Vaccination of healthy children between six months and five years of age is universally recommended (AIII).

3. Both political authorities and healthcare workers should redouble their efforts in order to boost vaccination against influenza virus among children belonging to target groups (A-III).

Rationale

Children presenting risk factors have an increased likelihood of developing complications and death from influenza virus infection. Therefore, their vaccination is considered a priority. A study conducted in the USA between 2010 and 2014 estimated that 53% of deaths in children occurred in those who had at least one of the described risk factors (241); during the epidemic season 2017-2018, 51% of deaths in children in the USA occurred in children presenting these risk factors (242).

Despite these facts, the influenza vaccine uptake recorded in children belonging to these groups in Spain is low (243-245). A higher level of awareness of authorities, healthcare workers, and the general population is desirable with regard to the importance of vaccination in these groups.

Individual recommendation of vaccination of healthy children between six months and five years of age is justified by the incidence and complications in this group. In Spain, each year, the highest incidence of epidemic influenza occurs in children younger than 14 years of age (243). While the incidence of hospitalization due to influenza virus infection is minimal in the group aged 6 to 14 years, children younger than or equal to 5 years of age represent the group with the second highest incidence after that of adults over 65. Although the effectiveness of the influenza vaccine varies from one season to the other, it is over 50% in most published experiences.

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Table 12 includes the list of circumstances in which vaccination is indicated for children and adolescents between 6 and 18 years of age (246).

Table 12 - Circumstances in which influenza virus vaccination is indicated for children and adolescents between 6 and 18 years old (246)

1- Chronic cardiovascular diseases
2- Chronic neurological diseases
3- Chronic pulmonary diseases (including asthma)
4- Metabolic disorders (including diabetes mellitus)
5- Morbid obesity (body mass index greater than or equal to three times the standard deviation above the mean or ≥3.5 in adolescents)
6- Chronic kidney disease and nephrotic syndrome
7- Hemoglobinopathies and chronic anemia
8- Hemophilia and chronic bleeding disorders
9- Asplenia or previous splenectomy
10-Chronic liver disease
11-Severe neuromuscular diseases
12-Immunosuppression (including solid organ transplantation and chronic treatment with systemic corticosteroids)
13-Solid organ cancer and hematological malignancies
14-Cochlear implant
15-Cerebrospinal fluid fistula
16-Celiac disease
17-Chronic inflammatory disease
18-Cognitive impairment
19-Down's syndrome
20-Prolonged treatment with acetylsalicylic acid
21-Children who can transmit the influenza virus infection to those who present a high risk for developing severe forms of influenza infection
22-Children between 6 months and 2 years of age with a history of prematurity (less than 32 weeks' gestation)

10.2 Among adults, who should receive the influenza vaccine?

Recommendations

1. Vaccination is recommended for all adults aged 65 years old or older (A-I).

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2. Vaccination is recommended for adults between 19 and 64 years of age in certain circumstances (see **Table 13**) (A-II).

3. Both political authorities and healthcare workers should redouble their efforts in order to boost vaccination against influenza virus among adults belonging to target groups (A-III).

Table 13 - Circumstances in which influenza virus vaccination is indicated for adults between 19 and 64 years old (246)

1- Chronic cardiovascular diseases
2- Chronic neurological diseases
3- Chronic pulmonary diseases (including asthma)
4- Metabolic disorders (including diabetes mellitus)
5- Morbid obesity (body mass index greater than or equal to 40)
6- Chronic kidney disease and nephrotic syndrome
7- Hemoglobinopathies and other anemias
8- Hemophilia and chronic bleeding disorders
9- Asplenia or previous splenectomy
10-Chronic liver disease
11-Severe neuromuscular diseases
12-Immunosuppression (including solid organ transplantation and chronic treatment with systemic corticosteroids and HIV infection)
13-Solid organ cancer and hematological malignancies
14-Cochlear implant
15-Cerebrospinal fluid fistula
16-Celiac disease
17-Chronic inflammatory disease
18-Down's syndrome
19-Dementias and other cognitive disorders
20-Residents of nursing homes and other long-term care facilities
21-Women who are or will be pregnant during the influenza season (all the trimesters of pregnancy) and women during the puerperium (up to 6 months after delivery and who had not been vaccinated during pregnancy)
22-Adults who can transmit the influenza virus infection to those who present a high risk for developing severe forms of influenza virus infection: healthcare workers; those working in geriatric institutions or in centers for the care of chronically ill subjects; students in practices in healthcare centers; adults who provide home care to high-risk or elderly subjects; adults living with others belonging to some of these high-risk groups

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23-Adults who work in essential public services: policemen; firefighters; people working in emergency services; personnel working in penitentiary institutions and other detention centers
24-People with direct occupational exposure to domestic birds or pigs on farms or poultry or pig farms, and also to wild birds

Rationale

Despite a higher incidence in children under 15 years of age, the incidence of severe cases of influenza virus infection requiring hospitalization is higher in adults 65 years old and over (243). This group represents 66% of the severe cases of influenza requiring hospitalization. Moreover, it has been estimated that 85% of deaths produced by influenza virus or its complications occur among people of this age group. It has also been verified that 88% of the severe cases of influenza present at least one of the risk factors described in **Table 13** (88, 247), a percentage that reached 98% with respect to those who died (243). Vaccination against influenza virus has been demonstrated to be safe in terms of rejection induction among solid organ transplant recipients (248).

The Panel of this Consensus Statement considers that vaccination is the best tool available for protection against infection among those having one or more of the aforementioned risk factors (249).

10.3 What type of vaccine is indicated for children?

Recommendation

1. Vaccination of children and adolescents with quadrivalent vaccine (against influenza virus A H3N2, influenza A H1N1pdm09, influenza B/Victoria lineage, and influenza B/Yamagata lineage) is recommended (B-III).

Rationale

The variables for considering recommendation of the quadrivalent vaccine are the burden of disease due to influenza B virus, the potential mismatch

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between the dominant B strain in the season and that included in the vaccine, and the efficacy-effectiveness of the vaccine and its possible cross protection.

A study conducted in 26 countries around the world evaluated the epidemiology of influenza between 2000-2013, estimating that the burden of disease produced by the B strain represented 22.6% of the total influenza burden (250). The study described a predominance of type B strains in the group of 5 to 17 years old and type A in the group of 18 to 64 years old. A study published about type B influenza in Spain estimated that the median of the proportion of type B virus during the 2007-17 seasons was 27.2% (95% confidence interval: 0.7%-74.8%) of the total burden of illness due to influenza virus (251). Influenza B virus circulated in eight out of ten seasons, presenting a discordance with the strain included in the vaccine in four out of ten of the seasons.

Some studies on influenza virus vaccine effectiveness have estimated an equivalent protection for the trivalent vaccine against the two lineages of influenza B virus when they have been detected in the same season. For example, in the USA, during the 2012-2013 season, an effectiveness of 66% against the lineage included in the vaccine and 51% against the mismatch strain (not statistically significant difference) (252) was detected. A similar result was observed in the USA in the 2011-12 season (253). A study developed in Spain estimated an effectiveness of 48% against the mismatch strain (254). Conversely, two clinical trials did not demonstrate a significant cross protection against type B strains when trivalent vaccine was used (253).

The Panel of this Consensus Statement considers that, even recognizing that trivalent vaccine might offer seroprotection against both circulating strains of influenza B virus, this protection can only be guaranteed for every epidemic season if quadrivalent vaccine is used.

10.4 What type of vaccine is indicated for adults?

Recommendations

1. For those older than or equal to 19 years of age in whom vaccination is indicated, a quadrivalent vaccine (against influenza A H3N2,

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influenza A H1N1pdm09, influenza B/Victoria lineage, and influenza B/Yamagata lineage) is recommended (B-III).

2. For adults for whose age group the vaccine is licensed, a quadrivalent (against influenza A H3N2, type A H1N1pdm09, influenza B/Victoria lineage, and influenza B/Yamagata lineage) enhanced seasonal influenza vaccine is recommend (either adjuvant (B-III), high-dose (B-II), or recombinant (B-II)).

Rationale

As established for children in section 10.3, the Panel of this Consensus Statement considers that, even recognizing that trivalent vaccine might offer seroprotection against both circulating strains of influenza B virus, this protection can only be guaranteed for every epidemic season if quadrivalent vaccine is used.

A lower clinical effectiveness of the A (H3N2) component of the influenza vaccine has been described, especially in the elderly (255). In order to improve the immunological response to influenza vaccine in general and to the influenza A (H3N2) component of the vaccine in particular, some strategies have been implemented. The main approach has been the development of enhanced seasonal influenza vaccines (either adjuvant, high-dose, or recombinant).

Adjuvants are substances added to the influenza vaccine in order to boost the immune response to the antigen. Several retrospective observational studies have compared the effectiveness of adjuvanted and non-adjuvanted vaccines. Some demonstrated a reduction in the incidence of pneumonia and hospitalization in elderly people previously vaccinated with an adjuvanted vaccine in contrast to those who received a non-adjuvanted vaccine. A study conducted in Italy during the 2006-09 seasons estimated a lower risk of hospitalization due to influenza and pneumonia in people aged 65 years and over vaccinated with adjuvanted (256). However, other clinical studies did not confirm this protective effect of the adjuvanted vaccine (257). Mathematical modelling indicated that the adjuvanted vaccine would be highly cost-effective in both the 65-74 and older than 75 year-old groups in terms of large

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reductions in consultations and hospitalizations (258). A prospective comparative clinical trial has demonstrated that older adults receiving enhanced vaccines showed improved humoral and cell-mediated immune responses compared to non-enhanced vaccine recipients. The group of enhanced vaccines included both an adjuvanted vaccine and antigen high-dose vaccines (259).

The strategy of using an influenza virus vaccine containing a higher antigen dose has also been explored in high dose and recombinant vaccines, observational studies, and clinical trials. A recent systematic review carried out by the ECDC supports a greater efficacy and effectiveness of high-dose and recombinant vaccines compared to standard-dose vaccines. The evidence provided comes from both clinical trials and observational studies (260).

The administration of two doses of influenza vaccine in a single season has also been proposed in order to increase its immunological response among solid organ transplant recipients (261); however, this has not been translated into official recommendations.

10.5 What is the correct schedule for vaccination?

Recommendations

1. One dose of the vaccine and another dose separated from the first one by an interval of four weeks is recommended for children between six months and eight years of age, if they have never before received a dose of influenza vaccine (A-I).

2. A single annual dose is recommended for younger than nine-year-olds who have been vaccinated in previous influenza seasons (A-I).

3. For everyone older than nine years of age, a single annual dose of the influenza vaccine is recommended regardless of vaccination in previous seasons (A-I).

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4. A full dose of 0.5 ml of the influenza vaccine is recommended for everyone, independently of their age (A.I).

5. The vaccine should be administered in October-November for those living in the Northern Hemisphere (A-III).

6. Vaccination is indicated until the end of the annual influenza season for those who did not receive the vaccine in October-November (A-III).

Rationale

Evidence from several observational studies and clinical trials indicates that children between six months and eight years of age require two full doses with an interval of four weeks between their administrations for optimal protection (253). There was a previous recommendation for the use of a half dose of the vaccine in children younger than 36 months old. This assessment was based on the greater incidence of adverse effects observed when the vaccines used were manufactured using whole virus. With the formulations in current use, a greater rate of adverse effects has not been described with the whole dose of the vaccine, while better immunogenicity is achieved (262).

One research study demonstrated a significantly higher immunological response to influenza vaccine when two doses of the vaccine (administered within an interval of five weeks) were used in comparison to a single dose. Notwithstanding the relevance of the study, the Panel of this Consensus Statement considers that some confirmatory studies including clinical outcomes should be developed before a recommendation for this schedule can be established for this population (261).

The timing for vaccination is determined by the need to reach immunological protection before the beginning of the influenza season and ensure the persistence of protection throughout that period of time (263). Considering the annual period of the annual epidemic season in the last few decades, it is considered that the months of October-November is the optimal moment for the administration of the vaccine for those living in the Northern Hemisphere. Nonetheless, the Panel would like to highlight the fact that

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vaccination is indicated until the end of the annual influenza season for those who did not receive the vaccine in October-November.

10.6 What are the contraindications for influenza virus vaccination?

Recommendations

1. Influenza virus vaccination should be avoided in those who previously developed a severe allergic reaction (e.g., anaphylaxis) to a previous influenza vaccine or any of its components (A-III).

2. Currently, egg allergy is not considered a contraindication for the administration of egg-cultured influenza vaccine (A-III).

3. Any acute disease of moderate or severe intensity (e.g., asthmatic crisis, decompensated heart failure, acute diarrhea), with or without fever, constitutes a temporary contraindication for the administration of the vaccine. In these circumstances, vaccination should be postponed until the acute illness is resolved (A-III).

Rationale

Allergy to egg protein has traditionally been considered a contraindication for influenza vaccination. Several modern studies (253, 264) have demonstrated similar risk of anaphylaxis with influenza vaccine in people allergic to egg protein than in people who are not. Despite this evidence, it is still recommended to restrict the administration of egg-cultured influenza vaccine (to subjects presenting allergy to egg protein) in health facilities with experience in the recognition, handling, and treatment of serious adverse allergic reactions (264, 265).

It has been classically recommended to avoid influenza vaccination for those who do not present a high risk of influenza-related complications but who have developed a Guillain-Barré syndrome (GBS) within six weeks of a previous vaccination. However, for most people with a history of GBS who are at a high risk of serious influenza complications, there is a consensus of experts who consider that the benefits of the vaccine justify its use, as influenza infection itself implies an increased risk for GBS relapse (266, 267). Further, non-recurrence after influenza vaccination has been verified in patients previously diagnosed with GBS (268). A French study estimated that the risk of GBS did not change after

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influenza vaccination, whereas it was four times higher after an acute respiratory infection (269).

11- Research priorities

Future studies should address several points concerning influenza infection (270). From an epidemiological point of view, it will be necessary to develop tools for a better prediction of epidemics, pandemics, and interactions with other respiratory viruses. We also need the development of new tools, for example machine learning, in order to diagnose influenza virus infection more accurately in the clinical context. In order to improve the diagnosis of infection, the development of easy-to-use “point-of-care” techniques that can give reliable information to the clinician to adopt immediate therapeutic decisions are necessary. The therapeutic armamentarium against influenza virus needs to be expanded with new oral antivirals to be administered in the early phases of the infection. New evidence is needed regarding the transmission of the virus (via droplets or aerosols) in order to set more accurate recommendations for isolation and personal protective equipment. Finally, vaccines that produce an enhanced immunological response are required, along with *universal* vaccines presenting activity against different types of influenza virus in order to avoid annual re-vaccination. Some lessons learned from the SARS-Cov-2 pandemic should be applied to dealing with the influenza virus in the future.

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