Final Master’s Thesis

INFLUENZA:
EPIDEMIOLOGY AND PREVENTION.

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Influenza is an acute respiratory illness, caused by influenza A, B and C viruses. The incidence is especially high in children and adults over 65 years old. Clinical illness follows a short incubation period and presentation ranges from asymptomatic to fulminant, depending on the characteristics of both the virus and the individual host. The flu virus shows a strong seasonal pattern: in the northern hemisphere the appearance peak occurs during February. Due to both circumstances, the gravity of the disease and its seasonality, makes it recommendable to have a vaccination programme, specially directed towards high risk patients, including children.

General aim and main objectives: To revise and compare through a literature review all the different vaccination methods against the flu. In order to achieve this general aim a literature review have been done which will also give an answer to other secondary objectives, including a review of the actual knowledge about influenza virus, its transmission, epidemiology, diagnosis, treatment and prevention, with special attention to the effects on children.

Three classes of licensed influenza vaccines are available, depending on the condition of the virus: inactivated virus, live attenuated virus, and recombinant haemagglutinin vaccines. Also we can further divide it in trivalent and quadrivalent vaccines. The first one will contain antigens from the influenza A H1N1 and H3N2 subtypes, along with the dominant circulating lineage of influenza B. On the other hand, quadrivalent vaccines will contain all the previous antigens together with a second lineage of influenza B. In this Final Master’s Thesis a literature review have been done comparing all the vaccination options, concluding that the live attenuated quadrivalent vaccine is the one that offers better results due to its higher efficacy, better coverage of antigens, nasal administration, good tolerance and high cost-effective ratio.
4. ACKNOWLEDGEMENTS.

At this last stage of my studies of Medicine in the Lithuanian University of Health Science, I would like to express my gratitude to several people who helped me during the preparation of this FMT, but also during the whole period of 6 years of intense learning and living.

First of all, I am very grateful to the professors of my medical faculty, but particularly to my supervisor of this FMT, Dr. Giedra Lieviniene. She has been a fundamental support for this final thesis and guided me very well along the way. Also, to my co-supervisor, Dr. Antonio Reyes, a paediatric specialist working in Spain, who has provided me with very useful suggestions for the completion of this thesis.

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5. CONFLICT OF INTEREST.

The author reports no conflict of interests

6. PERMISSION ISSUED BY THE ETHICS COMMITTEE

Do not apply.

7. ABBREVIATIONS.

CDC: Centers for Disease Control and Prevention
IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine
RHV: Recombinant Haemagglutinin Vaccine
PCR: Polymerase Chain Reaction
WHO: World Health Organization
RNA: Ribonucleic Acid
DNA: Deoxyribonucleic Acid
USA: United States of America
AIV: Avian Influenza Viruses
AAP: American Academy of Pediatrics
ACIP: Advisory committee on Immunization Practices
FDA: Food and Drug Administration
8. TERMS

**Antigenic drift**: Minor variations that take place after the accumulation of punctual mutations in the genes that codify proteins H and N. These mutations affect the influenza viruses A and B.

**Antigenic shift**: This is the appearance in the human population of a new influenza virus with new proteins H and N very different to those in the viruses of the preceding years. These new viruses are the cause of pandemics.

**Flu**: Influenza

**Influenza**: a serious, easily spread disease caused by different viruses and characterized by sneezing, coughing, fever, and exhaustion.

**Pandemics**: (of a disease) having spread among humans throughout an entire country or continent or the whole world.

**Vaccine**: a preparation introduced into the body to prevent a disease by causing the body to produce antibodies against it, usually a weakened substance containing the virus causing the disease against which the body can react.

**Virus**: a very small living thing causing infection, which reproduces only within the cells of living hosts, mainly bacteria, plants, and animals.
9. INTRODUCTION

Influenza is an acute respiratory illness caused by influenza A, B and C viruses. One of the most important characteristics of these viruses is its ability to spread efficiently from person to person, this promoting the occurrence in seasonal epidemics. Each year there are periods in which there is a bigger activity and circulation/spreading of the Influenza virus, with predominant activity in November to March months. After a short incubation period, the clinical presentation could range from asymptomatic to fulminant, depending on the characteristics of the virus and the host. Influenza A viruses can also cause sporadic infections or spread worldwide in a pandemic when novel strains emerge in the human population from an animal host (Webster et al., 2013).

During each pandemic, a novel influenza virus arose, either directly from an avian or pig host and spread through the human population, causing substantial morbidity and mortality, which was often associated with bacterial pneumonia. The most severe pandemic occurred in 1918 (the so-called spanish flu) and caused over 50 million deaths worldwide (Monto and Webster, 2013).

The flu is an important public health issue, due to its direct or indirect mortality, its complications and its economic and social cost. The proportion of infected population is higher than 50% in closed population groups (classromms, asylum, etc). The World Health Organization (WHO) has estimated around 3-5 millions of severe illness and 300.000-500.000 deaths caused by influenza each year. The economic losses are very high, with an estimation of total costs of 87,1 billion dolars per year (10.4 billion dollars per year in direct medical costs), (Jernigan and Cox, 2013).

Due to the high capacity to present variations in the surface antigens, new flu virus strains develop to which humans have no protection. There are different vaccines with a really high effectiveness to control the flu, but due to the high capacity of the virus to change each year, the vaccine needs to be updated every new season and administered annually.

The general aim of this thesis is to review the actual knowledge about influenza epidemiology and prevention.
10. AIM AND OBJECTIVES

The general aim of this thesis is: To review the actual knowledge about influenza epidemiology and prevention.

Objectives:

In order to achieve this general aim a literature review have been done which will also give an answer to other secondary objectives, in which we can find:

1. Review the actual knowledge about influenza viruses, epidemiology, diagnosis and treatment.
2. Annalise and compare the different vaccines to prevent influenza.
3. Annalise the convenience of a global vaccination campaign.
4. Review the surveillance protocol for influenza in Spain
11 and 12. METHODS: LITERATURE REVIEW

Given that this Final Master Thesis is a literature review on the subject, the methodology only includes the literature review criteria and the publications read, including research papers, review papers, technical reports and book chapters. All the literature used is referred in the bibliography section.

We consulted different databases including Google Scholar, Science direct, electronic resources of Cadiz University library, Web of Science and PubMed for articles published in the past 10 years pertaining to influenza and each of the topics discussed in this paper. Search terms included “influenza”, “influenza in children”, “influenza and systematic reviews”, “influenza and diagnosis”, “influenza and therapy”, “influenza and prevention and control”, “influenza and pandemic”, “influenza and epidemiology”, “influenza and clinical”, “influenza and vaccines”, “influenza and transmission”, and “influenza and risk factors”. The most relevant and recently published references were then selected. Relevant textbook chapters were also included. A total of 7 books, 24 research papers (10 of them review papers), 7 technical reports and several webpages (mainly from official health institutions) were used to prepare this Master Thesis. 88% of the literature cited is less than 10 years old (30 out of 34), with 62% of cited references published in the last 5 years (21 out of 34).
A) INFLUENZA: ETHIOLOGY, EPIDEMIOLOGY AND CLINICAL ASPECTS

A.1. Ethiology and influenza viruses

Influenza viruses belong to the Orthomyxoviridae family. There are three types of influenza — A, B, and C — named in the order of their discovery. Type C rarely causes human infection and is relatively unimportant. Type B can cause epidemics, but the course of infection is milder, and the spread of the virus is slower, with less impact on human society. Type A, which poses the greatest threat to human health, is the one associated with an explosive spread and high rates of morbidity and mortality. Most of the work presented below pertains this type A.

Influenza viruses are very simple organisms, composed by RNA (ribonucleic acid) divided in 8 gene segments, and surrounded by a lipid envelope with glycoproteins of two types in the outer side: hemagglutinin (H) and neuraminidase (N) (Fig. 1).

Fig. 1.- Structure of the Influenza virus [from Florid State University webpage]

The high capacity of the influenza viruses to generate epidemics is a
consequence of their facility to suffer variations in proteins H and N. These variations belong to two different types:

**Antigenic drift**: Minor variations that take place after the accumulation of punctual mutations in the genes that codify proteins H and N. These mutations affect the influenza viruses A and B, and they are the main reason explaining people that get ill with flu more than once in their life given that the antibodies generated in a previous illness are not effective enough to protect against a new infection with a mutated virus. Also this is the reason why the influenza vaccine must be modified each season to adapt it to the new strains.

**Antigenic shift**: This is the appearance in the human population of a new influenza virus with new proteins H and N very different to those in the viruses of the preceding years. Periodically a new gene segment or segments can be introduced through reassortment, resulting in the appearance of a novel variant to which there is little population immunity. These new viruses are the cause of pandemics, characterized by affecting many populations around the world with a high overall attack rate.

Influenza A virus is further classified into subtypes on the basis of its two surface antigens (Haemaglutinin <H> and Neuraminidase <N>): There are 17 types of protein H and 10 types of protein N, with a total of 170 different strains as a result of the combination of all these types. The nomenclature of viruses follows the sequence HxNy, being x the type of protein H and y the type of protein N. For example a strain A(H3N2) will mean a strain of virus A with type 3 haemaglutinin and type 2 Neuraminidase. The most common subtypes of virus A that currently are present in humans and that are annually included in “antigripal” vaccines are A(H1N1) and A(H3N2). Viruses B and C have a lesser degree of variation, therefore they don't have a further classification into subtypes.

While Influenza viruses B and C have been only detected in humans, Influenza A viruses have been isolated from several species besides human beings, including birds, pigs, dogs, cats, horses, and marine mammals.
Waterfowl and shorebirds are the natural reservoir of influenza A viruses and the source of all strains that infect domestic avian species and mammals (Paules and Subbarao, 2017).

A.2. Epidemiology

A.2.1. Transmission of influenza virus

Transmission of influenza virus occur through three mechanisms: aerosol, droplet, and contact transmission. When an infected individual sneezes or coughs, they expel infectious particles ranging from 1 µm to 100 µm in diameter. Fine particles (aerosols) and droplet nuclei, generated from the rapid desiccation of larger droplets, have a diameter less than 5 µm and are able to remain airborne for minutes to hours, but are vulnerable to changes in temperature and humidity. They can be inhaled and deposited in the upper or lower respiratory tract. Larger droplets are deposited in the upper respiratory tract or settle quickly in the environment, generally within 2–3 m of the infected individual. The virus remains infectious for a short time on the hands but can remain infectious on non-porous surfaces in the environment for up to 48 h (Paules and Subbarao, 2017).

Influenza viruses have been detected in the air from patients’ rooms, urgent care centres, and emergency rooms, and epidemiological observations point to a substantial contribution of aerosol transmission in outbreak settings. The World Health Organization (WHO) recommends the use of a surgical mask when caring for a patient with influenza (Bin-Reza et al., 2012). Data suggest that the use of surgical masks can prevent most influenza transmission events in health-care settings with appropriate air exchange, good hand hygiene practices, and immunity to seasonal influenza through previous exposure or vaccination. However, aerosols can play an important role in influenza transmission. Thus, respirator use is recommended during aerosol-generating procedures and might also be prudent for all patient care activities during an influenza pandemic when population immunity is low.
Persons affected by influenza are normally the origin of the infection, but some influenza viruses affect several animals (birds, horses, pigs, etc) that could generate new subtypes affecting humans. This capacity of the virus to jump the interspecific barrier gets the influenza an illness very difficult to eradicate.

Young children are, together with adults older than 65 years, the main subject of influenza illness and the most important in the transmission of the epidemic. More than a half of the influenza cases are reported in children younger than 5 years. The pick of hospitalizations normally occurs one week after the maximum of the epidemic, while the maximum of deaths normally occurs 2 weeks after the epidemic maximum (Terebuh et al. 2003, fig. 2).

![Hospitalizations per 100,000 inhabitants at different age classes in United States](from Terebuh et al. 2003)

Children are the main transmissors and propagators of influenza. In an average influenza epidemic, around 35% of children are infected, and these infected children disseminate the infection to other people in their communities. Children can disseminate the virus in the 6 days previous to any symptomatology (while it is only 1 day in adults) and they are spreading viruses until 14 days after the starting of the infection (while adults only can spread the infection during 4,5 days) (Lewing, 2010; Paules and Subbarao, 2017).

The presentation of influenza in children can differ from that in adults.
Children have higher maximum temperatures than do adults, and infants can present with an undifferentiated fever or febrile seizures. Laryngotracheobronchitis (croup), bronchiolitis, and bronchitis can occur. Children report severe myalgia in the calf muscles, and myositis is a more frequent complication than in adults. Gastrointestinal symptoms are seen with higher frequency in children than in adults (Long et al. 2012).

Children and immunocompromised patients shed virus for a longer duration than do healthy adults (Esposito et al. 2011). Adults can transmit influenza from a day before the symptoms to 3-7 days after the beginning of the illness, but children can transmit influenza more than 7 days after the beginning of the symptoms.

A.2.2 Pandemics

Influenza pandemics occur when a novel virus emerges (by genetic shift) for which a majority of the population has little or no immunity. Global spread follows over a relatively short period of time. The most catastrophic pandemic of influenza occurred in 1918 – the so-called Spanish pandemic flu– which killed an estimated 50 million people globally, and the more recent has occurred in 2009. In both cases, an influenza virus H1N1 was the responsible. Some comments for both pandemics episodes are given below.
The 1918 pandemic was a very high mortality event that occurred at the beginning of the twentieth century, during the last year of the First World War. It infected 500 million people around the world, and resulted in the deaths of at least 50 million (three to five percent of the world's population), making it one of the deadliest natural disasters in human history.

The place of origin of the viruses of the 1918 pandemic has been debated (Oxford et al., 2002). To maintain morale within the soldiers at war, censors minimized early reports of illness and mortality in Germany, the United Kingdom, France, and the United States. Papers were free to report the epidemic's effects in neutral Spain (such as the grave illness of King Alfonso XIII), thus creating the false impression of Spain as especially hard hit, thereby giving rise to the pandemic's nickname, Spanish Flu. Although the origin of this pandemic is not clear, several candidates include Austria, France, USA, China and Spain (Monto and Webster, 2013).

Explanations about the extreme severity of the 1918 pandemic had previously focused on the fact that, as in seasonal outbreaks, bacterial
superinfection was involved in many of the deaths. However, why such bacterial infections would have been more lethal in 1918 remains unclear. Recent studies associate the polymerase protein PB1-F2 of the 1918 virus with synergy between bacterial and viral infection. The bacterial agents frequently involved were *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Haemophilus influenzae*. The pathology observed in at least some cases was not seen before in typical bacterial pneumonia; cases in which lungs were fluidfilled and hemorrhagic were particularly novel. “Dusky cyanosis” (purple color of the face) was thought to be unique to this pandemic. At that time these observations were ascribed to a virulent viral infection. It must be taken into account that the 1918 influenza pandemics came in a period in which no antibiotics to control bacteria coinfections were known (Monto and Webster, 2013).

The 2009 H1N1 influenza pandemic came as a complete surprise. There was general acceptance that the pandemic influenza viruses of the past century had emerged by reassortment between influenza viruses in the aquatic bird reservoir and the circulating human influenza virus. As H1N1 viruses that re-emerged in 1977 were still circulating globally in the human population, the human population was considered immunologically “primed” to this subtype and no thought was given to the possibility that this subtype could cause a pandemic. The pandemic H1N1 2009 that emerged in Mexico was detected in California in April 2009. It is possible that the virus had been circulating in humans for some time before and had not been detected. Antigenic and sequence analysis confirmed that the virus was an H1N1 subtype antigenically related to the 1918 Spanish influenza virus, further raising the concern of a severe pandemic. Fig. 4 shows the higher mortality in children after this pandemic of 2009 compared with other seasons around from 2002 to 2012. It is also clear at this figure 4 the occurrence of deaths all the year round, with less stationality than other seasons (Wong et al., 2013).
Fig. 4. Mortality in children affected by influenza from 2004 to 2012.
[Data from Wong et al., 2013]

At the beginning of the pandemic, some countries had large stockpiles of antivirals, mainly because of concern for A (H5N1). Strategies for antiviral distribution varied significantly. In Japan, large amounts of the antivirals were used, and the lower mortality observed compared with other countries was later attributed to early drug use in treatment. In the United Kingdom, oseltamivir was initially used in prophylaxis to contain spread. When this approach did not succeed, the drug was then employed mainly for treatment.

Nonpharmaceutical interventions were rarely used except early in the pandemic when severity had not yet been established. In some countries, school closings were routine during influenza outbreaks. It became clear that the characteristics of this pandemic were very different from those seen earlier. Children were frequently infected; some were hospitalized, but deaths were infrequent. Hospitalizations of younger adults were unusual, with approximately 70% occurring in those with pre-existing conditions. There was little evidence of bacterial superinfection. In adults, pregnant women and those with morbid
obesity were at high risk of developing severe events. Those older than 64 years were not frequently infected because of immunity from past infections. In typical outbreaks, 90% of mortality occurs in this population, so overall in 2009 deaths occurred less frequently than in seasonal influenza (Monto and Webster, 2013; Paules and Subbarao, 2017)

Following Monto and Webster (2013), the study of pandemics from the past can provide an insight into the future. Some lessons learned from the past pandemics include:

- Zoonotic origin and unpredictability of pandemics
- Surveillance in swine was inadequate
- Antigenic and structural similarities are not predictors of severity
- An influenza pandemic can arise anywhere in the world
- Pandemic influenza can emerge in any season
- Initial retention of avian receptor binding characteristics in pandemic influenza viruses
- Vaccines to pandemic influenza viruses are not available during the first wave of infection.
- Antivirals are the first line of defense
- Further pandemics of influenza are inevitable, as the ultimate reservoirs of influenza A viruses in wild aquatic birds cannot be eradicated.

A.3. Clinical aspects of influenza

A.3.1 Symptoms

The presentation of seasonal influenza ranges from an asymptomatic infection to a fulminant illness, depending on the characteristics of both the host and virus. Symptoms appear suddenly after an incubation period of 1–2 days and are characterised by various systemic features, including fever, chills, headache, myalgia, malaise, and anorexia, accompanied by respiratory
symptoms, including non-productive cough, nasal discharge, and sore throat (Zambon, 2013). Ocular symptoms can also be present and include photophobia, conjunctivitis, lacrimation, and pain with eye movement (Nicholson, 1992).

When present, fever is the most important physical finding and temperatures can be as high as 41°C in the first 24 h of illness. A clear nasal discharge might be present and eyes might be injected or watery. Small cervical lymph nodes might be palpable and tender. About 25% of cases have diffuse rhonchi or rales upon auscultation of the lungs. Fever and associated systemic symptoms typically last for 3 days but can persist for up to 8 days. Cough and malaise can persist for up to 2 weeks after resolution of fever (Paules and Subbarao, 2017).

Some symptoms of influenza are common at every ages, but other are more specific at certain age groups. For example, in old adults it often appears respiratory difficulties or the production of sputum, while in children more frequent symptoms include othitis or abdominal pain. These abdominal pain including nausea, vomit or diarrhea are also very frequent in adults.

Primary influenza-associated pneumonia is quite common. Bacterial pneumonia as a complication of influenza infection was first documented during the 1918 pandemic. The most common organisms isolated from sputum are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* or *Streptococcus pyogenes* (Campbell and Grohskopft, 2018). A large proportion of fatalities during the 2009 pandemic was associated with bacterial pneumonia (Shieh et al., 2009).

In addition to pulmonary complications, several effects on other organ systems can be seen in influenza. Renal failure can occur and can persist for 4–6 weeks. Cardiac complications of influenza include myocarditis, pericarditis, and exacerbation of underlying cardiac disease. Influenza has also been associated with neurological manifestations, including Reyes syndrome, encephalomyelitis, transverse myelitis, Guillain-Barre syndrome, aseptic
meningitis, and encephalitis. Reyes syndrome is characterised by acute encephalopathy without evidence of inflammation on analysis of cerebrospinal fluid, associated with liver function abnormalities and elevated serum ammonia concentrations. This syndrome occurred mostly in children receiving aspirin and is now a rare event because aspirin use in children has declined substantially.

Children younger than 5 years, and particularly those less than 2 years, are at higher risk for severe outcomes due to influenza, including influenza-associated hospitalizations and death. Complications of influenza in children include pneumonia, asthma, exacerbations, dehydration and, less commonly, lung abscess/empyema, acute renal failure, myocarditis and neurologic complications such as encephalopathy and encephalitis (Campbell and Grohskopft, 2018). Children with underlying medical conditions, such as immunosuppression, and pulmonary, cardiac, hematologic or neurologic disorders are at higher risk for influenza complications, including bacterial coinfection. However, many influenza-hospitalizations and deaths occur in healthy children without known high-risk conditions (Campbell and Grohskopft, 2018).

Although in some cases complications may appear, most of the affected persons recovers in one or two weeks.

A.3.2. Diagnosis

The diagnosis of influenza is normally clinical, when a case is detected with signals and symptomatology compatible with influenza within an adequate context (seasonal period, other cases close to the infected person, etc). But symptoms of infected persons with influenza virus range in severity and overlap with those caused by other respiratory viruses, difficulting the clinical diagnosis.

There are some laboratory tests that can help the influenza diagnosis and can be used to guide treatment decisions, avoid inappropriate use of antibiotics, and provide information for influenza surveillance. These tests are
not necessary during the influenza season. The most important are: **Viral isolation, viral proteins detection, nucleic acid detection and quantification of antibodies in blood.** The first three technics require respiratory secretions that can be taken through nasopharyngeal swabs, nasal washes and nasopharyngeal aspirates; for the last one a blood sample is needed during the acute phase of the illness.

Clinicians are likely to appropriately diagnose influenza infection when fever and cough are part of the case definition, when influenza rates are high in the community, and when patients are severely ill or are at an increased risk of developing complications.

In recent years, new molecular technologies based in PCR allow the detection of influenza A, B and the different subtypes of influenza A. This diagnostic technique can detect influenza virus in a period of 30 minutes to few hours. The use of genetic sequencing, although expensive, allows rapidly characterize the viruses with advantages for diagnosis, surveillance and public-health policies.

**A.3.3. Treatment**

The main goal of influenza treatment is trying to minimize the effect that the virus produces. Four classes of antiviral drugs are approved for the treatment of influenza: adamantanes, neuraminidase inhibitors, membrane fusion inhibitors, and RNA-dependent RNA polymerase inhibitors (Ison, 2015). Of these, only the adamantane derivatives and neuraminidase inhibitors are licensed for use in the European Union and the USA. The adamantane derivatives include two oral agents, amantadine and rimantadine, which inhibit the matrix 2 ion channel of influenza A, but not B, viruses (Bennet et al. 2015). Due to point mutations in the matrix 2 protein, all currently circulating seasonal influenza viruses are resistant to the adamantane derivatives and so the use of these agents is not recommended.
Neuraminidase inhibitors inhibit the function of the influenza virus neuraminidase (Bennet et al., 2015). During the 2015–16 influenza season, oral oseltamivir and inhaled zanamivir were recommended for use in the European Union and the USA. Treatment of influenza infection is indicated for patients admitted to hospital with suspected or confirmed influenza and individuals at high risk of developing influenza-related complications. Treatment can also be considered for uncomplicated influenza infections in low-risk individuals who present within 48 h of symptom onset (Paules and Subbarao, 2017).

Resistance to neuraminidase inhibitors can occur through multiple mechanisms. Some resistance conferring mutations change the catalytic framework of the neuraminidase molecule or lead to internal deletions in the neuraminidase so that the drug cannot bind, whereas others alter the haemagglutinin so that neuraminidase activity is not required to release the virus from the infected cell. These mutations confer variable changes in viral fitness and could yield resistance to one or more of the available neuraminidase inhibitors. During the 2007–08 influenza season, substantial resistance to oseltamivir emerged in influenza A H1N1 viruses through a histidine to tyrosine substitution (H275Y) in the neuraminidase protein.

Since the emergence of H1N1pdm09 influenza A viruses and their establishment as circulating epidemic strains, resistance to neuraminidase inhibitors has been uncommon. As of March, 2016, all circulating influenza A H3N2 and influenza B isolates in the USA were susceptible to the licensed neuraminidase inhibitors and only 5% of influenza A H1N1pdm09 isolates were resistant to oseltamivir and peramivir. Rates of oseltamivir resistance were lower than 5% in the European Union, with resistance observed in less than 1% of influenza A H1N1pdm09 isolates (European Centre for disease prevention and control. Influenza. 2018).

Antiviral treatment is recommended for children with suspected or confirmed influenza who are hospitalized, for those who have severe or progressive illness, and for the children at high risk for influenza complications. Antiviral treatment can shorten the duration of illness and may reduce the risk of
complications (Campbell and Grohskopf, 2018). Table 1 schedule the main treatment options for influenza infections in the USA and Europe (from Paules and Subbarao, 2017)

**Table 1. Treatment options for influenza infections in USA and Europe**

[from Paules and Subbarao, 2017]

<table>
<thead>
<tr>
<th>Route</th>
<th>Treatment dose</th>
<th>Prophylactic dose</th>
<th>Location availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oseltamivir</strong> (Tamiflu, Roche)</td>
<td>Oral Adults: 75mg twice daily for 5 days Children: weight based dosing twice a day for 5 days</td>
<td>Adults: 75 mg once daily for 7-10 days Children: weight based dosing once a day for 7-10 days</td>
<td>Available in USA and European Union</td>
</tr>
<tr>
<td><strong>Zanamivir</strong> (Relenza, GlaxoSmithKline)</td>
<td>Inhaled 7 years and older: 10 mg twice daily for 5 days</td>
<td>5 years and older: 10 mg once daily for 7-10 days</td>
<td>Available in USA and European Union</td>
</tr>
<tr>
<td><strong>Peramivir</strong> (Rapivab; BioCryst Pharmaceuticals)</td>
<td>Intravenous 18 years and older: 600 mg in a single dose</td>
<td>-</td>
<td>Available in USA</td>
</tr>
</tbody>
</table>

B) PREVENTION: VACCINATION

The most effective method for prevention and control of influenza infection is vaccination (Houser et al. 2015). Three classes of licensed influenza vaccines are available: inactivated virus (IIV), live attenuated virus (LAIV), and recombinant haemagglutinin vaccines (RHV). In table 2 the different types of licensed influenza vaccines are shown.

**Table 2. Types of influenza vaccines licensed for use in the United States (2015-2016 and 2017-2018 seasons)**

[Combined from Paules and Subbarao, 2017; and Campbell and Groshkopf, 2018]

<table>
<thead>
<tr>
<th>4 vs 3-valent</th>
<th>Available formulations</th>
<th>Route</th>
<th>Approved age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated</td>
<td>Quadrivalent</td>
<td>Standard dose, unadjuvanted</td>
<td>intramuscular</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Quadrivalent</td>
<td>Standard dose, unadjuvanted</td>
<td>intradermal</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Trivalent</td>
<td>Standard dose, unadjuvanted</td>
<td>intramuscular</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Trivalent</td>
<td>Standard dose, adjuvanted</td>
<td>intramuscular</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Trivalent</td>
<td>High dose, unadjuvanted</td>
<td>intramuscular</td>
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<td>--------------</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Quadrivalent</td>
<td>intramuscular</td>
<td>&gt;18 years</td>
</tr>
<tr>
<td>Recombinant</td>
<td>Trivalent</td>
<td>intramuscular</td>
<td>&gt;18 years</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>Quadrivalent</td>
<td>intranasal</td>
<td>2-49 years</td>
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For the last several decades until the 2013-14 influenza season, the vaccines were trivalent, containing hemagglutinin derived from 3 influenza viruses: A(H1N1), A(H3N2) and a B virus. Influenza B viruses consist of two lineages (called Victoria and Yamagata), which have cocirculated during most seasons since 1980, generally with one lineage predominating. There is no antibody protection against influenza B viruses of the other type (Rota et al., 1990). Quadrivalent influenza vaccines, first available in the season 2013-14, contain an influenza B virus from each lineage, providing broader protection against circulating B viruses. However, both types of vaccines are available at 2017-18 season, and no preferential recommendations are made for any specific product (Campbell and Groshkopf, 2018).

Until 2016 the use of live attenuated influenza vaccines was recommended in young children in the USA on the basis of clinical results and observational data in this age range (see for example Belshe et al., 2007 and their main result in fig. 5).
Based upon results as this one from Belshe et al. (2007), later confirmed by Ambrose et al. (2012), in June 2014 the US health authorities made a preferential recommendation for LAIV over IIV for healthy children 2 through 8 years of age (Groshkopf et al., 2014). However, Gaglani et al. (2016) analysed data for the 2013–14 influenza season (the first season that quadrivalent LAIV was available) in fully vaccinated children aged 2–17 years, and showed that for influenza A H1N1pdm09 (the virus strain that produced the 2009 pandemics) the live attenuated vaccine provided inferior protection (effectiveness 17%) to that of the inactivated vaccine (60%). This was the first season since the start of the 2009 pandemic during which A(H1N1)pdm09 was the predominant circulating virus. This finding and similar effectiveness data during the 2015–16 influenza season (e.g. Chung et al. 2016; AAP 2016), together with higher effectiveness of IIV, led the US health authorities to recommend that live attenuated vaccines were not used in the 2016–17 and 2017-18 influenza seasons (Campbell and Grohskopf, 2018; Paules and Subbarao, 2017).

At a meeting of ACIP (Advisory committee on immunization practices) in June 2016, data were presented on influenza vaccine effectiveness from four observational studies conducted in subgroups of the pediatric population during the 2015-2016 influenza season. Two of the studies were conducted in the United States – one by the company MedImmune as part of its postmarketing commitment to FDA and one by the Center for Disease Control (CDC). A third study was conducted in the United Kingdom by Public Health England in collaboration with other partners. The fourth study was conducted in Finland by the Finland National Institute for Health and Welfare. Three of the studies (MedImmune’s U.S. study, the U.K. study, and the Finland study) showed statistically significant effectiveness of the LAIV Quadrivalent vaccine against all influenza strains combined, ranging from 46% to 58% effectiveness. This level of overall effectiveness is comparable to vaccine effectiveness against vaccine-
similar strains obtained from observational studies in children for both LAIV and inactivated influenza vaccines in prior seasons. In contrast, CDC’s U.S. study did not show statistically significant effectiveness of LAIV Quadrivalent for all influenza strains combined.

Reasons for discordant results among the studies, particularly between the two U.S. studies, are not clear but may include limitations inherent in observational study designs and problems of thermostability of the LAIV vaccine (FDA webpage). A manufacturing change that could be implemented in time for the 2015-2016 influenza season, allowed vaccine effectiveness for the 2015-2016 influenza season suggesting that this change led to improved LAIV Quadrivalent effectiveness against Influenza A (H1N1) compared to that previously observed in the 2013-2014 influenza season. However, these data also suggest that factors other than thermostability may be contributing to the lower than expected effectiveness of LAIV Quadrivalent observed in recent years. FDA is continuing to work to better understand these findings (FDA webpage).

By contrast, European data have continued to show protection with live attenuated vaccines (LAIV) in children, although effectiveness against influenza A H1N1pdm09 is lower than against influenza B. The live attenuated vaccine continues to be recommended in many European countries (Hawkes 2016), but further investigation is needed to optimise vaccination strategies. It seems that LAIV is not as effective as before the 2009 pandemic, although results are unclear. For example Shim et al (2016) conclude that the effectiveness of IIV is higher than LAIV, while Ambrose et al. (2014) support the higher effectiveness of LAIV. This controversy also appears at the different recommendations given at USA (IIV) and Europe (LAIV). An interesting resume of this controversy is given in the “personal view” paper by Singanayagam et al. (2017).

Other difference between USA and Europe concern the target people recommended for vaccination. In Europe, most countries recommend influenza
vaccination in individuals at high risk of developing complications, including elderly people, pregnant women, individuals with medical comorbidities, residents of long-term care facilities, and health-care workers. In the USA, annual influenza vaccination is recommended for all individuals aged 6 months or older and is particularly emphasised for individuals at high risk of developing complications of influenza infection, and for health-care workers (Groshkopf et al., 2015).

However, the response of the population to this universal recommendation for vaccination has been much lower than expected. The health authorities estimated that in the 2014–15 influenza season only 47% of children and adults were vaccinated, with the lowest rates (33%) seen in healthy adults aged 18–49 years. Higher rates were seen in adults older than 65 years (67%), adults aged 18–64 years with high-risk conditions (48%), pregnant women (50%), and children aged 6 months to 17 years (59%). Only 40–50% of pregnant women in the USA were vaccinated during the 2014–15 influenza season. Maternal vaccination is the primary mechanism to protect young infants because vaccines are not licensed for infants younger than 6 months. However, pregnant women frequently defer vaccination because of concerns regarding the safety of the influenza vaccine during pregnancy. Several reviews have shown no increase in adverse maternal or fetal effects after administration of inactivated seasonal influenza or H1N1pdm09 influenza vaccines (Naleway et al., 2014). Pregnant women should therefore be informed of the benefits of vaccination for themselves and their infants, and should be reassured of the safety of inactivated influenza vaccines (Paules and Subbarao, 2017).

Several studies have shown that influenza vaccination is most effective when the vaccine strain matches the circulating epidemic strain (Houser and Subbarao, 2015). Effectiveness rates of 50–60% are reported for well matched influenza vaccines in healthy adults and children (Jefferson et al., 2014). Vaccine benefit is greatest among high-risk groups such as individuals older than 65 years (especially those with comorbidities), immunocompromised patients, and young children. In the 2013–14 influenza season, the health
authorities in USA estimated that influenza vaccination led to 90,000 fewer overall hospital admissions than if no vaccination had taken place (Reed et al. 2014). When seasonal influenza viruses undergo antigenic drift after a vaccine has been distributed, a marked decrease in vaccine effectiveness occurs. Vaccine effectiveness may also be influenced by previous vaccination. Some studies have suggested that annual vaccination could result in decreased vaccine effectiveness, but additional data are needed to investigate this issue and its implications for vaccine policy (Paules and Subbarao, 2017).

Concerning the safety of vaccines for children, currently licensed influenza vaccines for children are generally well-tolerated. Serious reactions are uncommon, although ongoing safety monitoring for rare events is important for all vaccines. Both IIV and LAIV vaccines are generally well-tolerated by children. Among the more frequent adverse events reported in IIVs are local symptoms at the injection site, including injection site pain or tenderness, redness, and swelling or induration. Systemic symptoms, such as headache, myalgia, malaise, and fatigue may also occur, as well as irritability and drowsiness among younger children. Fever, which is generally more commonly among younger children, may occur following receipt of IIVs. Other serious reactions to influenza vaccines among children have been reported. Increased reports of narcolepsy among children and adults were noted during pandemic influenza vaccination campaigns in several European countries, mainly in association with ASO3-containing monovalent (H1N1)pdm09 vaccines (Campbell and Groshkopf, 2018).

In the case of LAIV vaccines, common reactions are generally self-limited and include runny nose, nasal congestion, sore throat, headache, vomiting, and myalgia; in general, symptoms are more severe with the first dose. LAIV contains live, attenuated, cold-adapted influenza viruses that replicate locally in the nasal mucosa (remember than this vaccine is administrated through nose). Shedding of vaccine viruses can occur following administration of LAIV (Campbell and Groshkopf, 2018).

A problem that sometimes emerges in vaccination has to do with egg
allergy. Currently available vaccines contain viruses that have been propagated in chicken eggs and may contain residual egg proteins (Campbell and Groshkopf, 2018).

Improving influenza vaccine effectiveness is an important goal. Potential novel approaches include strategies to improve immunogenicity, such as high-dose or adjuvanted vaccines, and nonegg-based production platforms including recombinant vaccines, cell culture-based or plant-based vaccines, and vaccines developed using virus-like particles, vectors, or DNA vaccines (Nachbagauer et al. 2017).

Antigenic drift of seasonal influenza viruses and the emergence of novel influenza viruses by antigenic shift, combined with the time required to develop an influenza vaccine, make new vaccine approaches an important component of influenza research. New approaches such as DNA-based vaccines, viral vectors, virus-like particles, cell-culture techniques, recombinant DNA, novel live attenuated vaccines, and adjuvants are being studied to improve vaccine development and immunogenicity (Paules and Subbarao, 2017).

Several such vaccines have been licensed in Europe for seasonal influenza and in the USA for individuals at high risk of exposure in the event of an H5N1 pandemic. A universal influenza vaccine that is broadly cross-protective could replace annual seasonal influenza vaccination and provide protection following the emergence of a novel influenza virus (Houser and Subbarao, 2015, Lee et al., 2014). Vaccines based on various viral targets, such as the haemagglutinin stem, matrix 2 protein, and consensus sequences of the haemagglutinin head, are in development (Houser and Subbarao, 2014; Paules and Subbarao, 2017).
C) HUMAN INFLUENZA: A GLOBAL CONCERN

Influenza viruses know no boundaries, circulating within species and occasionally jumping between them, causing infections around the globe. The impact of influenza is wide-ranging with effects on every corner of the planet. The growing interconnectedness and complexity of the actual world presents an increasing challenge to influenza prevention and control. As people and the animals that support them increase in numbers and interactions, the opportunities for virus adaptation and cross-species transmission increases as well (Jernigan and Cox, 2013). The estimation of the World Health Organization (WHO) is that around 1 thousand millions cases of seasonal influenza in persons appear each year, with 3-5 millions of severe illness and 300,000-500,000 deaths per year. The economic lost only in USA 10,4 billion dollars per year in direct medical costs and around 87,1 billion dollars in total costs (including lost of working hours).

The world population has increased dramatically in the last century (fig. 6), with an estimation of 11.000 million humans in 2050. 80% of this total population is expected to inhabit less developed countries, with most of the people living in megacities, which are growing at a high rate, with a population dominated by children and young people, with deficient infrastructures and poor sanitary services. There is also a clear growing of birds and pigs, the two main animals with an important role as sources of novel influenza viruses capable of causing pandemics (fig. 6). There is a rising demand for meat, with chicken and pig (the main animal reservoirs of influenza) as the most demanded, with an increase in consumption of 150% from 1960 to 1990 (Jernigan and Cox).
Fig. 6. Global population and travel trends, 1961-2010. [From Jernigan and Cox, 2013]

An increasing population density not only provides an opportunity for influenza to be shared within the community, it also provides opportunities for influenza to be carried to other communities through travellers. Nowadays a person can travel (for business or tourism, both growing exponentially, fig. 6) to any place within the incubation period of influenza. The interconnection between communities has an important role in influenza epidemiology. Whereas influenza transmission within communities is predominantly driven by children, transmission between communities is predominantly driven by those who travel frequently, mainly adults.

With a growing number of younger individuals, a high frequency of interaction among the population, and a higher number of animals acting as vectors, influenza viruses are given all the right circumstances for efficient and sustained transmission. This global interconnectedness requires a global
coordination and response improving virologic surveillance for human influenza. Influenza viruses do not respect boundaries between countries, international efforts for common approaches are challenging.

On the other hand, our actual world has new tools for global detection and surveillance. The 2009 pandemic was the first one that took advantage of new molecular technologies, instant information in highly connected communities, and convergence of multiple data sources to improve forecasting and for focusing interventions. The 2009 pandemics was the first one during the era of molecular diagnostic. PCR (polymerase chain reaction) allows the rapid detection of influenza virus A and B and subtypes H1, H3 and H5. The greatest benefit has been the use of genetic sequencing for rapidly characterize the viruses for directing public-health decision making.

The greater access to rapid sequencing capabilities will transform influenza diagnosis and surveillance. Influenza is a global challenge, and the prevention and control of influenza requires a global response in which molecular diagnosis and genetic sequencing capabilities are available to public health authorities, researchers and clinicians for rapidly determining appropriate treatment, control measures and prevention strategies.

Therefore, given the above arguments it’s crucial to annalise the convenience of a global vaccination campaign to have an efficient control and prevention of an important global concern such as influenza virus epidemics.
D) SURVEILLANCE FOR INFLUENZA IN SPAIN

Influenza surveillance in Spain is coordinated by the Group of Influenza Surveillance, adscribed to the Health Institute Carlos III. The last complete report corresponds to the season 2016-2017, but there are weekly reports corresponding to the season 2017-18 published in their website (http://www.isciii.es). In this last part of the TFM the main results of the surveillance made at these last two years are shown.

D.1. Influenza surveillance in Spain, season 2016-17

Influenza in Spain during the season 2016-17 had a moderated impact, and was associated with the circulation almost exclusively of influenza virus A(H3N2), with a very few contribution of virus B in the last weeks of the surveillance period (fig. 7). The epidemic started early around mid-december 2016, reaching its maximum activity in the week 3/2017 during a total duration of nine weeks.

![Fig. 7. Weekly incidence rate of influenza and number of viral detections. Season 2016-17. Sentinel system (from “Informe de Vigilancia de la gripe en España 2016-17”)](image-url)
Children under the age of 15 were the most affected group, with a higher incidence rate between 0-4 years old (fig.8). Prevalence rate for influenza among the elderly (older than 64 years) was one of the highest since 2009 pandemy, exceeded only by 2014-15 season.

*Fig. 8. Evolution of the incidence of influenza incidence by age group. 2016-17 season. Sentinel system. Spain (from “Informe de Vigilancia de la gripe en España 2016-17”)*

There were 47 confirmed flu outbreaks throughout the season. 38 of them took place in geriatric institutions, 7 in health institutions and 2 in other institutions. In 46 outbreaks influenza A virus was identified as the causative agent, and in only 1 outbreak the agent identified was influenza B virus.

There were a total of 2,874 influenza confirmed hospitalized severe cases, from which 619 cases were admitted in ICU and 464 died. The main characteristics of the population with these confirmed influenza hospitalized severe cases were:
Average age: 76 years old

Highest proportion rate: > 64 years

Influenza virus type: A In more than 99%, specially A(H3N2).

Cases with previous risk factors: 91%

Recommended patients for vaccination not vaccinated: 48%

The hospitalization rate of confirmed influenza hospitalized severe cases is shown in fig. 9 for the last 4 seasons. A clear U-shaped graph can be seen for every season, with highest rates of hospitalization within children smaller than 4 years, and persons older than 64 years as the most frequent severe cases.

Figure 9.- Cumulative hospitalization rate of confirmed influenza hospitalized severe cases by age group. 2013-14/2016-17 seasons. (from “Informe de Vigilancia de la gripe en España 2016-17”)

The dead persons within this group of severe hospitalized cases had the following characteristics:
**Average age:** 81 years old  
**Highest proportion rate:** > 64 years  
**Confirmed influenza virus type:** A(H3N2) mainly  
**Cases with previous risk factors:** 95%  
**Recommended patients for vaccination not vaccinated:** 50%

**D.2 Influenza surveillance in Spain, season 2017-18**

Data for influenza in Spain during the season 2017-18 is only available until the 14\textsuperscript{th} week (2\textsuperscript{nd} – 8\textsuperscript{th} of April). The type of virus at this season has changed clearly: The influenza illness this year is mainly associated with the circulation of influenza virus B (59%), with some contribution of virus A (41%), specially A(H3N2) (fig. 10). The timing of the epidemic is very similar to the previous year, starting early around mid-december 2016, reaching its maximum activity in the third week of 2017.

The epidemic period has already ended for the season 2017-18, and a basal intensity level is notified. The spread of the disease is already sporadic or absent, and the flu activity progress seems to be stable or even decreasing.

![Weekly incidence rate of influenza and number of viral detections. 2017-18 season. Sentinel system. (from “Informe de Vigilancia de la gripe en España 2017-18”)](image-url)
From the total amount of influenza virus detections until the 14th week of this season, 59% are type B and 41% are type A [59% of A(H3N2)]. There is a clear difference when we compare these data with those at the previous season. Fig. 11 shows in a sectors diagram the percentage of incidence of each virus type at both seasons, with a clear dominance of virus A in the season 2016-17 and a clear change in 2017-18 with predominance of virus B.

![Chart showing viral detection by type/subtype for 2016-17 and 2017-18 seasons.]

Fig. 11. Sentinel viral detection of influenza by type/subtype of virus. 2016-17 (left) and 2017-18 (right) season. (from “Informe de Vigilancia de la gripe en España 2016-17” and “Informe de vigilancia de la gripe en España 2017-18”)

This change in the predominant virus type is also clear when data from the whole European community are shown (Fig. 12). It is clear the dominance of virus type A (H3N2) during 2016-17 season with a peak in the third week of 2017, and the dominance of virus type B during this last season 2017-18, with a peak in the fourth week of 2018.
Coming back to influenza in Spain during this last season 2017-18, children under the age of 15 were the most affected group, with a higher incidence rate among 0-4 years old (fig. 13). Prevalence rate for influenza among the elderly (older than 64 years) was one of the highest since 2009 pandemic, exceeded only by 2014-15 season. The influenza incidence among spanish population by year groups remains the same as in the 2016-17 season.
Since the start of the 2017-18 season, there have been 26 confirmed flu outbreaks. One took place in a healthcare institution, another one in a long-stay residence, three in school facilities and twenty one in geriatric institutions.

There were 2,874 influenza confirmed hospitalized severe cases, from which 619 cases were admitted in ICU and 464 died. The main characteristics of the population within confirmed influenza hospitalized severe cases were:

- **Highest proportion rate**: > 64 years
- **Confirmed influenza virus type**: B in 56% of cases (specially A(H3N2)).
- **Recommended patients for vaccination not vaccinated**: 53%

Fig. 14 shows the viral detections in confirmed influenza hospitalized severe cases by age group, in which clearly appear people older than 64 years as the highest.
Finally, the deaths within these hospitalizaded severe cases had the following characteristics:

**Average age**: 82 years old

**Highest proportion rate**: < 64 years

**Recommended patients for vaccination not vaccinated**: 49%
There is a clear correspondence between the mortality by every cause and the influenza incidence that can be seen every year. Fig. 16 shows the tendencies of both variables during the last 8 seasons in Spain, clearly showing the simultaneity of mortality by any cause and mortality by influenza.

Fig. 16. Weekly mortality by every cause and weekly influenza incidence. From 2010 until 2017-18 (week 14). (from “Informe de Vigilancia de la gripe en España 2017-18”)
15. CONCLUSIONS

1) Influenza viruses can infect humans resulting in clinical illness that range from mild to severe. Severe illness and death may occur, particularly among younger children and those with underlying medical conditions, but also in previously healthy children of any age.

2) Although the effectiveness of vaccination varies annually, the best way to prevent seasonal influenza in children is to vaccinate before each season with recommended vaccines.

3) There are discrepancies between USA and Europe strategies concerning the use of IIV (USA) vs LAIV vaccines (Europe), and also in the recommendation of universal vaccination (USA) or high-risk population (Europe).

4) Live attenuated quadrivalent vaccine is the one that offers better results due to its higher efficacy, better coverage of antigens, nasal administration, good tolerance and high cost-effective ratio.

5) The world of influenza is complex and interconnected. The opportunities for exchanging viruses between species and for reasortment of their genes have increased as the populations of humans, swine and birds have increased, all in close proximity to one another in growing urban communities, and living only one flight (and one incubation period) from each other.

6) Surveillance for influenza in Spain during these last two seasons 2016-17 and 2017-18 conclude a moderated impact associated to different virus types, with Influenza A(H3N2) as the most abundant during 2016-17 and virus influenza B during 2017-18. The period of appearance has been very similar in both seasons.
16. PRACTICAL RECOMMENDATIONS

(1) A global vaccination campaign is recommended as the main prevention for influenza epidemic and/or pandemic.

(2) The live attenuated quadrivalent vaccine is the recommended one in Europe, given that offers better results due to its higher efficacy, better coverage of antigens, nasal administration, good tolerance and high cost-effective ratio.

(3) Surveillance for influenza is highly recommended. Common protocols and coordination from international health authorities are encouraged.

(4) Some practical recommendations during the episodes of influenza include: Good hand hygiene practices, avoid contact with other people, for children it is recommended to stay at home when influenza symptoms appear and appropriate air exchange.
17. REFERENCES


Hawkes, N. 2016. UK stands by nasal flu vaccine for children as US doctors are told to stop using it. BMJ 353. Doi: 10.1136/bmj.i3546.


