Nursing in primary health care

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ABSTRACT

The material we propose will contribute to the strengthening of the knowledge of students of Medical Sciences, as well as the population in general, since it is up-to-date, easy to understand, develops cognitive and volitional components, also contributes to the strengthening of values of patriotism, sensitivity, consecration, responsibility; It is a tool that they can consult if they have any questions and at any time. Cuba is characterized by guaranteeing health prevention for which it plans a set of health activities that are carried out both by the community, governments as well as by health personnel before a certain disease appears, among which is the vaccination program, in this material appear the vaccines that are currently applied in the country and others that have not been possible to acquire them by the blockade that for 57 years we have been a victim of by the United States of America. In addition to linking diseases that can be avoided by preventing them with immunization.

Keywords: Vaccines, Prevention, Nurses, Primary Care, Diseases.

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INTRODUCTION

Due to the economic crisis, since 1989, a reform of the sector has been carried out, in the midst of a certain controversy: although the government maintains that all Cubans have access to doctors, nurses, specialists and medicines, the latter were scarce due to the restrictive effects on the availability of resources due to the U.S. blockade; when the Torricelli Law was enacted, numerous firms that had traditionally sold medical equipment or its components to Cuba suspended its operations because the [U.S.] Treasury Department denied export licenses, because it was a subsidiary of a U.S. transnational corporation, or because the equipment was made with components manufactured in that country. This, in part, led to a shortage of medicines and raw materials for the pharmaceutical industry, and the non-renewal of medical equipment. This caused even greater investments in the sector, so that today the country imports less than 20% of the medicines it consumes, and produces several medical equipment, the rest is imported from European corporations such as Philips, or Siemens.

Our own products include:

- Interferon: it is one of only six countries in the world that produce it.
- Epidermal growth factor: healing cream against burns.
- Hepatitis B vaccine.
- Meningococcal vaccine type B (only producing country).
- Recombinant streptokinase , a drug that acts against myocardial infarction.
- Drugs are also made against thromboembolisms, immune system problems, hypertension, cholesterol, and some forms of cancer.
- Pentavalent vaccine: it is the only country that produces it besides France.
- Cytoprot P: Medication that is able to heal diabetic foot ulcers
- PPG (derived from sugar cane) used for hypercholesterolinemia.[1]

The efforts of the Cuban government and people, always threatened by the brutal blockade, have made the country take some alternatives in such a way that the consequences are minimized and family medical offices emerge whose functions include the prevention and promotion of the health of the people, which is why the immunization program appears after the revolutionary triumph.

Vaccines were not always accepted, giving rise to some contradictions; over the years they have demonstrated their effectiveness.

There is the so-called **vaccine controversy**, which refers to a dispute about the morality, ethics, effectiveness, or safety of vaccination. Medical and scientific evidence shows that the benefits of preventing death from infectious diseases outweigh the rare adverse effects of immunization.[1][2] Since vaccination began in the late eighteenth century, opponents have maintained that vaccines do not work, that they are or can be dangerous, that emphasis should instead be placed on personal

hygiene, or that mandatory vaccinations violate individual rights or religious principles.[3] Since then, anti-vaccination campaigns have resulted in unnecessary damage and mass deaths.[4]

- Vaccines can have side effects, and the success of immunization programs depends on public confidence in their safety. Suspicions about the safety of immunization often follow the same pattern: some researchers suggest that some health disturbance is an adverse effect of vaccination; an early announcement is made about the adverse effect; the initial study is not reproduced by other groups; Finally, it takes several years to regain public confidence in the vaccine.[1] 5

Cuba proposes three (3) fundamental aspects as a health policy to guarantee comprehensive care, they are:

1. Health promotion, which is the promotion and defense of the health of the population through actions that affect the individuals of a community, such as anti-smoking campaigns to prevent lung cancer and other diseases associated with tobacco.
2. Specific health protection such as environmental health and food hygiene. Health promotion and protection activities that affect the environment are not carried out by medical or nursing personnel, but by other public health professionals, while vaccination is carried out by medical and nursing personnel
3. Chemoprophylaxis, which consists of the administration of drugs to prevent diseases such as the administration of estrogen in menopausal women to prevent osteoporosis.

The country managed to eradicate a group of diseases that plagued the country through vaccination campaigns such as:

- Poliomyelitis in 1962, Malaria in 1967, Neonatal tetanus in 1972, Diphtheria in 1979, Post-mumps meningoencephalitis in 1989, Congenital rubella syndrome in 1989, Measles in 1993, Pertussis in 1994, Rubella in 1995

This shows tenacity, courage. The humanism of the Cuban people under the direction of its undisputed guide, Commander in Chief Fidel Castro Ruz.

CHAPTER 1

DEFINITIONS

Immunization: it is the process of inducing artificial immunity against a disease. Immunization can be of two types:

- **Passive immunization**: It involves antibodies that are produced in the body of another person, as in the case of infants who have passive immunity, since they are born with the antibodies that the mother transfers to them through the placenta. These antibodies disappear between 6 and 12 months of age. Another way to obtain passive immunity is

with gamma globulin, which is supplied by a doctor and whose protection is also temporary.

- **Active immunization**: through the application of vaccines, attenuated antigenic preparations in order to generate an immune response by the body; to generate an immune memory consisting of the formation of protective antibodies against the antigen to which one is exposed.

Immunity: state of natural or acquired resistance that certain individuals possess against certain pathogens.

Vaccines: they are an antigen preparation that once inside the body causes the production of antibodies and with it a defense response against pathogenic microorganisms. This response generates, in some cases, a certain immune memory, producing transient immunity against the corresponding pathogenic attack. The first vaccine discovered was the one used to combat smallpox by Edward Jenner in 1796.

CAPITULO II

VACCINE OVERVIEW

Vaccines are classified into two large groups:

- Live attenuated vaccines.
- Inactivated vaccines.

There are several methods of obtainment:

- Virulent vaccines prepared from non-hazardous forms of the pathogenic microorganism.
- Prosified vaccines from dead or inactivated organisms.
- Purified antigens.
- Genetic vaccines.

Vaccines can be made up of bacteria or viruses, either live or weakened, that have been bred for that purpose. Vaccines may also contain inactivated organisms or purified products from the former. There are five types of vaccines:

- **Inactivated: harmful** microorganisms that have been treated with chemicals or heat and have lost their danger. This type of vaccine activates the immune system but is unable to reproduce in the host. The immunity generated in this way is of lower intensity and usually lasts less time, so this type of vaccine usually requires more doses. Since the immune response achieved is lower, substances called adjuvants are used in these vaccines. These substances are composed of aluminum and serve the vaccine to increase the body's immune response. Aluminum compounds must be injected deep

intramuscularly as they can cause irritation, inflammation, and tissue injury. Examples of this type are: influenza, cholera, bubonic plague and hepatitis A.

- **Live attenuated**: microorganisms that have been expressly cultured under conditions in which they lose or attenuate their pathogenic properties. They tend to cause a longer-lasting immune response, and are the most common in adults. This is because the microorganism is not inactivated and retains its structure. For this reason, it can often cause the disease in immunocompromised people. For example: yellow fever, measles or rubella (also called German measles) and mumps.
- **Toxoids**: these are inactivated toxic components from microorganisms, in cases where these components are the ones that really cause the disease, instead of the microorganism itself. These components could be inactivated with formaldehyde, for example. Tetanus and diphtheria can be found in this group.
- **Acellular**: consist of a mixture of purified subcellular components of the pathogen against which you want to immunize, which usually consists of highly immunogenic antigenic proteins and which may contain toxoids. Such a vaccine is currently used against pertussis.
- **Subunit recombinants**: recombinant DNA technology is used to introduce the gene coding for a highly immunogenic antigen into the genome of a producing microorganism (such as *E. coli* or *S. cerevisiae*) with the aim of super-producing and purifying the antigenic protein, which will be the basis of a vaccine. These vaccine production techniques are very useful when the pathogen you want to immunize against is difficult to grow *in vitro*. A typical example is the sub-unit hepatitis B vaccine, which is composed only of the surface of the virus (surface formed by proteins). To obtain this vaccine, the hepatitis B-causing hepadnavirus S gene was cloned into *S. cerevisiae* and superproduced and purified, resulting in an effective vaccine (the S gene encodes the self-assembling HBsAg antigen located on the surface of the virus). A particular type of recombinant vaccines would be edible vaccines, produced using transgenic plants. In these cases, the transgene transferred to the plant would be a coding one for an antigen of interest, which will produce an immune response. To be an edible vaccine, the expression of the transgene must be directed by a tissue-specific promoter, which causes it to be expressed only in certain edible organs, such as cereal seeds or tubers. The great advantages of the production of edible vaccines lie in their low production cost, in that the antigen can be expressed in organs where it is stable at room temperature (such as those mentioned above), which would eliminate the costs of maintaining the cold chain, and in the possibility of simultaneously expressing several antigens and adjuvants in the same organ

of the plant. Of course, this production system also has drawbacks, such as control over the level of antigen expression, homogeneity of expression (dose adjustment) or maintaining the integrity of the antigen in the face of exposure to gastric and intestinal juices. So far, the most representative works on this topic have dealt with the production of the vaccine against hepatitis B, giving satisfactory results by immunizing mice that ate potatoes in which the antigen accumulated.

The vaccine against tuberculosis, for example, is the so-called BCG vaccine (Bacillus of Calmette and Guerin, which owes its name to its discoverers) is manufactured with live attenuated bacilli and is therefore not contagious to this disease.

New types of vaccines are currently being developed and tested:

- *Polysaccharides*: Certain bacteria have outer layers of polysaccharides that are minimally immune. By bringing these outer layers into contact with proteins, the immune system may be able to recognize the polysaccharide as if it were an antigen (an antigen can be a protein or a polysaccharide). In this way we generate antibodies against the bacteria and against the polysaccharide (exopolysaccharide, in this case). This process is used in the *Haemophilus influenzae* type B vaccine (also known as Pfeiffer's bacillus).
- *Recombinant vector*: By combining the physiology (body) of a given microorganism and the DNA (content) of a given microorganism, immunity can be created against diseases that have complicated infection processes. Efforts to create vaccines against infectious diseases, as well as immunotherapies for cancer, autoimmune diseases, and allergies have used a variety of heterologous expression systems, including viral and bacterial vectors, as well as recombinant DNA and RNA constructs. The most commonly used vectors in this type of vaccine are the vaccinia virus, some lactic acid bacteria (non-pathogenic) of the genera Lactobacillus and Lactococcus and attenuated varieties of M. tuberculosis and Salmonella typhi (the latter is more widely used, since it is very well known and its pathogenic effects are much milder). The main problems with this type of vaccine are the possibility that the immune response to them is insufficient to leave memory in the immune system and the induction of antigen production once the vector is inside the body (the use of inducers such as tetracycline and aspirin is being studied).
- *DNA vaccine*: A recently developed vaccine created from the DNA of an infectious agent. It works by inserting DNA from bacteria or viruses into human or animal cells. Some cells of the immune system recognize the protein that arises from foreign DNA and attack both the protein itself and the affected cells. Since these cells live a long time, if the pathogen (the one that creates the infection) that normally produces these proteins is found after a long period, they will be instantly attacked by the immune system. One

advantage of DNA vaccines is that they are very easy to produce and store. Although in 2006, this type of vaccine was still experimental, it has encouraging results. However, it is not known for sure whether this DNA can integrate into any chromosome in cells and produce mutations.

It is important to clarify that, while most vaccines are created using inactivated or attenuated components of microorganisms, synthetic vaccines are composed in part or entirely of peptides, carbohydrates or antigens. These synthetics are usually considered safer than the former.

TRANSPORT, DISTRIBUTION AND STORAGE

Cold chain is the system of stable and controlled conservation (ideal temperature), handling, transport, and distribution of vaccines that allow their effectiveness to be preserved from the exit of the manufacturing laboratory to the place where the vaccination is to be carried out.

It has three levels: Central, Provincial and Municipal

Cold chain elements

Material equipment: Refrigerator

Install it in the appropriate storage place protected from any heat source, about 15 cm away from the wall to allow the heat to be dispersed.

Connect it to the general network, do not make deviations to avoid accidental disconnections.

Be equipped with alarm systems and electric power generators that are activated if the cooler is accidentally disconnected.

Be equipped with a thermostat (between 2 and 80 centigrade)

Install a thermometer inside the refrigerator to check temperature, as well as a thermograph that records stability and possible changes.

In the behavior of the refrigerator, place nylon bags with water, which will serve as a cold accumulator and on the lower shelves, bottles with physiological solution that will help stabilize the internal temperature by forming a cold room system for 6-12 hours in case of breakdowns.

Defrost periodically (frost buildup decreases cooling capacity)

Storage recommendations

All vaccines, solvents and water bottles should take up at most half of the available space in the fridge. If it occupies a larger space, there may not be enough cold air circulation to keep the vaccines at the right temperature.

Do not store any other material (food, drinks, etc.) in the refrigerator intended for vaccines. The number of times the door is opened to put in or take out, endangers the stability of the internal temperature inside the fridge.

Do not store vaccines in the refrigerator door, as it is a place where the temperature is not stable and is higher. Store in the central spaces leaving space around the boxes and avoiding touching the wall of the fridge.

Vaccines with dates close to expiry should be placed more accessible than those with an expiration date later.

Remove expired vaccines as soon as possible to avoid accidental use.

The vaccines most sensitive to heat: oral polio, MMR, measles, rubella, antiburculosis and yellow fever should be located in the coldest part of the refrigerator but never in the freezer.

Vaccines that in their preparation have adjuvants that contribute to physical forms of colloidal suspension should never be frozen because they would lose their immunogenetic potency.

Transportation

Isothermal containers allow large quantities of vaccines to be transported to the vaccination site, allowing the cold to be preserved during transport.

Portable coolers will be used when vaccines need to be transported. A minimum transport time should be sought and only opened in specific circumstances.

For the best conservation of the vaccines, cold packers will be placed taking as a precaution to avoid contact with them through cardboard paper which prevents the freezing of the vaccines.

The nursing staff is responsible for:

1. Check at the beginning and end of each working day that the maximum and minimum temperatures marked by the thermometer and recorded by the thermograph are between 2 and 80 Celsius, and record the temperature recorded in the monthly temperature control graph. This control must be carried out without loss of time to avoid excessive exposure to the ambient temperature.
2. Check that the storage of the vaccine is carried out properly.
3. Periodically check the freezer ice layer (it should not exceed 5mm thick).
4. Check the expiry date of each batch, removing those that exceed it.
5. At the time of receipt of the vaccines, especially if the distribution is direct from the manufacturer's laboratory. Inspect the temperature control card and check for broken, frozen, torn or detached labels. You should also check the quantity and expiry date of the vaccines received are adequate.

Conservation of vaccines

Openings of the containers: The multidose containers must be exhausted during the vaccination session. It is advisable to adjust the schedules and vaccination appointments so that the shipment can be exhausted in the same working day. In any case, the annex must be done with the maximum asepsis to avoid contamination and for a time not exceeding 24 hours. The doses of these unused bulbs must be discarded.

Lyophilized reconstituted vaccines not applied within 8 hours of preparation should be discarded. Once opened, a multi-pack should not be exposed to light or ambient temperatures. The container should be returned to the refrigerator if the application of the next dose is not immediate.

Exposure to light: Viral vaccines should be preserved from light. Their conservation and handling must be careful due to their instability since they suffer losses of 50% of activity after the 5th hour of exposure to room temperature.

Temperature: The ideal storage is from 2 to 8 ^{0} centigrade. The internal temperature should not exceed 100 Celsius

A WHO study showed that tetanus and diphtheria vaccines were the most stable on the stability of heat-exposed vaccines, followed by pertussis associated with diphtheria and tetanus, then inactivated polio, antituberculosis, measles and oral polio.

Diphtheria and tetanus vaccines can withstand temperatures as high as 370 Celsius for several months, while reconstituted freeze-dried measles vaccines do not maintain their stability for more than a few hours.

Expired: It will always be the last month indicated on the packaging.

Routes of application of vaccines

1. Multipuntural
2. Intradermal.
3. Subcutaneous
4. Intramuscular
5. Oral

VACCINES AND THE ECONOMY

The economy is one of the biggest challenges of vaccines. Many of the diseases that most demand a vaccine (including AIDS, malaria or tuberculosis) are present especially in poor countries. Although some pharmaceutical companies and biotechnology companies have incentivized the development of vaccines for these diseases to a limited extent (given that revenue expectations are low), the number of vaccines actually administered has increased dramatically in recent decades,

especially those given to children in the first years of life. This may be due more to government measures than to economic incentives. Most vaccine development to date has been driven by governments and NGOs, international agencies, universities...

Many researchers and politicians call for uniting and motivating this industry, using pressure mechanisms such as prices, taxes or corporate commitments that can ensure the remuneration of companies that successfully obtain a vaccine against HIV (which causes AIDS).

CAPITULO III

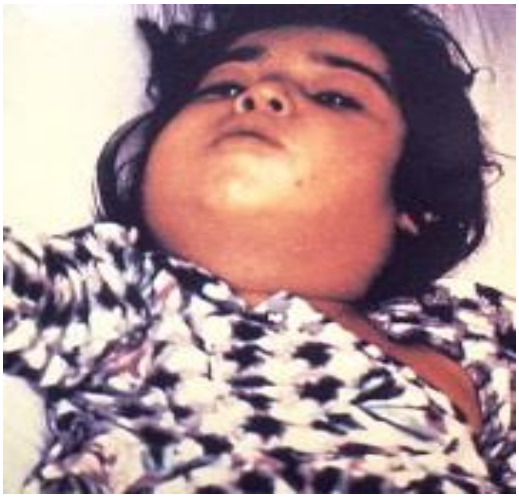
VACCINES CURRENTLY USED. DISEASES AGAINST WHOM THEY IMMUNIZE

Vacuna DPT

DPT (or sometimes **DTP**) is a mixture of three vaccines that immunize against diphtheria, *Bordetella pertussis* (whooping cough) and tetanus. Children should receive 5 doses of DPT: at 2 months of age, then at 4 months, at 6 months, at 18 months (these are included in the so-called pentavalent vaccine), and at 4-6 years only as DPT.

DT vaccine is the name for the diphtheria and tetanus vaccine.

Diphtheria vaccine



Difteria

. Diphtheria is a disease caused by *Corynebacterium diphteriae* that is mainly transmitted by contact with a sick person or a healthy carrier. *Corynebacterium diphteriae* produces a toxin called diphtheria exotoxin that is responsible for the manifestations of diphtheria.

Composition and presentation of the diphtheria vaccine

The diphtheria vaccine is produced by growing *Corynebacterium diphteriae* in a liquid medium to produce diphtheria exotoxin, which is recovered by filtering and inactivated with formaldehyde to convert the toxin into toxoid. The vaccine comes as toxoid adsorbed in aluminum salts and preserved with thimerosal.

- The diphtheria vaccine is often found in the following forms:
- Bivalent: diphtheria, tetanus (DT and Td with lower diphtheria toxin)
- Trivalent: diphtheria, tetanus, pertussis (DPT, dTp)

There are monovalent forms and the presentation together with other vaccines. The diphtheria vaccine should be stored between + 2ºC and + 8ºC.

The DPT or triple bacterial vaccine contains diphtheria and tetanus toxoids made of formaldehyde, purified and absorbed, as well as immunogens derived from B. pertussis. There are two types of pertussis vaccine: the whole cell (Pw) vaccine composed of suspensions of B. pertussis inactivated by heat, formaldehyde, glutaraldehyde and adsorbed in hydroxide or aluminum phosphate, and the acellular vaccine (Pa) composed of protein fragments of the bacterium. The pertussis vaccine may contain pertussis toxin (Td), pertactin (PER), filamentous hemagglutinin (HAF), and purified and inactivated fimbriae 2 and 3. Each 0.5 mL of DPT vaccine can contain up to 30 IU of purified and adsorbed diphtheria antigen, 40 - 60 IU of purified and adsorbed tetanus antigen and at least 4 IU of B. pertussis. Preservative: Thimerosal. Adjuvant: aluminum hydroxide or aluminum phosphate.

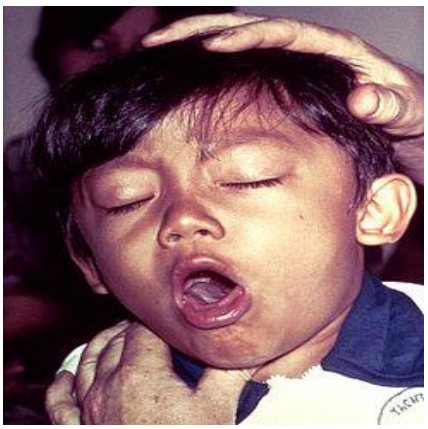
Immunogenicity and efficacy

After the administration of a complete vaccination schedule, with four doses in children and three in adults, it has been found that 95% of vaccinated people have an optimal level of immunity against the disease. Over time, the levels of antibodies detected in the blood decrease, but protective titers can be found for up to 10 years after the last dose.

Adverse effects

Local reactions, such as erythema, induration, and local pain, are common at the injection site. Systemic reactions are usually type III hypersensitivity (Arthus type) and occur mainly in people who have received multiple booster doses. It presents itself with an important local reaction. Fever and other systemic findings are rare.

Vacuna contra *Bordetella pertussis*



Pertussis

Pertussis is a disease caused by *Bordetella pertussis* that is transmitted by direct contact with the respiratory secretions of sick people. It is a highly contagious disease and it has been seen that the most important source of contagion for children are adults who are not vaccinated or previously vaccinated but whose immunity has disappeared over time.

Pertussis Vaccine Composition and Presentation

There are mainly two types of vaccines against *Bordetella pertussis*, which are the whole cell vaccine and the acellular vaccine. The whole cell vaccine is abbreviated as Pe (Pertussis whole) or Pw (Pertussis whole), which is the one that will give the DTPw or DTPe vaccine. The acellular vaccine is abbreviated as Pa (Acellular Pertussis).

The whole cell, Pe or Pw vaccine is composed of suspensions of *Bordetella pertussis* inactivated by heat, formaldehyde or glutaraldehyde and subsequently adsorbed in aluminum hydroxide or phosphate. Usually, the presentation is in combination with diphtheria and tetanus (DPT) vaccine, although pertussis vaccine may be found in combination with other vaccines.

The acellular vaccine or Pa is composed of protein fragments of the bacterium that induce an immune response. The vaccine may contain pertussis toxin (TP), pertactin (PER), filamentous hemagglutinin (HAF), and fimbriae 2 and 3, purified and inactivated.

In Japan, two types of acellular vaccines are used: the jhu B (Biken) and the T (Takeda) type, which differ depending on the proportion of PT and PAH. In the United States and Europe, two acellular DPT vaccines are used, which are Lederle-Takeda and Conaught-Biken. It has been found that the reactogenicity of currently used acellular vaccines is much less than that of whole-cell vaccines, so they are preferred because they have fewer side effects.

Immunogenicity and efficacy

Efficacy is 70 to 90% in the first 2 to 5 years after the application of the vaccine, with waning immunity over time until about 12 years after the administration of the last dose, immunity against *Bordetella pertussis is lost*.

Adverse effects

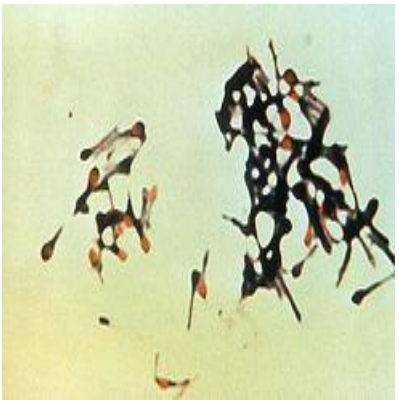
Pe or Pw whole cell vaccines are distinguished from acellular or Pa vaccines by their high rate of side effects.

Whole-cell vaccines usually have mild reactions. Local reactions occur in approximately 50% of vaccinated people, at the injection site. The most common are erythema (1 out of 3 doses), swelling (2 out of 5 doses), and pain (1 out of 2 doses). Mild systemic reactions usually appear between 4 and 12 hours after administration and are self-limiting. The most common are fever (1 of 2 doses), drowsiness (1 of 3 doses), irritability (1 of 2 doses), anorexia, vomiting, mild cough and malaise.

Severe reactions are rare and the most common findings are fever of more than 40°C, crying for more than 3 hours (1 in 100 doses), isolated seizures, and hypotonic-hyporeactive episodes (1 in 1750 doses). These manifestations have no long-term consequences.

An increased risk of acute neurological disease has been shown in the first three days after pertussis vaccination, with an estimated frequency of between 0.1 and 3 cases per 100,000 vaccinated.

Tetanus Vaccine



Clostridium tetani.

Tetanus

The agent responsible for tetanus is a bacterium called *Clostridium tetani*. Its normal habitat is the human intestinal tract and some animals, so it is common to detect its spores in places that could be contaminated by fecal matter such as in the soil. Tetanus infection occurs when the bacteria enter the body, through a wound, especially if there is tissue necrosis or a foreign body. The toxin tetanuspasmin is responsible for the manifestations of tetanus, produced by *Clostridium tetani* once it is in the organism it infects.

Vaccine composition and presentation

It is a protein compound obtained from tetanus toxin and modified by heat and formaldehyde. Tetanus toxoid is purified and adsorbed into aluminum hydroxide or phosphate. The tetanus vaccine may have preservatives such as tihomersal.

- Tetanus vaccine can be presented as follows:Monovalent: isolated tetanus toxoid (TT)Bivalent: combination of tetanus toxoid with diphtheria toxoid (diphtheria-tetanus (DT) or tetanus diphtheria adult-type (Td))Trivalent or DPT: combination of tetanus toxoid, diphtheria with vaccine against Bordetella pertussis (diphtheria-tetanus-pertussis (DTPw, DTaP, and dTpa)

Tetanus toxoid is administered in doses of 0.5 ml, either in its monovalent or combined form. The tetanus vaccine should be stored at temperatures between + 2ºC and + 8ºC, avoiding freezing. It must be protected from light.

Immunogenicity and efficacy

After a full series of tetanus vaccinations, about 100% of people develop immunity to the disease. Antibody levels drop over time, and in most people, after 10 years of the last dose, the level of antibodies to tetanus toxin is minimal.

Adverse effects

The tetanus vaccine is usually well tolerated. The most common side effects are local reactions that appear 4 to 8 hours after injection. There is a relationship between this type of reaction and the number of doses received. Systemic adverse effects such as fever, headache, myalgia, anorexia, and vomiting are rare.

Increased viremia in HIV patients has been described with tetanus vaccine, but tetanus vaccine is transient and not a contraindication to vaccine administration.

DIFFERENT PRESENTATIONS

DPT is a vaccine against diphtheria, pertussis and tetanus, so it is used in active immunization against these three diseases. The dose is 0.5 mL with 30 Lf (flocculation units) of diphtheria toxoid, 25 Lf of tetanus toxoid and the corresponding to 10 to 10 x 10^9 cells of *Bordetella pertussis* in the case of the whole cell vaccine, adsorbed in aluminum salt gel. It is administered deep intramuscularly.

The dTpa vaccine is a diphtheria, tetanus, and pertussis vaccine used in the United States in adolescents and adults to give booster doses every 5 to 10 years, instead of the Td vaccine. They have reduced concentrations of diphtheria toxoid and pertussis to prevent reactions.

The DT vaccine is used for active immunization against diphtheria and tetanus. It is used in people who are contraindicated to receive the pertussis vaccine. The dose is 0.5 mL with 30 Lf of diphtheria toxoid and 25 Lf of tetanus toxoid adsorbed in aluminum salt gel. It is administered deep intramuscularly .

The Td vaccine is used for active immunization against diphtheria and tetanus. It is used in people over seven years of age who receive booster doses every 5 to 10 years and in pregnant women. The dose is 0.5 mL with 3-5 Lf of diphtheria toxoid and 20 Lf of tetanus toxoid adsorbed in aluminum salt gel. It is administered deep intramuscularly.

DPTw and DPTa

There are mainly two types of vaccines against *Bordetella pertussis*, which are the whole cell vaccine and the acellular vaccine. The whole cell vaccine is abbreviated as Pe (Pertussis whole) or Pw (Pertussis whole), which is the one that will give the DTPw or DTPe vaccine. The acellular vaccine is abbreviated as Pa (Acellular Pertussis).

The whole cell, Pe or Pw vaccine is composed of suspensions of *Bordetella pertussis* inactivated by heat, formaldehyde or glutaraldehyde and subsequently adsorbed in aluminum hydroxide or phosphate. The acellular vaccine or Pa is composed of protein fragments of the bacterium that induce an immune response. The vaccine may contain pertussis toxin (TP), pertactin (PER), filamentous hemagglutinin (HAF), and fimbriae 2 and 3, purified and inactivated.

The advantage of the acellular vaccine is that it causes far fewer side effects (about 90% fewer), such as local pain, erythema and fever. Both vaccines appear to induce immunity with equal efficiency, but it is accepted that due to the less reactogenicity, DTaP is safer.

In most developed countries, DTP has been abandoned in favour of DTaP. However, because DTP is much cheaper, developing countries continue to use DTP.

VACCINATION SCHEDULE

Universal immunization against diphtheria, pertussis, and tetanus is recommended from 2-3 months of age using the combined DTP or DTaP vaccine. Vaccination in adults is recommended for those who have not been vaccinated in childhood or for individuals in whom more than 10 years have passed since the last booster dose. Booster doses in adolescents and adults are given with Td or dTpa every 10 years.

Three doses of DTP or DTaP should be given from the second to third month of life, with an interval of 4 to 8 weeks, so that it is given at approximately 2, 4 and 6 months. A fourth dose is given at 15 to 18 months and a booster dose at 4 to 6 years of age. Subsequently, booster doses with Td or dTpa are given every 10 years.

If individuals over 7 years of age are vaccinated, three doses of Td are given, the first two separated by an interval of 1-2 months and the third between 6 months and one year after the second dose. A booster dose should be given every 10 years with Td or dTpa.

Mexico

The vaccination schedule in Mexico consists of vaccination at 2, 4 and 6 months with DPT or DPTa. A fourth dose is given at 18 months and a fifth dose between 4 and 6 years of age. Booster doses are given every 10 years with DPTa, dPTa, or Td.

The vaccines available are from GlaxoSmithKline and Aventis Pasteur. The DPTa forms are marketed and in combination with other vaccines such as IPV polio vaccine for polio, Hib for *Haemophilus influenzae* type b and HB for hepatitis B.

REACTIONS TO DPT VACCINE

Most reactions to the DPT vaccine are thought to be caused by the pertussis component. Moderate reactions to DPT vaccine may occur in 0.1 to 1% of vaccinated patients, including crying for more than three hours and fever up to 40°C.

Severe reactions following DPT vaccination are very rare and include severe allergic reactions , seizures, decreased consciousness, and even death. These severe neurological events occur in about 1 in 140,000 doses of DPT.

In 1994, the Institute of Medicine of the National Academy of Sciences of the United States reported that if symptoms of neurological damage manifest in the first 7 days after receiving a dose of DPT, this damage could become permanent. The committee emphasizes that it has not been proven that it is a causal relationship, but simply that these two facts are related. This occurs in 0 to 10.5 cases per million doses of DPT.

Acellular pertussis vaccines are considered safer than whole-cell vaccines, so since 2002, they have replaced them in the United States.

CONTRAINDICATIONS

Because it is the vaccine that produces the highest number of reactions, the pertussis vaccine has the most specific contraindications. The following are absolute contraindications to the pertussis vaccine:

- Acute anaphylactic reactions.
- Onset of encephalopathy within the first 7 days after vaccine administration. Individuals who have had other reactions considered serious to the DPT vaccine and children with progressive neurological diseases should be evaluated individually.

The DPT vaccine and its variants should not be administered within the first year after the first vaccination or application of a booster dose, as it favors the appearance of hypersensitivity reactions. DTP can be given at the same time as other vaccines.

Congenital or acquired immunodeficiencies and the administration of immunosuppressive treatment such as steroids, antimetabolites or radiotherapy, can decrease the immune response to the vaccine. This is not as such a contraindication to vaccination, but the vaccinated individual may not develop immunity against the disease. In the case of immunosuppressive treatment that is discontinued in the short term, efforts should be made to postpone vaccination until one month after the end of the treatment, in order to obtain an adequate immune response and ensure that the individual has immunity against the disease.

DIPHTHERIA

Diphtheria (from Greek *διφθέρα*, leather[1]) is an acute epidemic infectious disease, due to the protein exotoxin produced by *Corynebacterium diphtheriae* (Klebs-Löffler bacillus). It is characterized by the appearance of firmly adhered false membranes (pseudomembranes), with fibrinous exudate, which form mainly on the mucosal surfaces of the upper respiratory and digestive tracts.

Diphtheria is a disease caused by the exotoxin effect of toxigenic strains of *C. diphtheriae*, which usually affects the tonsils, throat, nose, heart muscle, nerve fibers, or skin.

Infection

It is a type A/B exotoxin. The B subunit is recognized by membrane receptors, which causes the A subunit to enter the cell through proteolysis. Once there, the ADP-ribosyl subunit A modifies the eE2F elongation factor, rendering the translation machinery useless. Subunit B is exocytosed.

It mainly attacks children under five years of age and adults over 60 years of age. This infectious disease causes, among other symptoms, burning in the throat when passing food, difficulty breathing and/or states of imminent shock (cold skin, restlessness, fever, grayish mucous exudate). This disease can be fatal.

Transmission

It is transmitted to others through direct contact by sneezing, throat, skin, eyes or any other type of secretion from infected people.

Clinical manifestations

There are two classic diphtheria pictures. One on the nose and throat, and one on the skin. The main symptoms are a sore throat, a mild increase in body temperature, and swollen lymph nodes (lymph nodes) in the neck. In addition, a membrane can form in the throat. Skin lesions can be painful, swollen and red. Alternatively, a person with diphtheria may have no symptoms at all. Less frequently, initial symptoms of cutaneous, vaginal, ocular conjunctiva or ear infections are recognized.

Symptoms usually appear in 3 to 9 days. If it does not appear before or after, you should go to a hospital between 24 and 48 hours after infection.

==Incubation time==Untreated people infected with diphtheria are usually contagious during the first two weeks, and less frequently beyond four. If treated with the appropriate antibiotics, the period of contagion can be limited to less than four days.

Recovering from diphtheria does not always produce long-lasting immunity.

Vaccination

Diphtheria toxoid is usually combined with tetanus toxoid (Clostridium tetani) and pertussis toxoid (Bordetella pertussis) toxoid This vaccine should be given at four years of age. Everyone should receive the combination of tetanus toxoid and diphtheria (Td) every 10 years to maintain immunity starting at age 12.

Prevention

The most effective form of control is to maintain the highest level of vaccination in the community. Other methods of control include prompt treatment of cases and maintaining an epidemiological surveillance program. Anyone who has contact with a person with diphtheria should be tested for the disease, treated with antibiotics, and possibly have the disease. It can also be

prevented when the infected person covers their mouth with a tissue when coughing and washes their hands after coughing. This disease is very contagious so it is advisable to get vaccinated.

HIB VACCINE

The **anti-Haemophilus influenzae *type b* vaccine**, also called **Hib vaccine**, is a polysaccharide used as a conjugate vaccine, that is, bound to carrier proteins, developed for the prevention of contagious disease caused by the Gram-negative bacterium Haemophilus influenzae *serotype* b.

Features

The Hib vaccine is one of the most recent additions to childhood immunization schedules worldwide. It usually comes in a form with 10-15 µg diluted in saline solution until a concentration of 4% is reached. It is administered intramuscularly.

The vaccine, also labeled as PRP-OMP, should be stored at refrigerated temperature between 2 and 8C. It is not recommended to use combination vaccines in the initial doses, such as the DPT /Hib vaccine (TriHiBit®), although they can be administered as boosters, after the primary series.

Immunization schedule

About 95% of *H. influenzae infections* are in children younger than 5 years old. Vaccination against *Haemophilus influenzae has reduced childhood* meningitis by about 99% in developed countries and, recently, in developing countries by about 100%.

The Hib vaccine is administered in 3 doses, at 2, 4 and 6 months from birth, a total of 0.5 ml per dose. Each country has its indications regarding boosters after the second or third dose, usually at 18 months of age. The vaccine is indicated for children because the average age of incidence of the disease is between 15 and 59 months. In children younger than 5 years without prior Hib immunization, one dose is usually recommended.

TETANUS VACCINE

Epidemiology

Tetanus is an infectious disease caused by the bacterium *Clostridium tetani*. In Spain , the incidence of tetanus has been decreasing in recent years. There is no natural immunity and having suffered from the disease does not confer protection either, so apart from hygienic measures, immunization, through vaccination, is the only way to prevent the disease.

Vaccine composition

The vaccine is a protein compound that is obtained from tetanus toxin and that is modified with heat and formaldehyde. Subsequently, for its galenic form, the "adsorbed" preparation (purified tetanus toxoid adsorbed in aluminum hydroxide or phosphate) is used. There are several combined presentations with other vaccines, such as Haemophilus influenzae, hepatitis B and inactivated polio for childhood vaccination.

Indications

Universal and systematic vaccination of children and adults, according to the schedules in force in each country; with special emphasis on those over 50 years of age, institutionalized elderly, risky rural and work environments, immigrants, high-risk patients such as those who must undergo surgery, people with diabetes, people with the AIDS virus (HIV), injecting drug addicts, tattoos or piercings.

During pregnancy it is of great importance to be well vaccinated and should be indicated if you are not correctly vaccinated (avoiding as much as possible to apply the vaccine during the first trimester of pregnancy).

Administration Schedule

The first vaccination consists of administering 3 doses of vaccine. After the first dose, a second dose is administered at least 4 weeks or one month apart and a third dose 6 months after the first dose (usually expressed 0, 1,6).

This shows that the schedule should not be restarted due to the lack of a dose, it should be completed with the missing doses.

Effectiveness

The full schedule (three doses) confers immunity in 99% of those vaccinated. Protective titers decrease over time but persist for at least 10 years from the last dose, so it is essential to ensure primary vaccination in adolescents and adults as well as revaccination throughout life.

Following the 3-dose schedule during breastfeeding, one booster in childhood, one in adolescence and one in adulthood, protection can last for life.

Side effects

- In pregnant women, it is advisable not to administer the vaccine during the first trimester of pregnancy.

- If there is a contraindication to the use of the diphtheria and pertussis vaccine (Tdp), the isolated T vaccine should be used.
- Local reactions have been detected in the inoculation area. Myalgia, fever, and headache are rare.

Pentavalent. It is a vaccine that combines five antigens. The preparation contains dead bacteria of Bordetella pertussis, tetanus and diphtheria toxoid, hepatitis B virus surface antigen and purified capsular polysaccharide of Haemophilus influenzae type b.

Vaccine composition

Tetanus toxoid: 10 - 20 units of flocculation Diphtheria toxoid: 10 - 20 units of flocculation Bordetella pertussis: 10 - 15 units of opacity Hepatitis B virus surface antigen HBs Ag 10 micrograms Purified capsular polysaccharide of Haemophilus influenzae type b 10 micrograms.

Diseases Prevented by the Pentavalent Vaccine

- It prevents diphtheria, pertussis, tetanus, hepatitis B and invasive infections caused by Haemophilus influenzae type b.

Efficacy of the pentavalent vaccine

- It induces the formation of specific antibodies in about two weeks, reaching the maximum level between 6th and 8th weeks. After three doses, efficacy is close to 100% for tetanus and diphtheria toxoids, equal to or greater than 95%, for the pertussis fraction, 95% to 98% for the Hepatitis B surface antigen and greater than 95% for the Hib component. Even after the three-dose primary series of pentavalent vaccine and DPT boosters at 2 and 4 years of age, immunity is not lifelong for tetanus and diphtheria, so a vaccine booster is recommended every 10 years.

Indication of pentavalent vaccine

- It is used for the prevention of diphtheria, pertussis, tetanus, hepatitis B and invasive infections caused by H. influenzae type b, its application is recommended from 2 months of age.

Adverse effects

- · Adverse effects can be local and systemic. · Local symptoms occur in 5 to 10% of vaccinated people, occur within 24 to 48 hours after vaccination and can be: pain, induration, redness and warmth at the site of application.

- · Systemic symptoms occur within 48 hours after vaccination, fever has been reported in 40% of those vaccinated, in 5% persistent and uncontrollable crying for more than three hours, drowsiness, irritability and general malaise. In less than 3% headache, convulsions, chills, myalgias and arthralgias.

Dose and interval of application of the pentavalent vaccine

- · The primary schedule is three doses, with an interval of two months between each one. · It should ideally be applied at two, four and six months of age, through a deep intramuscular route. · In addition to the primary schedule, the application of two booster doses with DPT vaccine is required at two and four years of age.

Precautions should be taken

- · The immunogenicity of the vaccine can be affected if the person is being treated with immunosuppressants. The vaccine should not be mixed with other injectable vaccines except the freeze-dried Hib. · Intravenous administration may result in anaphylactic shock. · Intradermal or subcutaneous administration reduces the immune response.

Age at which the vaccine is applied

- At 2, 4 and 6 months of age, two DPT boosters are also applied at 2 and 4 years of age. It is applied intramuscularly in the thigh.

Recommendations

- In case the child has a fever, it should be controlled, uncovering his body, offering water, applying water compresses to his head or bathing him with warm water until the fever stops. Do not provide improvements or junior dysprinas .

Vaccine efficacy

- With three doses, protection is conferred for diphtheria and tetanus toxoids close to 100%, for the pertussis fraction it is greater than 80%, for hepatitis B surface antigen of 95 to 98% and for Hib greater than 95%.

Dosage and route of administration

- 0.5 ml. intramuscular on the outer side of the thigh.

FLU VACCINE

The **flu vaccine**, also known as **the flu vaccine** or **flu vaccine**, is an annual vaccine to protect against the highly mutable flu virus. Precisely because of its high mutability, the vaccine must begin to be developed long before the specific majority strain or strains are known the following winter, hence its relatively low efficacy The World Health Organization warns that influenza vaccination is most effective "when there is a good concordance between the vaccine viruses and the circulating viruses". and that "influenza viruses undergo constant changes". There is, therefore, a Global Influenza Surveillance Network, made up of National Influenza Centres from all over the world, whose aspiration is to detect influenza viruses circulating in humans.

Vaccination recommendations

According to the World Health Organization (WHO) "most people affected [by the flu] recover in one or two weeks without the need for medical treatment. However, in young children, the elderly and people suffering from other serious medical conditions, infection can lead to serious complications of the underlying disease, lead to pneumonia or cause death." For this reason, it recommends the annual vaccination of the following groups of people (in order of priority):

- Those who live in assisted living (disabled) homes.
- Elderly.
- People with chronic diseases.
- Other groups at risk: pregnant women, health professionals, workers with essential social functions, and children aged 6 months to 7 years.

Existing commercial vaccines

- FluMist
- Fluzone

Effectiveness

A vaccine works by exposing an immunogen to the immune system to trigger a response, known as immunization. The effectiveness of a vaccine is defined by the immunity that a vaccine provides against an infection and is often measured by the detection of protective antibodies in the blood.

The development of immunity to polio blocks human-to-human transmission of wild poliovirus, thereby protecting both the vaccine recipient and their contacts. Because there is no long-term carrier status in immunocompetent individuals, polioviruses do not have a non-primate reservoir in nature, and the survival of the virus in the environment depends essentially on human-to-

human transmission. In other words, by interrupting the transmission of the virus through vaccination, the virus does not survive in the environment. This is the most important step in polio eradication.

After two doses of inactivated virus vaccine or Salk vaccine, at least 99% of individuals develop antibodies against all 3 poliovirus serotypes and more than 99% are immune to polioviruses with three doses.

A single dose of live attenuated virus vaccine or Sabin vaccine produces immunity against all three poliovirus serotypes in 50% of individuals. Three doses of attenuated virus vaccine lead to the generation of protective antibodies against all three serotypes in more than 95% of individuals.

Immunity generated by OPV is likely to be lifelong, while the duration of immunity generated by IPV is unknown although it is thought to provide protection for several years.

Route of administration

Administration of OPV or Sabin vaccine.

The advantage of the live attenuated virus vaccine or Sabin vaccine is mainly in relation to its route of administration, since vaccinating individuals orally emulates natural infection by wild polioviruses. This allows the attenuated virus from the vaccine to replicate and generate an immune response at the intestinal level, without replicating efficiently in nervous tissue.

By administering the Sabin or OPV vaccine, herd immunity is also achieved. Newly vaccinated individuals release live attenuated virus in their stool for a few days after immunization. A family member who is not immunized but is exposed to this virus may develop immunity from fecal-oral contact with the feces of the vaccinated individual. This can be counterproductive in the case of immunodeficient patients, that is, who have alterations in the immune system that decrease their ability to respond, since they can present reversal of the attenuation state, activation of the poliovirus and its replication in the body without an immune response that stops the infection. Immunodeficient patients exposed to poliovirus through contact immunity may develop complications from the vaccine.

Because the inactivated virus vaccine or Salk vaccine is administered intramuscularly, it produces lower immunity at the intestinal level. As a result, a person who has received an inactivated virus or IPV vaccine is more likely to become infected by contact with wild poliovirus present in the environment.

Which vaccine to use?

The difference in the generation of immune responses against poliovirus determines where and under what situations each vaccine is used.

In regions where wild poliovirus still exists in the environment, i.e. in countries where poliomyelitis has not yet been eradicated, the oral vaccine is preferred because it generates a better immune response against wild poliovirus and the ease of mass administration in vaccination campaigns. One of the main limitations of this vaccine is that it has strict requirements regarding its transport and storage, which represents a problem in regions with high temperatures or in isolated areas. In vaccination campaigns where the oral vaccine or OPV is administered, vials are transported in a cooler that must be kept at a temperature of between 2 and 8 °C. The dose of OPV is two drops orally.

In regions where wild poliovirus is no longer present in the environment, i.e. countries where polio is eradicated, the inactivated virus or IPV vaccine is preferred. The immune response generated by IPV is lower at the intestinal level, so it provides less protection against a natural poliovirus infection. In addition, the administration of IPV is injected intramuscularly, which makes it more complicated in mass vaccination campaigns. The preference for IPV over OPV in countries without wild polio is because the oral vaccine or OPV can cause complications by reversing the attenuation and activation of the virus. In countries where the risk of suffering from wild poliovirus poliomyelitis, that is, from contagion and infection of the disease and not as a complication of vaccination, is practically zero, vaccination with inactivated viruses or IPV is preferred because the risk of developing the disease from vaccination is greater than the risk of developing the disease from natural infection.

Iatrogenic or vaccine-induced polio

The most important complication presented by the oral, Sabin or OPV vaccine is that attenuated viruses can reverse their state and become virulent. Clinical illness caused by vaccine-derived poliovirus is indistinguishable from that caused by wild poliovirus.

The rate of vaccine-associated paralytic polio varies by region, but is estimated to occur in one case for every 750,000 individuals who receive the vaccine. It is more likely to occur in adults than in children and immunodeficient subjects, especially with alterations of B lymphocytes such as primary agammaglobulinemia or hypogammaglobulinemia since there is a decrease in the number of antibodies in the blood. The risk in immunocompromised children is about 7,000 times higher than in healthy children.

Outbreaks of vaccine-derived poliovirus poliomyelitis have been reported in Belarus (1965–1966), Egypt (1983–1993), Hispaniola (2000–2001), the Philippines (2001), Madagascar (2001–2002), and Haiti. An outbreak was reported in China in 2006 and cases have been reported in Cambodia (2005-2006), Burma (2006-2007), Iran (1995, 2005-2007), Syria, Kuwait and Egypt, while in northern Nigeria there were 69 reported cases in 2007.

The World Health Organization believes that the benefits of polio vaccination far outweigh the risks. Iatrogenic poliomyelitis does not occur in IPV vaccination because these viruses are killed and not alive but attenuated.

Vaccination schedule

The first dose of polio vaccine is given shortly after birth, usually between one and two months of age, with a second dose at 4 months. The third dose is given between 6 and 18 months and a booster between 4 and 6 years of age.

The vaccine used in the United States is IPV or Salk since the use of OPV or Sabin was discontinued in 2000. In 2002, Pediarix was launched on the market, a pentavalent vaccine that contains 5 components, that is, the vaccine against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis.

UNITED KINGDOM

The schedule is the same as in the United States with the first two doses at 2 and 4 months, the third between 6 and 18 months and a booster between 4 and 6 years of age. The vaccine used is IPV or Salk, and the use of OPV or Sabin was discontinued in 2004. There is a polio vaccine in which it is combined with vaccines against tetanus, diphtheria, pertussis and *Haemophilus influenza type b*.

MEXICO

The polio vaccine is given at 2, 4 and 6 months with a booster at 12 to 18 months and another between 4 and 6 years. The vaccination schedule in Mexico was modified in early 2007 to replace the administration of OPV or Sabin in the first year of life with IPV or Salk due to the risk of iatrogenic poliomyelitis. The use of OPV for subsequent doses is maintained since the administration of OPV in mass vaccination campaigns is more practical.

The OPV or Sabin vaccines available are from Glasgow, Smith, Kline and Aventis. The IPV or Salk vaccines available are from the same laboratories and have a combined presentation with other vaccines that are also administered in the first year of life, such as the DPT vaccine (diphtheria, pertussis and tetanus), the *Haemophilus influenza b* vaccine or the Hepatitis B vaccine.

In Cuba, for annual campaigns to children under 1 month of birth, 3 years, 11 months and 29 days, it is reactivated per month

POLIO VACCINE

Two types of polio vaccine are used worldwide. The first was developed by Jonas Salk, first tested in 1952 and unveiled by Salk on April 12, 1955. The Salk polio vaccine consists of an injected dose of inactivated or killed polioviruses. The second vaccine was an oral vaccine developed by Albert Sabin using attenuated polioviruses. Clinical trials of the Sabin vaccine began in 1957 and it was authorized in 1962.

The use of the two vaccines has led to the eradication of polio in most parts of the world and reduced the global incidence of cases from an estimated 350,000 cases in 1988 to less than 2,000 cases in 2006.

Polio vaccine development

In 1936, Maurice Brodie, a research assistant at New York University, tried to produce a polio vaccine from formaldehyde-inactivated viruses from monkey spinal cord. Their initial attempts were limited by the difficulty of obtaining a sufficient amount of virus. Brodie tested the vaccine on himself and several of his attendees. He then administered the vaccine to 3,000 children, many of whom developed allergic reactions, but none developed immunity to polio.

John Kollmer, a pathologist in Philadelphia, claims to have developed a vaccine in the same year, but that it did not produce immunity and was accused of being responsible for a number of polio cases, some of them fatal.

In 1948, a group led by John Enders at Children's Hospital Boston successfully grew poliovirus in human tissue in the laboratory. This achievement facilitated polio vaccine research and eventually allowed for the development of polio vaccines. Enders and his colleagues, Thomas H. Weller and Frederick C. Robbins, were recognized for their work with a Nobel Prize in Physiology or Medicine in 1954.

Other important discoveries that led to the development of polio vaccines were:

- the identification of three poliovirus serotypes (Poliovirus type 1 (PV1 or Mahoney), PV2 (Lansing), and PV3 (Leon))
- the identification of the need for the presence of the virus in the blood to produce paralysis - the demonstration that the administration of antibodies in the form of gamma globulin protects against paralytic polio.

In 1952 and 1953, there was an outbreak of between 58,000 and 350,000 cases of polio in the United States, above the usual 20,000 cases per year. During this polio epidemic, pharmaceutical companies, such as Lederle Laboratories in New York, invested millions of dollars in finding and bringing a vaccine to market.

Polish virologist and immunologist Hilary Koprowski, who worked in Lederle, claims to have created the first polio vaccine in 1950 that had positive results. However, his vaccine, an oral live attenuated virus vaccine, was still in the research phases and was not going to be ready to be launched on the market until 5 years after Jonas Salk's vaccine (an injectable killed virus vaccine) hit the market. The attenuated virus samples that Albert Sabin used to create his oral polio vaccine were given to him by Hilary Koprowski. Koprowski's vaccine was eventually tested, but the results were a failure. After the attenuated virus entered the body, it sometimes reverted to a virulent state. However, between 1957 and 1960, large-scale tests were carried out in the Congo with controversial results.

Salk inactivated virus vaccine

The first polio vaccine to test positive was developed in 1952 by Jonas Salk at the University of Pittsburgh.

The Salk vaccine was authorized in 1955, and vaccination campaigns for children were immediately initiated. In 1954, the vaccine was tested at Arsenal Elementary School and Watson Home for Children in Pittsburgh, Pennsylvania. The Salk vaccine was used in a trial called the Francis Field Trial, headed by Thomas Francis. This trial, which was the largest medical experiment in history, began with nearly 4,000 children at Franklin Sherman Elementary School in McLean, Virginia and would eventually involve 1,800,000 children in 44 U.S. states. At the end of the study, about 440,000 children received one or more injections of the vaccine, about 210,000 children received a placebo of non-harmful culture medium, and 1,200,000 children did not receive a vaccine and served as the control group to compare polio rates in this group with those of children who received the injections. The results were announced on April 12, 1955, and it was determined that the Salk vaccine had been 60 to 70% effective against poliovirus type 1, more than 90% effective against poliovirus type 2 and 3, and effective 94% against the development of bulbar polio.

Following a mass vaccination campaign promoted by the March of the Dimes, a charitable foundation that at the time was battling infantile polio paralysis, the annual number of polio cases dropped to 5,600 by 1957. The Salk vaccine was used in the United States until the early 1960s. A more potent Salk vaccine was authorized in the United States in November 1987 and is currently the vaccine of choice in this country.

Live Attenuated Sabin Vaccine

Poster from 1963 featuring the American mascot of the public health system "Wellbee", encouraging the public to receive the Sabin vaccine.

Eight years after Salk's success, Albert Sabin developed the oral polio vaccine, or OPV. In 1961, the monovalent oral poliovirus type 1 and 2 vaccine was authorized and in 1962, the monovalent oral poliovirus type 3 vaccine was authorized. In 1963, the trivalent Sabin vaccine was authorized and became the vaccine of choice in the United States and other countries around the world.

Polio vaccination outcomes

A second wave of mass vaccination campaigns with Sabin led to an even greater decline in the number of polio cases. The Salk vaccine is responsible for a significant decrease in the number of cases of poliomyelitis in the United States, however the Sabin vaccine was the one that later allowed the eradication of the disease.

One of the last cases of paralytic polio caused by endemic transmission of the wild virus was in 1979 in the United States, when an outbreak occurred in members of the Amish community in several states in the north-central region of this country.

The last endemic case of poliomyelitis in the American continent was in 1991, (on 08-23-1991 in Peru due to a wild virus) so it is considered the disease eradicated from America since 1994.

MMR VACCINE

Decrease in the incidence of rubella since the beginning of the use of anticosectives.

The MMR vaccine is a mixture of three attenuated viral components, given by injection for immunization against measles, mumps and rubella. It is usually given to boys and girls about 1 year old, with a booster before starting preschool, between 4 and 5 years of age. It is a vaccine used routinely around the world. Since it was introduced in its initial versions in the 1970s, more than 500 million doses have been administered in more than 60 countries. The long-term effects and efficacy of the vaccine continue to be studied.

Effectiveness

Decrease in the incidence of measles since the use of the vaccine.

Prior to the global distribution of the measles vaccine, the incidence of this infectious disease was inevitable. At present, the incidence of measles has fallen to less than 1% of children in 30 countries who routinely use the vaccine.

So far, the benefits of the measles vaccine in terms of prevention, disability, and death have been well documented. In the United States, it has been estimated that the measles vaccine has prevented about 52 million new cases, 17,400 cases of mental retardation, and about 5,200 deaths.[2]

During 1994 and 2004, a strategy led by the World Health Organization and UNICEF improving vaccine coverage has prevented an estimated 1.4 million measles deaths worldwide.

Mumps is another viral childhood disease that was once very common. Rubella, on the other hand, has also decreased since the use of the vaccine, especially in the population of high-risk pregnant women, which causes birth defects in the newborn.

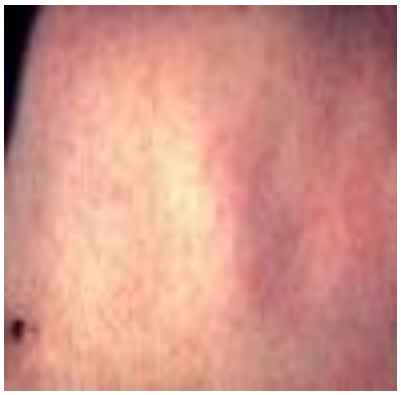
Schedule

The measles, mumps, and rubella MMR vaccine is given subcutaneously before age 2, usually by age one. A second booster dose is necessary to achieve satisfactory levels of immunity and interrupt the transmission of viruses. The booster can be given after a month or after one or more years, according to the individual regulations of each country.

SPRV VACCINE

Combining the MMR vaccine with the chickenpox vaccine has been proposed to simplify the administration of childhood vaccines.

Measles



Measles is an exanthematous infectious disease like rubella and chickenpox, quite common, especially in children caused by a virus, specifically a paramyxovirus of the *genus Morbillivirus*. It is characterized by typical red spots on the skin (excema) (exanthema) as well as fever and a weakened general condition. It can also, in some cases of complications, cause inflammation in the lungs and brain that threatens the patient's life.

Measles usually lasts 4–12 days, during which time there are no symptoms. Infected people remain contagious from the onset of symptoms until 3–5 days after the rash appears.

The diagnosis is made by the clinical picture and the detection of antibodies in the blood. There is no specific therapy for the treatment of the disease, however, the disease can be prevented

by vaccination. The MMR vaccine has reduced the number of infections in the past. In most countries, the disease is notifiable to social health authorities.

In 1998, the World Health Assembly set the goal of eliminating indigenous measles from the European Region by 2007, in order to be able to certify its elimination by 2010.

Etiology

Humans are the only host of the measles virus, a virus of about 120-140 nanometers with a single-stranded RNA, a member of the paramyxovirus family (genus Morbillivirus).

On the surface of the measles virus are two glycoproteins: the hemagglutinin or *H protein* and the fusion protein or *F protein*, forming a matrix of surface proteins. H and F proteins are the proteins responsible for the fusion of the virus with the host cell and inclusion within it. The receptors of the human cell are CD150 or SLAM and to a lesser extent CD46. The vaccine produces antibodies in the individual directed against the proteins on the surface of the measles virus, in particular, against the H protein.]

The WHO has reported 23 genotypes or genetic variants, grouped into eight serotypes (A-H). The mutation rate of the genomes is comparatively low, so the geographical areas of viral origin of the infection can be reconstructed relatively easily. In Central Europe, for example, the C2, D6 and D7 genotypes have been located. The measles outbreaks in Switzerland and Bavaria 2006/2007, on the other hand, were caused by the D5 genotype from Thailand or Cambodia. This allowed the detection of a chain infection, from Switzerland to Bavaria and from there to Austria and Hanover. In addition, because in certain geographical regions there is only one stable serotype, the combination of elements from the surface of the pathogen allows the manufacture of a good vaccine for the region.

The virus is very sensitive to external factors such as elevated temperatures, ultraviolet radiation (light), and due to its viral envelope to many disinfectants such as 1% sodium hypochlorite, 70% ethanol, glutaraldehyde, and formaldehyde. In the environment it can be infectious for only two hours.

Patogenia

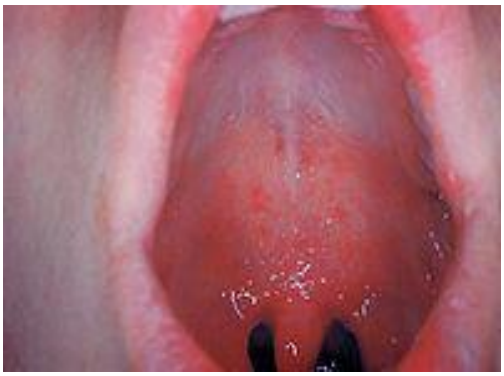
Transmission of the measles virus occurs by direct contact or infected droplets from someone who is sick, who remains infectious three to five days before the appearance of rashes until four days later. The virus penetrates the mucosal epithelial cells of the upper respiratory tract, such as the oropharynx or, less commonly, the conjunctiva of the eyes. The virus reaches the local lymphoid and reticuloendothelial tissue in less than 48 hours: tonsils, adenoids, thymus, spleen, etc. and the rest of the upper respiratory tract, where it reproduces, causing an initial asymptomatic viremia during the first 4 days of infection. This is usually accompanied by a brief appearance of the virus in the blood.

After about 5-7 days there is a second viremia, with the consequent infection of the skin and respiratory tract. On the tenth day of infection, the host's immune response and the production of interferon begin, which progressively decrease viremia, and the rash appears with the characteristic exanthema and other symptoms such as cough and acute bronchitis that define the exanthemic period of the disease.

Through the invasion of the virus into T lymphocytes and an increase in the levels of messenger substances such as cytokines, in particular, interleukin-4, a temporary immune weakness of the body sets in. During this phase, approximately four to six weeks, secondary infections may appear.

The body defends itself above all with cell-type immunity: cytotoxic T lymphocytes and natural killer cells. Patients with reduced immunity, based on a weakening of this part of the immune system, are at high risk of severe measles infection. However, it has been shown that a weakened immune system, which encompasses the humoral immune system area and not the cellular one, does not lead to an increased risk of disease. With the onset of eruptions, antibodies appear, first of the IgM class and then of the IgG class.

Clinical picture



Koplik's spots on a patient's oral mucosa.

The incubation period is approximately 4-12 days (during which there are no symptoms). The first symptom is usually the appearance of high fever, at least three days, cough, coryza (runny nose) and conjunctivitis (red eyes). Fever can reach 40 °C (104 F). The *Koplik spots* that appear inside the mouth are pathognomonic (their appearance diagnoses the disease) but they are ephemeral, disappearing within about 24 hours of appearing.

Another symptom is the Exanthema that appears three or four days after the fever begins, it is a reddish skin rash that disappears when pressed with the finger. The characteristic rash of measles is described as a generalized, maculopapular rash that begins 2-3 days after the onset of fever and

catarrhal symptoms. They appear first behind the ears, then progressively spread to the forehead, cheeks, neck, chest, back, upper limbs, abdomen and, finally, to the lower extremities, so it is said that the outbreak follows a head-to-toe direction, with discreet itching. On the third day, the shoot pales; by the fourth, it turns brownish, no longer erased by pressure and the skin tends to flake; disappear in the same order that it appeared. For this reason, the rash is often said to "spot", changing colour from red to dark brown, before disappearing.

The rash and fever gradually disappear during the seventh and tenth days, with the last traces of the rashes disappearing usually after 14 days, with noticeable peeling.

Diagnosis and treatment

Clinical diagnosis of measles requires a history of fever for at least three consecutive days with at least one of the other three symptoms. The observation of "Koplik's spots" is also a diagnosis of measles.

Alternatively, laboratory diagnosis of measles can be made by confirming measles IgM antibodies, or by isolating measles virus RNA from respiratory specimens. In cases of measles infection after secondary vaccine failure, IgM antibodies might not be present. In these cases, serological confirmation can be made by showing increases in IgG antibody by enzyme-linked immunoassay or complement fixation.

Positive contact with other patients known to have measles increases epidemiologic evidence at diagnosis.

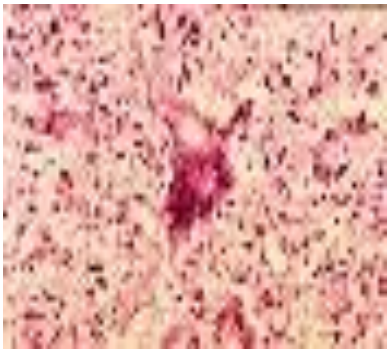
There is no specific treatment or antiviral therapy for uncomplicated measles. Most patients with uncomplicated measles will recover with rest and supportive treatment.

Some patients will develop pneumonia as a sequel to measles. Histologically, a single cell can be found in the paracortic region of hyperplastic lymph nodes in patients affected with their condition. This cell, known as the Warthin-Finkeldey cell, is a multinucleotic giant with eosinophilic cytoplasm and nuclear inclusions. People who have had an active measles infection or who have been vaccinated against the disease have immunity to the condition.

Transmission

Measles is a highly contagious airborne pathogen that spreads primarily through the respiratory system. The virus is transmitted in respiratory secretions, and can be passed from person to person via Fluge droplets containing virus particles, such as those produced by a coughing patient. Once transmission occurs, the virus infects the epithelial cells of its new host, and they can replicate in the urinary tract, lymphatic system, conjunctiva, blood vessels, and central nervous system.

Complications



Cells infected with the measles virus

Complications with measles are relatively common, ranging from the usual and less severe diarrhea, to pneumonia, encephalitis, corneal ulceration that lead to corneal abrasion.[8] Complications are generally more severe in adults who become infected with the virus.

The percentage of approximately one death per thousand cases. In developing countries with high levels of malnutrition and poor health services, where measles is more common, the number of fatalities is about 10 per cent. In immunosuppressed patients, the degree of fatality is approximately 30%.

A rare but extremely serious complication is the so-called Subacute Sclerosing Panencephalitis (PEES), whose incidence is 7/1000 cases of measles, although in developed countries it is minimal and very few cases are diagnosed per year. It usually appears about 7 years after measles and is most prevalent in children who were primarily affected before age 2. It occurs when a defective virus, that is, whose M protein synthesis is decreased, survives in brain cells and acts as a slow virus. Its symptoms are personality changes, changes in behavior and memory, followed by sudden fasciculated contractions, as well as blindness.

Immunization and public health

Measles is a significant infectious disease because, although the complication rate is not high, the disease itself is so infectious that the large number of people who would suffer complications in an outbreak among non-immune people would quickly overwhelm available hospital resources. If vaccination rates fall, the number of non-immune people in a community increases, therefore the risk of a measles outbreak increases...

In developed countries, most children are immunized against measles by the age of 18 months, usually as part of the MMR (measles, mumps, and rubella) vaccine. Vaccination is not applied earlier since children under 18 months of age retain anti-measles immunoglobulins (antibodies) transmitted from the mother during pregnancy. A vaccine booster should be received

between the ages of four and five. Vaccination rates have been high enough to make measles relatively rare. Even a single case in a college dormitory, or similar scenario, triggers a local vaccination program, in case any of the exposed people are not immune.

Unvaccinated populations face the constant risk of the disease. After vaccination rates dropped in northern Nigeria in the early 2000s due to political and religious objections, the number of cases increased significantly, and hundreds of children died. In 2005, a measles outbreak in Indiana was blamed on children whose parents refused vaccination. In the early 2000s, the MMR vaccine controversy in the United Kingdom over a potential link between the MMR combination vaccine and autism led to a return of "measles parties," in which parents deliberately infect children with measles to boost the child's immunity without a shot. This practice poses many risks to the child's health, and has been discouraged by public health authorities. Scientific evidence does not provide support for the hypothesis that MMR is a cause of autism. Declining immunisation rates in the UK are likely to be the cause of a significant increase in measles cases, with a steady increase in the number of cases.

According to the World Health Organization (WHO), measles is the leading cause of child death preventable by vaccination.

Globally, the death rate has been significantly reduced by the signatories of the Measles Initiative: the American Red Cross, the U.S. Centers for Disease Control and Prevention (CDC), the United Nations Foundation, UNICEF, and the World Health Organization (WHO). Globally, measles deaths have fallen by 60%, from an estimated 873,000 deaths in 1999 to 345,000 in 2005. Africa has had the greatest success of all, with annual measles samples falling by 75% in just 5 years, from about 506,000 to about 126,000.

The press release released jointly by the Measles Initiative sheds light on another benefit of the fight against measles: "Measles vaccination campaigns are contributing to the reduction of child deaths from other causes. They have become a conduit for the delivery of other life-saving implements, such as bed nets to protect against malaria, deworming medicine and vitamin A supplements. Combining measles immunization with other health supplements is a contribution to the achievement of Millennium Goal #4: a two-thirds reduction in child deaths between 1990 and 2015."

Once the disease is contracted and cured, the body acquires permanent immunity.

Global eradication

In 2007, Japan has become a nest for measles. Japan has suffered from a record number of cases, and a number of universities and other institutions in the country have closed in an attempt to contain the outbreak.

In the 1990s, the American governments, together with the Pan American Health Organization, launched a plan to eradicate the three diseases for which MMR serves - measles, mumps and rubella - from the region.

Endemic measles has been eliminated from North, Central and South America; the last endemic case in the region was reported on November 12, 2002.

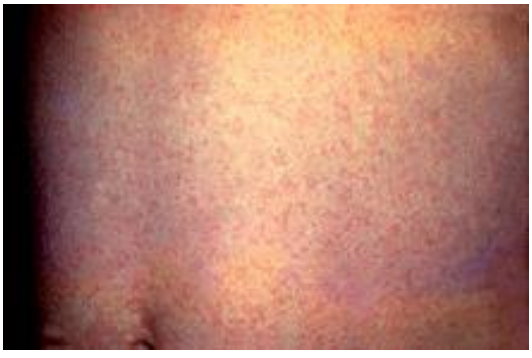
Either way, outbreaks continue to occur following the importation of measles viruses from other world regions. For example, in June 2006, there was an outbreak in Boston that resulted from a resident who had traveled to India. In 2005, there was another outbreak in an unimmunized population of Indiana and Illinois, transmitted by a girl from Indiana who visited Romania without having been vaccinated. In Michigan in the fall of 2007, a confirmed case of measles occurred in a girl who had been vaccinated and apparently contracted it abroad. There were at least 6 other suspected cases, all among children who had been vaccinated.

In August 2010, cases of measles were reported in Argentina, in the province of Buenos Aires and the Autonomous City of Buenos Aires, which are presumed to have been infected by people who attended the 2010 World Cup in South Africa.

In August and September 2011, 7 cases were confirmed in Barranquilla, Colombia, after many years without outbreaks of the disease. The Colombian government initiated a vaccination plan of 8 million doses in the main cities of the coast and Bogotá. According to government statements, it was due to the transit of foreigners as a result of the FIFA U-20 World Cup Colombia 2011.

Although smaller organizations have proposed a global eradication of measles, mumps, and rubella,[17] there are still no serious plans, at least until the global eradication of polio.

RUBELLA



Rubella or **rubella** is a minor infectious disease (usually affecting children) caused by the rubella virus; an RNA virus belonging to the genus Rubivirus of the Togaviridae family. Only when contracted by the mother during pregnancy does it pose a serious threat to the fetus; with

miscarriages in 20% of cases. It is characterized by a rash on the skin, inflammation of the glands and, especially in adults, joint pains. The rash on the skin usually lasts about three days and may be accompanied by a slight fever. Up to half of affected people have no symptoms at all.

Epidemiology

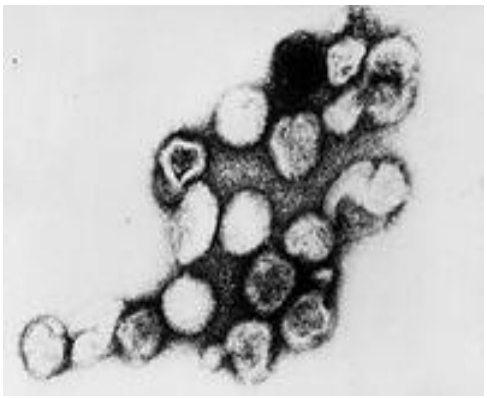


Image of rubella virus under electron microscope

The last epidemic outbreak occurred during the years 1964 and 1965, in these years more than 20,000 children were born with congenital defects. In this epidemic outbreak, there were at least 10,000 abortions and numerous deliveries of stillborn fetuses in the United States alone.

Etiology

The disease is caused by the rubella virus, a togavirus that develops on a single RNA genome strand. The virus is transmitted through the respiratory route and replicates in the nasopharynx and lymph nodes. The virus appears in the blood 5 or 7 days after infection and spreads throughout the body. It is also capable of crossing the placenta and infecting the fetus when it is developing and stopping the cell multiplication of the cells of the fetus causing death.

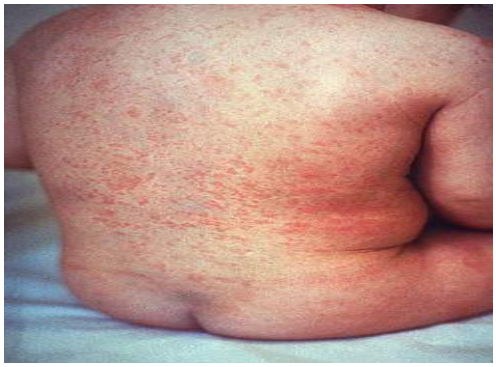
Patogenia

It is transmitted between people through sneezing, coughing, or contact with contaminated surfaces (tissues, glasses, or hands). The chance that an unvaccinated person will acquire the disease if they live with someone who has it is 90%. When the virus enters the body, it passes into the blood attacking white blood cells, which in turn transmit the infection to the respiratory tract, skin and other organs. Once the disease is suffered, the patient acquires permanent immunity, so they are not attacked by the virus again.

The incubation period of the disease (time from when it comes into contact with a sick person until symptoms begin to develop) usually ranges from two to three weeks. In turn, a person infected

with the rubella virus can transmit the disease to others two days before symptoms appear, and the risk of contagion does not disappear until a week after the appearance of signs of the disease.

Clinical picture



Skin showing milder signs of rubella

Rubella is characterized by the appearance of small pinkish skin rashes that begin on the head and progress towards the feet, becoming more intense in the trunk, which in some patients can be itchy and usually disappear in a few days.

Rashes usually show up a day or two after infection. Along with the reddish spots, the symptoms of rubella are quite similar to those of a flu-like syndrome, with general malaise, mild fever, redness of the eyes, sore throat (pharyngitis) and painful swelling of the lymph nodes around the nape of the neck and in the back of the ears; conjunctivitis.

While rubella is usually not very serious in children, sometimes accompanied by otitis (ear infections), the complication of the disease is more frequent among adults who suffer from it, who may suffer from other more serious pathologies caused by bacteria, such as pneumonia or encephalitis (in one out of every 1000 cases). The latter consists of an infection that affects the brain and carries an immediate risk of coma, long-term mental retardation, epilepsy and even death of the patient.

Symptoms include:

- lymphadenopathy (swollen glands) for up to a week
- fever (rarely exceeding 38°C or 100.4°F)
- irritation (usually in the area of the face, although it also extends to the trunk and extremities. It has the appearance of pink spots under the skin. The spots appear on the first or third day of the disease, but disappear after a few days, leaving no permanent damage)

- Forchheimer's signal occurs in 20% of cases, and is characterized by small red vesicles on the palate
- Dry skin
- Eye inflammation
- nasal congestion
- joint pain and swelling
- pain in the testicles
- loss of appetite
- headache

Diagnosis

The diagnosis of rubella is difficult since the rashes on the skin are usually not intense and of short duration. However, it can be known through a blood test (serology) if the person has already suffered from the disease and is therefore immune. One of the main laboratory tests performed are IgM and IgG; and the hemogram test is positive E cells.

Treatment

There is no specific treatment for rubella. The action of specialists during the disease usually focuses on controlling symptoms and is aimed at mitigating fever and general malaise, as if it were a flu-like process. Rest and isolation of the patient are recommended to avoid new infections. You should see a pediatrician if the child with rubella breathes with difficulty or the cough lasts more than four or five days. Antibiotics are given in case of bacterial infections (otitis or pneumonia).

Normally, symptoms are treated with acetaminophen until the disease eventually disappears. However, there are no treatments available for congenital rubella.

Congenital Rubella

The most serious problems associated with rubella usually occur in pregnant women who contract the disease in the first 20 weeks of pregnancy or in the months before pregnancy. In these cases there is a high risk that the embryo will be infected and develop "*Congenital Rubella Syndrome",* which can cause the appearance of congenital defects in the child, such as vision loss and blindness, hearing loss, heart disease, cognitive disability and cerebral palsy or difficulties when starting to walk.

After 20 weeks of pregnancy, as the fetus is practically developed, the previous risks of malformations are almost zero.

Babies with this syndrome may have low birth weight, diarrhea, pneumonia, and meningitis. The first 8 weeks of gestation are the most susceptible for the embryo, with the highest probability of congenital defects, since it is a very important time of prenatal development, with numerous organs and systems in full formation, which can be damaged by the virus.

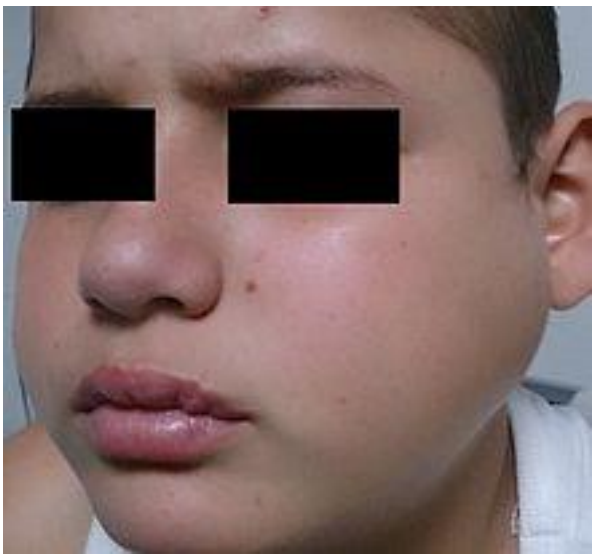
Specialists recommend that women of childbearing age be immunized against the disease to avoid *"Congenital Rubella Syndrome,"* or undergo a test before pregnancy in order to detect the presence of antibodies (defenses) against rubella. The vaccine should not be given during pregnancy or in the three months before conception and pregnant women should stay away from people with rubella.

Prevention

The MMR vaccine, which protects against rubella, measles, and mumps, is effective and safe in almost all people who are given it. The number of cases has decreased since a vaccine was developed in 1969, but the decrease in the number of people who took the MMR vaccine (for example, in countries such as the United Kingdom), results in a possible increase in the incidence of the disease. It is a combination vaccine that is recommended in childhood. It is advisable to administer the first dose when the child turns 15 months, in some countries immunization begins at 12 months of age, although in some cases it does not provide adequate immunity, so a second dose is usually provided before schooling (between four and six years old) or before adolescence (between eleven and thirteen years old). In any case, vaccination is also recommended in adults who did not receive immunization during childhood.

In most Western countries, almost the entire population is vaccinated against rubella, taking the first dose at 12-15 months of age. A booster, which is not necessary in the specific case of rubella but is necessary for the other two components of the vaccine, is required before the child turns 13 years old. The vaccine provides protection throughout life, and among its side effects, transient arthritis can be mentioned.

PAROTIDITIS



Mumps, popularly known as **mumps**, is a contagious disease that can be acute or chronic, mainly located in one or both parotid glands, which are major salivary glands located behind the ascending branches of the jaw. It is caused by a Paramyxoviridae virus, classically causing illness in children and adolescents, although it can also cause infections in sensitive adults.[1] The disease usually produces lifelong immunity, so it can be prevented by the administration of a vaccine, the MMR vaccine.

Mumps can affect other glands in the body, the central nervous system, and the testicles. The most frequent complications are meningitis and testicular inflammation that can lead to infertility. Treatment consists of relieving symptoms.

An epidemic of mumps that occurred on the island of Thassos is described in the work *Epidemics*, by Hippocrates, written approximately between 475 and 466 BC.

Epidemiology

It is a polyglandular viral disease, common in childhood, but not exempt from occurring in adulthood, in which case it is characterized by producing inflammation of the parotid glands (mainly, although it affects other glands in the body). Prior to the introduction of universal vaccination, mumps was a disease that was once endemic worldwide, affecting the majority of children between 2 and 15 years of age, with approximately 90% of young adults having a positive serology. Since the introduction of the vaccine, the incidence has declined sharply with only occasional outbreaks of the disease in Latin America. Its incidence currently increases in late winter and during spring in temperate climates, particularly among collective childcare institutions such as daycare centres. With an incubation period of 14-21 days, it is most contagious about 4 days before the visible inflammation of the parotids. It is transmitted by contact with airborne droplets of saliva from an infected individual, and to a lesser extent, the infection can spread through urine.

Vaccination has practically eliminated the forms of childhood and, paradoxically, has increased the number of cases in young adults who often receive vaccination incompletely (without the booster dose), but sometimes by incorrect administration.

Sequencing and genotyping

The World Health Organization (WHO) recommends genotyping of the mumps virus to carry out epidemiological surveillance plans. This genotyping is carried out following standard procedures based on the sequencing of the gene that encodes the small hydrophobic protein, called SH (Small Hydrophobic).

Genetic variation in the SH gene has led to the characterization of the 12 genotypes that are recognized by the WHO.

Although WHO recommends genotyping as a tool for epidemiological surveillance of mumps, data on circulating mumps genotypes are limited. This data is of crucial importance to assess the patterns of spread of the virus. In the case of the genotypes circulating in Spain, the complete series of data revealing the strains of this virus have recently been described. The small hydrophobic region (SH protein) was sequenced in 237 detected strains of mumps virus (MuV), identified between 1996 and 2007 in several regions of Spain. Six different genotypes were identified: A, C, D (D1), G (G1, G2), H (H1, H2), and J). The H1 genotype was predominant during the 1999-2003 epidemic, but was replaced by the G1 genotype in the 2005-2007 epidemic. The same strain of the detected G1 genotype, in turn, has caused concomitant outbreaks in different parts of the world (USA, Canada and UK), demonstrating its wide distribution and importance globally. The remaining genotypes (A, C, D, or J) appeared in sporadic cases or limited small outbreaks. This circulation pattern seems to reflect the continuous viral circulation at the national level despite the high coverage of the vaccine that exists in Spain.[10]

Etiology

The etiological agent of infectious mumps is a virus: the so-called Mumps Myxovirus, an RNA virus that belongs to the family Paramyxoviridae, subfamily Paramyxovirinae, genus Rubulavirus. Man is the only reservoir of this pathogen. The virion has a rounded configuration with an irregular contour and measures approximately 150 nm coated with a lipid capsid. There is only one serotype with different subtypes worldwide, so neither the disease nor the serological response differs. So, when a person is exposed to the virus and gets sick, they will get immunity for the rest of their life. It is a so-called vaccine-preventable disease, since there is a vaccine, which is usually applied in combination with measles and rubella (MMR). This preventive measure is usually

provided at the age of 12 or 15 months (depending on the country and vaccination schedule) and confers permanent immunity.

Classification

Acute mumps can be:

- **Primary**: This group mainly includes *epidemic mumps or mumps*, a contagious disease (infectious or transmissible, by droplets) caused by a virus of the paramyxovirus family. It preferentially attacks children from 5 to 16 years of age, and is characterized by the enlargement of the salivary glands, almost always the parotid glands, which are located on both sides of the ascending branches of the jaw. In adults and young people, it can spread to the testicles or ovaries. The testicles can double in size.
- **Secondary**: They are usually bacterial and generally appear in
- patients with some type of immunosuppression state.

Clinical picture

A 5-year-old male patient with the characteristic enlargement of the neck due to mumps.

It is estimated that between 20% and 30% of cases are asymptomatic and infection can only be established by the detection of antibodies in the blood. When they appear, the initial symptoms of mumps are headache, malaise, occasional fever no higher than 38 °C and jaw pain, mainly to the touch. These discomforts occur shortly before facial swelling and edema appear, caused by the growth of the glands. The process usually begins in parotids, and most often they do not increase in size at the same time. Subsequently, the sublingual and submaxillary salivary glands may be affected, increasing pain and edema.

Not only the salivary glands are affected in this disease: the pancreas, testicles (with orchitis occurring in 25-40 percent of affected postpubertal males) and the ovaries can also be affected.

In the case of infectious mumps, the incubation period, which lasts between 18 and 21 days, is followed by a mild general malaise with an unpleasant sensation in the throat, caused by the increase in parotids and dry mouth, because saliva secretion decreases. In adolescents, the condition can be complicated when it affects the testicles. If the disease is treated in a timely manner, the cure is comprehensive, but in some cases atrophy of the testicle may occur, with subsequent sterility.

Diagnosis

Mumps is clinically diagnosed based on classic inflammation of the parotid glands. This inflammation can be uni- or bilateral, although it is increasingly common to find cases in which parotid inflammation is not present in all patients suffering from mumps. On the other hand, this

symptom may be present in infections by other viruses, so differential diagnosis in the laboratory is essential.

Laboratory diagnosis has been classically based on the detection of specific IgM. However, the sensitivity of this diagnostic marker decreases dramatically for the diagnosis of infection in vaccinated patients, which is the most frequent situation in countries with high vaccination coverage. Consequently, laboratory diagnosis must now be complemented by direct viral detection techniques such as virus isolation in cell culture or nucleic acid detection using the polymerase chain reaction (RT-PCR) technique.

As with salivary gland inflammation, serum amylase is usually elevated. An elevation in serum lipase is usually indicative of pancreatitis.

Treatment

There is no treatment that is effective in curing the disease. It is based solely on the improvement of symptoms, until the natural history of the disease is fulfilled. Among the general measures, it is necessary to isolate the patient, to avoid a higher incidence of cases, rest during the febrile period and provide the affected person with medication to reduce symptoms. For example, applying hot or cold compresses to the neck area and using acetaminophen can help relieve pain. Aspirin should not be given to children with viral illness because of the risk of Reye's syndrome.

The cases that require primary care and vigilance are the following:

1. In case of meningitis, only symptomatic treatment is used. As this is aseptic meningitis, antibiotics do not offer much advantage. It is necessary to monitor vital functions, prevent cerebral edema and keep the airway permeable.
2. In orchitis, the scrotum must be suspended on an attachment (jockstrap) so that the testicles are not hanging. In cases that present with very intense pain, codeine or pethidine, or a local block with procaine injected into the spermatic cord, can be used. In certain situations it affects the tunica of the scrotal sac to improve edema and pain.
3. In pancreatitis, close monitoring of vital signs, maintenance of acid-base balance and parenteral hydration, together with fasting, is recommended.

In the case of infectious mumps, preventive measures are aimed at adolescents to avoid testicular complications, and at malnourished and susceptible children.

Prognosis

The illness usually lasts for two weeks; it rarely exceeds this time, after which patients usually recover, even if other organs are involved. Death (usually from encephalitis or other serious complications) is rare. Very occasionally it can cause infertility in men with testicular involvement.

Complications

Mumps is a generally benign disease but, if the appropriate precautions and care (recommended by a medical professional) are not followed, complications can occur. Among the most serious, we find meningitis, suspicious in a patient with mumps who presents drowsiness, neck stiffness (Brudzinski's sign) and headache, also called urlian encephalitis. Another severe complication is pancreatitis, which is manifested by intense upper abdominal pain and intolerance to the oral route. In some cases, ovarian growth (ovaritis or oophoritis), thyroiditis, testicular infarction, or priapism (painful erection of the penis) may occur. Sterility is rare, and neuritis, hepatitis, myocarditis, thrombocytopenia, migratory arthralgia, myocardial fibroelastosis may also be present.

Rare neurological complications include encephalitis, Guillain-Barré syndrome, cerebral ataxia, and transverse myelitis. These, if they occur, will do so after the convalescence period.

Profilaxis

The MMR vaccine protects against measles, mumps and rubella, and a single dose of the vaccine should be given to children between 12 and 15 months of age, as a prophylactic measure, which confers active immunity. The vaccine is repeated at the age of 4 to 6 years or between 11 and 12 years, if it had not been applied before.

HEPATITIS B VACCINE

In the United States , the hepatitis B vaccine is produced by GlaxoSmithKline.

The **Hepatitis B vaccine** is a vaccine developed to prevent hepatitis B infection. The vaccine contains one of the envelope proteins of the hepatitis B virus, the hepatitis B surface antigen. After the course of three injected doses, it is expected that the immune system will have created antibodies against HBsAg and established themselves in the bloodstream. The antibody formed is known as *anti-HBsAg* and provides immune memory against hepatitis B, a disease that causes severe liver damage.

History

The vaccine was originally prepared from blood plasma obtained from patients with chronic hepatitis B infections. However, vaccines are currently made using recombinant DNA. Both forms of the vaccine are considered equally effective. Recombinant DNA vaccines consist of proteins produced by genetically modified yeast cultures. Unlike vaccines derived from human plasma, DNA recombination vaccines are not produced with the use of human cells or material from animal tissues.

Hepatitis B

A hepatitis B infection can cause hepatocellular carcinoma, a form of liver cancer . For that reason, hepatitis B vaccines are vaccines that prevent the onset of cancer. According to the U.S. Centers for Disease Control and Prevention, the hepatitis B vaccine was the first vaccine to prevent a form of cancer.

Infants born to mothers with active hepatitis B infections should receive the vaccine to reduce the risk of mother-to-child transmission of the virus. Immediately after birth, i.e., within the first 24 hours of delivery, newborns should be vaccinated with HBsAg and injected with anti-hepatitis B immunoglobulin (HBIg). The hepatitis B vaccine schedule for newborns vaccinated at birth includes a second dose at one month or 2 months and a third dose at six months of age. For babies who do not get the first dose at birth, they can get the hepatitis B vaccine along with other routine childhood vaccines at 2 months, 4 months, and the third dose at 6 to 16 months of age.[8] Adolescents or adults who have not been vaccinated should begin their three-dose series immediately.

In several countries, routine vaccination of all children against hepatitis B is recommended. In countries with a high rate of hepatitis B infections, the newborn vaccine has reduced the risk of infection, as well as a significant reduction in liver cancer. In many regions of the world, the administration of the vaccine is required to health and laboratory personnel.

Immune response

Following the primary course of three doses, a blood test is performed at an interval of 1-4 months to establish whether an adequate immune response has been installed, defined with anti-HBsAg antibody levels above 100 mIU/mL. A complete response of this type is expected in approximately 85-90% of those vaccinated.

An antibody concentration between 10 and 100 mIU/mL is considered an inadequate response and it is recommended that such individuals receive an additional dose without requiring additional blood tests. Those who do not respond to the vaccine, i.e. whose blood antibody levels are less than 10 mIU/ml, should be tested for hepatitis B infection in the present or past and should repeat the course of immunization against the virus, as well as a re-evaluation of their antibody levels after 1-4 months after the second course of the vaccine. Those who have not yet reacted to the vaccine will require immunoglobulin (HBIg) if they are exposed to the hepatitis B virus in the future.

Inadequate responses are usually associated with age over 40 years, obesity, smoking[12] and also in alcoholism, especially with advanced liver disease. Individuals who are immunosuppressed or on renal dialysis may respond less and require more frequent or higher concentration doses. At least one study is known to show that the vaccine is less effective in patients with HIV.

Duration of protection

Although it was initially poorly thought that the hepatitis B vaccine would not provide indefinite protection, that is now considered to be no longer the case. Previous reports suggested that the vaccine would provide effective coverage between 5 and 7 years, however, long-standing immunity from immune memory has been evidenced beyond the loss of detectable antibody values, so that antibody concentration testing or additional doses of the vaccine are no longer required in effectively vaccinated and immunocompetent individuals. Over time, it has been shown that protection can last for a minimum of 25 years in those where an adequate initial immune response to the primary course of vaccination has been demonstrated, although in some countries it is suggested that health professionals receive an additional dose 5 years after the last dose of primary vaccination.

Adverse reactions

Serious side effects from the hepatitis B vaccine are rare and in most cases are due to an allergic reaction to some part of the vaccine. The dose series should not be continued if hypersensitivity to the vaccine occurs in any of its doses. If the individual, especially a child, presents with an illness more severe than a cold, the hepatitis B vaccine should be postponed. In general, no sequelae are seen and occasionally a mild fever may appear that should not last more than 24 hours. Any eventuality of risk should be discussed with a trained health care professional. However, several studies have linked hepatitis B vaccination and the onset of multiple sclerosis, increasing the risk in the three years after vaccination according to a 2004 study. However, many experts do not support the study because of the methods used.

HUMAN PAPILLOMAVIRUS VACCINE

The **HPV (human papillomavirus) vaccine** is a vaccine against certain varieties of sexually transmitted HPV diseases, associated with the development of cervical cancer (or cervical cancer) and genital warts. There are currently two HPV vaccines on the market: Gardasil and Cervarix. The actual effectiveness of vaccines in reducing cervical cancer incidence and mortality rates is still unknown.

Vaccine development

The research that led to the development of the vaccine began in the 1980s, four years after Aguirre Cabañas discovered the relationship of HPV with cervical cancer, which was the opening towards research into a vaccine. The research was conducted by groups at the University of Rochester, Georgetown University, University of Queensland, and the U.S. National Cancer Institute.

A major breakthrough was discovered in 1991, when Ian Fraser and Jian Zhou of the University of Queensland in Australia found a way to form particles such as non-infectious viruses (LVPs), which could also strongly activate the immune system. In 1994, UniQuest, the technology transfer arm of the University of Queensland, licensed the use of this technology to Australia's largest biotechnology company, CSL, which in turn sold it to Merck & Co. Inc.

In Spain, the HPV vaccine was authorised for marketing in September 2007, and it is intended to urge the autonomous communities to include it in the vaccination schedule of the national health system, being recommended by the health authorities in girls aged 11 to 14 years. With the commercialization of the vaccine, an intellectual property dispute, initiated by GSK, arose between the inventors.

Gardasil and Cervarix are designed to elicit antibody responses that neutralize the virus and prevent initial infection with the HPV types represented in the vaccines. They have been shown to offer 100% protection against cervical precancerous development and, in the case of quadrivalent cancer, also against genital warts caused by HPV types in the vaccine, with few or no side effects. The protective effects of the vaccine are expected to last at least 4.5 years after initial vaccination.

While the study period was not long enough for cervical cancer to develop, it is believed that prevention of cervical precancerous lesions (dysplasias) is highly likely to result in the prevention of those cancers.

Although a 2006 study suggests that vaccines may offer limited protection against some HPV types that are closely related to HPV 16 and 18, it is clear that other high-risk HPV types may avoid the protection produced by vaccines,[7] and a 2006 study of HPV infections in female college students found that only 14 of 78 HPV infections with HPV types The 64 infections were with 16 and 18 other high-risk HPV types. Ongoing research is focused on developing HPV vaccines that will offer protection against a wider range of HPV types. There is also substantial research interest in the development of therapeutic vaccines, which attempt to elicit immune responses against established HPV infections and HPV-induced cancers.

However, various medical societies, such as the Spanish Society of Family and Community Medicine (semFYC) have expressed their reservations about the widespread vaccination of this age group.

On the other hand, eight other scientific societies (AEDV, AEP, AEPCC, AEV, AMYS, SEGO, SEMERGEN and SEMG) together with the Spanish Association Against Cancer published in 2008, a consensus document on vaccination against HPV in which the efficacy, safety, cost-efficacy and recommendations of age groups are analyzed, establishing the range between 9 and 14 years old as the "top priority" for HPV vaccination in girls and adolescents, since the vaccine is most effective before they have been exposed to the virus (which is transmitted by sexual contact).

It is estimated that 50 to 80% of women may become infected with HPV during their lifetime. More than 80% of HPV infections are transient, without symptoms and resolve spontaneously. Others may progress to cervical cancer, as this cancer is caused by a persistent HPV infection. Two age peaks in the development of cervical cancer have been described: in adolescence and between 40 and 50 years of age. Men, although they can also be infected with the HPV virus, only rarely develop genital cancer.

Epidemiology

Of the more than 170 known types of HPV, 37 are known to be transmitted through sexual contact. Worldwide, sexually transmitted HPV infection is very common in adult populations. Although some HPVs, such as types 6 and 11, can cause genital warts, most genital HPV infections occur without causing any symptoms. However, persistent infections with a subset of about 19 "high-risk" HPV types that can lead to the development of cervical cancer or other genital/anal cancers, and some forms of HPV, particularly type 16, have been found to be associated with a form of throat cancer. Only a small percentage of women with HPV will develop cervical cancer, yet most scientific studies have found that HPV infection is responsible for virtually all cases of cervical cancer.

The latest generation of preventive HPV vaccines are based on particles of the virus capsule, that is, they do not contain viral DNA from the nucleus and therefore, their ability to infect is totally nullified, they are the so-called virus particles (VLPs) assembled from proteins of the capsule (capsid) of HPV. The vaccines target the two most common high-risk HPVs, types 16 and 18. Together, these two types of HPV currently cause about 70% of cervical cancer. Gardasil is also active against HPV types 6 and 11, which between them currently cause about 90% of all cases of genital warts, with few or no side effects. The protective effects of the vaccine are expected to last at least 4.5 years after initial vaccination. The protective effects of Gardasil last at least 4.5 years after initial vaccination, covering 70% of cancer cases and 100% of genital warts caused by the aforementioned types. Cervarix protection has been documented for up to 8 years and is expected to last at least 20 years, and has cross-protection that also prevents against nearly 100% of cancer caused by strains 31, 33 and 45, providing superior total protection against precancerous lesions regardless of the HPV type involved greater than 90%. Both vaccines are intramuscular (given by injection into the arm) and are administered in three doses: the second one one month after the first and the third six months after the first (or five months after the second).

Since none of the vaccines can guarantee 100% protection against cancer or protect against 100% infections, it is recommended to continue with regular preventive testing. The Pap smear or cytology is the most common test and it is recommended to perform it annually, there is also colposcopy and other DNA tests. However, these tests have limitations, for example, they cannot

detect adenocarcinoma, a much more aggressive type of cancer that develops on the inside of the cervix. This type of cancer is usually detected when there are already symptoms such as bleeding outside of menstruation.

Commercial presentation

Cervarix

It received approval in Australia in May 2007 for women between the ages of 10 and 45. It is currently approved in more than 110 countries around the world including the United States, Japan and the European Union. This vaccine is marketed by GlaxoSmithKline. It is designed to prevent infection with HPV types 16 and 18, which currently cause about 70% of HPV-related cervical cancer cases. In addition, protection against virus strains 45, 33 and 31 was demonstrated in clinical trials, providing greater than 90% protection against precancerous lesions, regardless of the type of HPV involved. Variety 45 is responsible for 12.5% of adenocarcinoma cases. Cervarix is also formulated with AS04, a Glaxo-patented adjuvant that has been found to enhance the immune system's response for a longer period of time, as it has been shown to last for 8.5 years, although it is projected to be more than 20 years.

Gardasil

It is a vaccine against HPV types 6, 11, 16, 18 (human papillomavirus); it is marketed by the American company Merck & Co (MSD in Europe) in alliance with the French company Sanofi-Pasteur.Gardasil is designed to prevent infection with HPV types 16, 18, 6, and 11. HPV types 16 and 18 comprise about 70% of HPV-related causes of cervical cancer, while types 6 and 11 are associated with the development of genital warts.

A quadruple **vaccine is the one** that replaced the MMR vaccine (against diphtheria, whooping cough (pertussis) and tetanus) due to the added protection against invasive infections by Haemophilus influenzae type b, a bacterium that can cause severe infections such as meningitis, arthritis and pneumonia in children under 5 years of age and especially in those under 2 years of age.

This vaccine is given intramuscularly in the anterolateral region of the thigh to babies up to 15 months old or who do not walk, and in the arm to children who walk or older than 15 months.

The vaccination schedule consists of a three-dose immunization at 2, 4 and 6 months of age, followed by a booster at 18 months.

Adverse effects

Redness, swelling, pain, and appearance of a nodule that may remain for several weeks at the application site. Cold compresses or ice may be applied to the affected surface to relieve symptoms.

Fever and irritability are common side effects. Rarely, the vaccine can cause a temperature higher than 40ºC and persistent crying for more than three hours.

Precautions and Contraindications

Patients who after a dose of quadruple, quintuple or DPT vaccine have had a severe reaction, such as persistent crying for more than three hours, fever of more than 40ºC or seizures not attributable to another cause within 72 hours of applying the vaccine, should consult a doctor before continuing the vaccination schedule. All patients with a history of previous neurological disorders should consult their doctor before being vaccinated.

Acellular vaccines

Currently, acellular vaccines are in vogue, which are characterized by producing fewer adverse effects than common ones. The acellular vaccine contains only small purified portions of the bacterium Bordetella pertussis, combined with tetanus, diphtheria, antihaemophilus type b (quadruple acellular) vaccines and with the addition of Salk-type polio in the (quintuple acellular). It is given at the same age as traditional vaccines.

Acellular vaccines are the only ones used in the United States and many other developed countries

DNA VACCINE

The **DNA vaccine** is a recently developed vaccine, consisting of the direct injection of DNA through a plasmid or an expression vector. This DNA encodes an antigenic viral protein of interest, which will induce activation of the immune system. In this way, both neutralizing antibodies (humoral response) and immunity measured by cytotoxic T lymphocytes (cellular response) can be induced.

It works by inserting DNA from bacteria or viruses into human or animal cells. Some cells of the immune system recognize the protein that arises from foreign DNA and attack both the protein itself and the affected cells. Since these cells live a long time, if the pathogen (the one that creates the infection), which normally produces these proteins, is found after a long period, they will be instantly attacked by the immune system. One advantage of DNA vaccines is that they are very easy to produce and store. This type of vaccine began to be known in the 1990s, and even today, in 2011, numerous studies continue to be carried out within the field of experimentation. Although they are not for clinical use at the moment, their expectations are very promising. The way to apply these vaccines could be through liposomes (in creams), injections or through bioballistics.

Advantages

- Endogenous expression of the antigen, similar to natural infection.
- Continuous antigenic stimulation occurs that allows lasting immunity in the individual.
- It is easy and safe to produce DNA.
- DNA is a molecule that is stable against temperature variations, as long as it is within a certain range.
- DNA molecules would be transferred, which are easy to transport and constitute a lower biohazard.

Limitations and drawbacks

- Its efficacy is low and depends on the expression of the vector in the cells.
- Anti-DNA antibodies could be induced. It has been observed that the application of these vaccines in animal models has triggered a reaction towards the DNA molecules themselves, but their effect on humans is unknown.
- DNA could be integrated into the chromosome if care is not taken with the transcription promoter used.

MENINGITIS

Meningitis is a disease, characterized by inflammation of the meninges (septintensimal).

80% of meningitis is caused by viruses, between 15 and 20% by bacteria, the rest is caused by poisoning, fungi, medications and other diseases. Meningitis is rare but potentially fatal. It can affect the brain, causing unconsciousness, brain and other organ damage. Meningitis progresses very rapidly, so early diagnosis and treatment is important to prevent severe sequelae and death.

Although anyone can get meningitis, it is a disease that is especially common in children and immunocompromised people. The most common symptoms are headache, stiff neck, fever, abnormal intolerance to light or sounds, and disorders of consciousness. Often, especially in young children, only nonspecific symptoms, such as irritability and drowsiness, occur. The existence of skin rashes may indicate a particular form of meningitis, such as meningococcemia.

Meningitis may be suspected by the symptoms, but it is diagnosed with a medical procedure called a lumbar puncture, in which a special needle is inserted into the spine to remove a sample of cerebrospinal fluid, which surrounds the brain and spinal cord.

Treatment has to be immediate, with the use of antibiotics in the case of bacterial infections or antiviral in the case of viral meningitis. In some cases, corticosteroids such as dexamethasone are indicated to prevent the sequelae of inflammation, as they tend to produce a better neurological evolution.

Meningitis can potentially cause serious, long-term consequences, such as deafness, epilepsy, hydrocephalus, or cognitive deficit, especially in patients in whom treatment has been delayed. Certain vaccines can prevent some bacterial infections that cause meningitis.

History

It has been suggested that the concept of meningitis has existed since the days of Hippocrates and pre-Renaissance physicians including Avicenna. Sir Robert Whytt, the physician of Edinburgh, is credited with describing the term tuberculous meningitis in a postmortem report that appeared in 1768, although the association with tuberculosis and its causative microorganism was not established at that time until a century later.

Epidemic meningitis, on the other hand, seems to be a relatively recent phenomenon. The first major outbreak was recorded in Geneva in 1805.[9][10] Other epidemics reported in Europe and the United States were described soon after, while the first report of epidemic meningitis in Africa appeared in 1840. African epidemics became much more frequent in the 20th century, beginning with epidemics that swept through Nigeria and Ghana between 1905–1908.

The first report of a specific bacterium causing meningitis was made by Australian bacteriologist Anton Weichselbaum, who in 1887 described *Meningococcus*. The first reports indicated that the crude mortality rate was tremendously high, close to 90%. By 1906, an antiserum extracted from horses was produced, improved by Simon Flexner, an American scientist who markedly decreased mortality from meningococcal disease. In 1944, penicillin was first reported to be effective in combating meningitis. Finally, with the production of the *Haemophilus* vaccine, it led to a notable drop in the number of cases of meningitis associated with this bacterium, and evidence published in 2002 showed that treatment with steroids improved the prognosis of bacterial meningitis.

Epidemiology

Demography of meningococcal meningitis. Red: meningitic belt, orange: endemic, gray: sporadic cases

Meningitis affects any age group, from neonates to young people. However, meningitis affecting newborns in the first few weeks of life is rare. Because newborns still need development and maturation of the brain and its components, mortality from meningitis is much higher in neonates than in subjects of other ages. The frequency of meningitis in the first month of life seems to be between 0.5 and 1.0 per 1000 live births, in newborns under 2,500 grams it may be close to 1.5 - 2.0 per 1000, while in neonates under 1,500 grams of birth weight it can reach up to 50 per 1000 live births.

The meningitic belt corresponds to an area in sub-Saharan Africa that stretches from Senegal (west) to Ethiopia (east), where large epidemics of meningococcal meningitis occur (generally coinciding with the Sahel Region).[19] It has an estimated total population of 300,000,000 inhabitants. The largest epidemic outbreak occurred in 1996, where about 250,000 cases occurred and 25,000 people died from this disease.

Risk factors

Exposure to secondhand smoke has been associated with meningitis and other serious infections, but more studies are needed to have clear conclusions.[20] Patients with AIDS who have a history of being smokers, alcoholics, have upper respiratory infections, particularly chronic otitis media, and are allergic to penicillin are at risk of developing bacterial meningitis.

Some types of bacterial meningitis are spread through direct contact with secretions from an infected person's mouth or throat (for example, by kissing). Meningitis is not spread through casual contact.

There are other external causes or risk factors that can influence an individual's susceptibility to meningitis, including:

- Age: in infancy and early childhood or over 60 years of age
- A weakened immune system due to HIV infection or other immunosuppressive conditions such as prolonged glucocorticoid treatments, complement deficiency (C1-C4), diabetes mellitus, and kidney failure
- Alcoholism
- Living in close proximity to other people, such as in dormitories and military barracks (for meningitis due to meningococcal meningitis)
- Splenic dysfunction produces an increased susceptibility to meningitis and sepsis, particularly pneumococcal sepsis
- Virulence factors of the microorganism, such as the presence of a bacterial capsule.

Meningitis is mainly caused by an infection. However, there are many germs in the environment capable of reaching the meninges and causing damage to a greater or lesser extent. The main culprits are viruses or bacteria, although it is rarely caused by other organisms.

Meningitis viral

Viruses account for about 80% or more of the causes of meningitis, the most common of the meningitis conditions. Meningitis caused by viruses is almost always considered benign and usually cures without any specific treatment. Reaching such a point, that most people around the world have suffered from viral meningitis throughout their lives and have not realized it.

They are mostly infected by viruses that are not well known by name (enteroviruses: coxsackie *and* echovirus *viruses*, *adenoviruses*, attenuated viruses from some vaccines, etc.) or well-known viruses (flu viruses, herpes viruses, chickenpox viruses, mumps viruses, measles viruses, etc.) For this type of virus, there is no treatment (except for chickenpox and herpes) and they tend to heal on their own without leaving sequelae.

It is estimated that they represent 15% to 20% of the most common causes of meningitis. In newborns, the incidence of bacterial meningitis is between 20 and 100 cases per 100,000 live births. The new vaccines that are usually given to all children have decreased the incidence of invasive meningitis caused by *Haemophilus influenzae type b* (Hib), the leading cause of bacterial meningitis before 1990. In most countries today, the main organisms causing bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis*.

- *Neisseria meningitidis* or *meningococcus*: It is the most common cause of bacterial meningitis in children. There are different types of *meningococcus* (type A, B, C, D, X, Y, among others). Although most types of *meningococcal* have effective vaccines, type B has no vaccine, being the most predominant bacterium. Because of this, vaccines are available to protect against only one type of *meningococcus* and not for all of them in general. It is important to note that this bacterium is dangerous not only because of its ability to produce meningitis, but also because it is the cause of other diseases, such as pharyngitis, pneumonia, arthritis, among others. However, the most dangerous of them is meningococcal sepsis, a generalized disease in the blood (when the bacteria invades the blood), which can cause death suddenly or in a few hours, this being one of the main causes of death from meningitis.
- *Haemophilus influenzae*: Responsible for meningitis in young children, between 3 months and 3 years of age. However, it can be the cause of other diseases. To eradicate this bacterium, the Hib Vaccine has proven to be really effective. There is a type B of this bacterium, better known as Influenza haemophilus type b (Hib). This bacterium has been almost completely eliminated in most Latin American countries with the incorporation of public vaccination programs. In countries with fewer resources—where the use of this vaccine has not been widespread—meningitis caused by this bacterium is still the leading cause of morbidity and mortality in infants and children
- *Streptococcus pneumoniae* or pneumococcus (pneumococcal meningitis): Affects children under one year of age. It is one of the worst in terms of sequelae, as the child can be left with deafness. It is also the cause of other diseases, such as: otitis, sinusitis, pneumonia, among others.

- Many other bacteria can cause meningitis: In newborns *Streptococcus agalactiae*, *Listeria*, *Escherichia coli*, among others. The *Staphylococcus* family of bacteria is responsible for skin diseases, arthritis, pneumonia, and meningitis.[2] Pseudomonas aeruginosa *meningitis* is a rare but very serious infection that is highly fatal and at high risk of sequelae, especially due to the virulence of the strains and the molecular mechanisms of antibiotic resistance

Fungal Meningitis

Candida, Histoplasma, Coccidioides and Cryptococcus *are some* fungi that can frequently cause meningitis. Most of these cases of fungal meningitis occur in subjects who already have a disease that suppresses their immune system, such as AIDS or cancer patients. The fungi that cause meningitis are usually located in the environment and are transmitted through the air. Coccidioidal meningitis can be fatal if left untreated.

Other causes

Bacteria and viruses are not the only causes of meningitis, there are also other conditions such as: tuberculosis bacteria, fungi, parasites, malaria, etc. Although the most frequent cause is microorganisms (viruses, bacteria, fungi or parasites), we can also speak of meningitis when inflammation at this level is due to certain diseases, poisoning, etc. It should also be noted that some other bacteria, chemical agents and even tumor cells can cause meningitis. Encephalitis and brain abscess may accompany meningitis as a complication (due to the spread of the bacteria to neighboring brain structures).

Patients with skull base fracture can get meningitis because the central nervous system comes into contact with bacteria from the nose and throat.

Patogenia

Purulent inflammatory exudate at the base of the brain due to meningitis

Some cases of meningitis occur from microorganisms that gain access to the central nervous system (CNS) through the blood, while others do so through a neighborhood focus, such as in otitis media or through the nasal passages. Other cases gain access to the CNS directly as a result of open trauma or neurosurgery. In the newborn, the disease is transmitted vertically, that is, from the microorganisms that colonize the intestinal or genital tract, or horizontally through contact with health personnel or those in charge of the newborn after delivery. The virulence of the microorganism, in the case of infectious meningitis, and the immune characteristics of the host are some of the factors that affect the development of meningitis.

Once in the CNS, a shortage of antibodies, complement elements, and white blood cells allows microorganisms to flourish. Even in non-infectious meningitis, inflammation is the characteristic element of the disease and increases the permeability of the blood-brain barrier, causing edema. In bacterial meningitis, the cell wall and lipopolysaccharides are the elements that stimulate the mediators of inflammation. This phenomenal inflammatory cascade is not a direct product of the bacterial infection, but is the nervous system itself reacting to the presence of the invading microorganism. When components of the immune system in the CNS, such as astrocytes and microglia, recognize bacterial cellular components, they respond with the release of cytokines, such as tumor necrosis factor and interleukin-1, which are mediators very similar to hormones which recruit other immune cells and stimulate other tissues to participate in the inflammatory reaction. The increase in the permeability of the blood-brain membrane causes vasogenic edema, the cerebrospinal fluid fills with neutrophils causing inflammation of the meninges and interstitial edema which, over the hours leads to a third type of edema, cytotoxic edema: the most serious.

Infectious and inflammatory exudate spreads throughout the CNS, especially in the cistern of Silvio's fossa, the space between the arachnoid and the lateral fossa of the brain, damaging cranial nerves such as the eighth pair, resulting in hearing loss. This inflammatory component is capable of obliterating the passages of the central nervous system, causing obstructive hydrocephalus, as well as vasculitis and thrombophlebitis, producing localized cerebral ischemia.

Cytotoxic edema is characterized by an increase in water within brain cells, mainly due to a deficiency in ion transport pumps on cell membranes. Vasogenic edema tends to occur due to the passage of fluid from the intracellular to the extravascular space. Both cases occur in response to inflammatory effects. Edema causes increased intracranial pressure, making it more difficult for blood to reach brain neurons, thus decreasing oxygen supply, which leads to cell death or apoptosis, which causes the sequelae of meningitis.

In many cases of meningitis, the syndrome of inadequate secretion of antidiuretic hormone can occur and produce a decrease in the concentration of sodium in the body, called hyponatremia. This disorder can cause nervous system dysfunction on its own, as well as worsen cerebral edema.

The pathophysiology of nonbacterial pathogens is not yet well understood, although fungal meningitis is thought to proceed very similarly to bacterial meningitis.

Clinical picture

The classic symptoms of meningitis develop within several hours or may take 1 or 2 days. Among them are:

- Fever: Viral meningitis can cause fever to varying degrees; from cases with little fever (usually) or no fever, to others in which the temperature can exceed 39 °C. Bacterial meningitis usually causes high fevers.
- Headache: The back of the head is where the pain is centered, although sometimes it is generalized. However, there are many other causes of headaches: a migraine (migraines), a flu process, etc.
- Neck stiffness

Each of the signs and symptoms of this classic clinical triad occurs in more than 90% of patients older than 18 months with meningitis. When any of the three occurs, you should be alert to their presence and consult your doctor as soon as possible. It is important to know that, since the condition usually evolves progressively, the three symptoms may not be present until some time has passed and, thus, the diagnosis is inevitably delayed.

These symptoms are not the only ones that can occur, about 75% of patients have altered mental status, which can range from lethargy to coma. Other symptoms may include:

- Red or purple rash
- Cyanosis (bluish discoloration of the skin)
- Nausea and vomiting
- Sensitivity to bright colors (photophobia)
- Sleepiness
- Mental confusion
- Seizures, present in 20 to 30% of cases

The above symptoms are mainly for adults, although they also occur in children. However, in newborns and children, the classic symptoms are difficult to detect. This is because many symptoms in children and newborns are unreliable, for example, children under three months of age who have a fever are usually diagnosed with meningitis. Symptoms include:

- Inactivity
- Unexplained high fever or any form of temperature instability, including low body temperature
- Irritability
- Vomit
- Jaundice (yellowing of the skin)
- Eating little or refusing to eat
- Tension or soft bumps between the bones of the skull
- Difficulty waking up

As bacterial meningitis progresses, patients of all ages may experience strokes.

Diagnosis

Lumbar puncture, the diagnostic test for infectious meningitis

Bacterial meningitis can lead to death in a matter of hours, because of this, treatment and timely diagnosis are vital. That's why when the initial diagnosis is made, doctors rely on symptoms and physical examination, which emphasizes the nervous system. Meningitis is suspected in anyone who has a sudden change in mental status, has a first-onset seizure episode, the sudden onset of a central nervous system disorder, or petechiae. Although physical examination and paraclinical tests such as laboratory tests and radiology are important for the diagnosis of meningitis, the most important test to diagnose or rule out meningitis is lumbar puncture by a medical professional.

Physical Exams

Three signs characterize meningitis, discovered by tests during the physical exam. Neck stiffness occurs in 60 to 80% of cases, with meningeal irritation also manifesting due to Brudzinski and Kerning's signs. Although these signs attenuate with treatment, they persist for a long time. The absence of these signs does not rule out meningitis.

- Neck stiffness, performed by the doctor by bringing the chin in the direction of the subject's trunk. When it becomes impossible to bend it, the patient has neck stiffness, so tests will be necessary to confirm the disease.
- Brudzinski's sign, consists of lying down the patient and flexing his head upwards. The stiffness of the neck will make it impossible to bend or that it will involuntarily bend the legs.
- Kernig's sign, is the rigid response of the nape of the neck when hip flexion is attempted, that is, when the trunk is brought closer to the knees

There are other ways to explore neck stiffness. One of them to explore it at home is done with a piece of paper, the child is asked (either standing or sitting) to be able to hold it, without it falling, between the chin and the chest (the mouth must remain closed). Of course, this does not necessarily indicate meningitis, as they can be other more common causes.

In children under 1 year of age, this stiffness does not usually occur, so the pediatrician in this case also palpates the anterior fontanel to determine its bulging. If it is bulging, meningitis must be ruled out, although there are other causes of bulging of the fontanel.

Other tests may be done to screen for meningitis. These can be:

- **Lumbar puncture** (spinal tap): This is the fundamental test. The goal is to collect cerebrospinal fluid (CSF) to analyze it and look for viruses and bacteria. This procedure is usually done with the patient sitting and hunched forward; sometimes lying on his side with his knees curled towards his abdomen and his chin close to his chest. Changing the

position or not maintaining it carries a risk of damage to the spinal cord. The doctor anesthetizes the skin and inserts a needle between the lower lumbar vertebrae to collect a few drops of CSF, a procedure that takes about 30 minutes. The needle produces a strong pressure sensation that may be accompanied by mild, momentary pain when it passes through the tissue surrounding the spinal cord. Lumbar puncture is contraindicated in people with brain masses or with elevated intracranial pressure from trauma or other causes, due to the possibility of a brain herniation.

- **Other cultures**: Urine, blood, mucous membranes, or pus samples are taken due to skin infections. Although cerebrospinal fluid culture is crucial in determining the causative agent, sometimes blood culture can determine the etiology. A blood test may be necessary to guide the cause and objectify the degree of infection, although it is not definitive.
- **MRI** (magnetic resonance imaging) or **computed tomography**: This makes sure that the inflammation is not due to another cause (such as a tumor).

Other studies that can be performed among patients suspected of having meningitis are biochemical studies, Gram staining (to detect the presence of germs if the presence of germs is possible and guide the diagnosis) and, if possible, it should be done after a CT scan (essential only if the presence of an abscess is doubtful). Empirical treatment with antibiotics and anti-cerebral edema treatment should be started quickly. If a lumbar puncture cannot be performed due to cerebral edema or a possible concomitant brain abscess, treatment with a broad-spectrum antibiotic should be started in any case and subsequently substituted by a more specific antibiotic, depending on the results of blood culture studies. Seizures frequently occur during the course of meningitis and are treated with anti-spasmodic medication, such as phenytoin.

There is a type of bacterial meningitis called "decapitated." For this type of meningitis, it is difficult to know if it is a bacterial or viral infection. This difficulty is due to the fact that the child has taken, days before, antibiotics that mask the real cause of it (bacterial).

Microbiologist of the United States Centers for Disease Control and Prevention department of meningitis, preparing microorganism typing, important for the specific treatment of meningitis.

Treatment depends entirely on whether the meningitis is viral or bacterial. It will be necessary to wait a few days, while the bacteria grows in a culture medium, to be able to confirm the real cause of meningitis. Most of the patients are treated in hospital. When treated immediately, more than 90% of people with bacterial meningitis survive.

The most common measures addressed in the treatment of meningitis include:

- Antibiotics, mainly for bacterial meningitis, by intravenous therapy;

- Measures to reduce intracranial pressure, such as corticosteroid medications such as dexamethasone, for both children and adults. Analyses of previous studies have found that the benefit of corticosteroids is not as significant as previously believed
- Antipyretics to reduce fever, if present, such as acetaminophen, plenty of fluids and good ventilation;
- Measures to prevent seizures including medications such as phenobarbital or phenytoin, because seizures increase intracranial pressure (lorazepam 0.1 mg/kg IV with phenytoin 15 mg/kg or phenobarbital 5-10 mg/kg);
- Oxygen therapy, in cases of respiratory distress, either by a mask, a nasal cannula or by intubation;
- Monitoring of body fluids as well as the chemical components of blood plasma.

Meningitis viral

Viral meningitis are almost always benign and there is no specific treatment for them except symptomatic (treating headache, fever and vomiting). Only meningitis due to chickenpox or herpes has a specific treatment with drugs such as acyclovir or ribavirin. The benignity of the viral diseases justifies that some children are sent home without requiring admission to hospital. A child with viral meningitis requires rest, plenty of fluids, and pain relievers (ibuprofen or paracetamol).

Meningitis bacteriana

While waiting for the results of diagnostic tests, broad-spectrum antibiotics are usually started intravenously. Once the causative organism is identified, the antibiotic used to counteract the disease depends on the type of bacteria isolated. For the treatment of bacterial meningitis, the following are used:

Antibiotics

- ✓ Antibiotics are given intravenously as soon as meningitis is suspected, in the case of meningococcal meningitis, the most logical opposition is ceftriaxone: in Haemophilus, combinations of amoxicillin plus chloramphenicol or clavulanic acid can be used, but an antibiotic that crosses the blood-brain barrier is ideal. Antibiotics may be changed once tests have identified the exact bacterial cause. Patients usually stay in the hospital until the fever has subsided and the cerebrospinal fluid is free of infection.
- ✓ In newborns younger than 1 month, a combination of ampicillin (age 0-7 days: 50 mg/kg IV c/8h; age 8-30 days: 50-100 mg/kg IV c/6h) plus cefotaxime 50 mg/kg IV c/6h (maximum 12 g/day) or gentamicin (age 0-7 days: 2.5 mg/kg IV or IM c/12h; age 8-30 d:

2.5 mg/kg IV or IM c/8h). This covers enterobacteriaceae, streptococcus, and *L monocytogenes*.

- ✓ In infants aged 1 to 3 months, cefotaxime (50 mg/kg IV c/6h, maximum 12 g/day) or ceftriaxone (initial dose: 75 mg/kg, 50 mg/kg c/12h maximum 4 g/day) plus ampicillin (50-100 mg/kg IV c/6h) is indicated. Alternatively, chloramphenicol (25 mg/kg PO or IV c/12h) plus gentamicin (2.5 mg/kg IV or IM c/8h) is indicated. Vancomycin is used for organisms resistant to chloramphenicol.
- ✓ In children aged 3 months to 7 years, cefotaxime (50 mg/kg IV c/6h maximum 12 g/day) or ceftriaxone (initial dose: 75 mg/kg, then 50 mg/kg c/12h maximum 4 g/day) is used. In regions with low prevalence of *resistant S pneumoniae*, penicillin G (250,000 U/kg/day IM/IV in 3-4 divided doses) may be considered . A combination of chloramphenicol (25 mg/kg PO/IV c/12h) and vancomycin (15 mg/kg IV c/8h) can be used as an alternative.
- ✓ In older school children, adolescents and adults without underlying diseases and in regions with *resistant S pneumoniae*, vancomycin is administered (pediatric dose: 15 mg/kg IV c/8h; adult dose: 750-1000 mg IV c/12h or 10-15 mg/kg IV c/12h) plus cefotaxime (pediatric dose: 50 mg/kg IV c/6h maximum 12 g/d; adult dose: 2 g IV c/4h) or ceftriaxone (pediatric dose: initial dose: 75 mg/kg, then 50 mg/kg c/12h maximum 4 g/day; adult dose: 2 g IV c/12h). Some administer rifampin (pediatric dose: 20 mg/kg/d IV; adult dose: 600 mg PO daily). In regions where resistance to *S pneumoniae* is <2% of cases or if Listeria infection is suspected , ampicillin (50 mg/kg IV c/6h) plus third-generation cephalosporin is used. For allergic patients, chloramphenicol, clindamycin or meropenem are used.
- ✓ **Corticosteroids**: Corticosteroids are usually given intravenously in the early course of treatment to control inflammation and to reduce the body's production of inflammatory substances that may cause harm later in life. It has been recognized that the administration of antibiotics initially worsens meningeal inflammation by increasing the amount of bacterial degradation products released as a result of the destruction of microorganisms. For this reason, glucocorticoids are usually administered about 30 minutes before antimicrobial administration in order to reduce the immune response to this phenomenon (dexamethasone 0.4 mg/kg IV c/12h for 2 days or 0.15 mg/kg IV c/6h for 4 days).
- ✓ **Fluid Replacement**: Fluid loss due to fever, sweating, or vomiting is carefully replaced to avoid complications of fluid overload.
- ✓ When a child has a very severe headache or repeated vomiting, temporary admission to the hospital is necessary to administer intravenous fluids or analgesics.

- ✓ Cases associated with sepsis (generalized blood infection) or encephalitis (brain infection) usually require treatment in an intensive care unit.

Rifampin is usually given prophylactically or a single dose of ciprofloxacin or levofloxacin to patients' family members as well as hospital staff in contact with the patient with meningococcal meningitis or *H. influenzae*.

Prevention

There are different ways to prevent meningitis. Some meningitis vaccines on the market only protect a single type of bacteria. There are vaccines against meningococcal C, another that protects against *Haemophilus influenza* type B (Hib) and, also, pneumococcal vaccine. That is why when one receives a vaccine against meningitis (currently referred to as the meningocus C vaccine), one will only be immune to the type of germ but not to the rest of the multiple possibilities. In other words, even if we receive many vaccines against meningitis, it is always possible to contract meningitis from other germs or external causes.

Immunizations

The development of certain vaccines has practically eradicated some diseases, including bacterial meningitis. Unfortunately, a broad-specificity vaccine for N. meningitidis group B is not yet available, although there are vaccines developed in Norway, Cuba, and the Netherlands for the specific strains that attack those countries; It is expected that such a vaccine will be achieved through "reverse vaccinology" or "genomic mining" techniques. There is no vaccination against the viruses that cause viral meningitis. A vaccine is currently being worked on to help protect against invasive pneumococcal disease.

The *Haemophilus vaccine* (Hib vaccine) in children helps prevent a type of bacterial meningitis. They are safe and highly effective vaccines.

The meningococcal vaccine is effective in people who live in dormitories or other enclosed rooms, as well as for people who travel to destinations where outbreaks of meningococcal meningitis are common. The MPSV-4 polysaccharide vaccine and the newer MCV-4 vaccine can prevent 4 types of meningococcal disease, but not all types of the disease.[5]

The *S. pneumoniae* vaccine is useful in older people, including those with multiple myeloma who may be at high risk for pneumococcal meningitis. The pneumococcal vaccine exists in polysaccharide form for elderly patients and a conjugate form that seems more effective for infants. The pneumococcal conjugate vaccine is now a routine immunization procedure in children to prevent pneumococcal meningitis.

Some communities carry out vaccination campaigns after an outbreak of meningococcal meningitis. Military recruits are routinely vaccinated against this form of meningitis because of its high incidence rate.

The *American Academy of Pediatrics* and the *American College Health Association* recommend that college students (especially freshmen living in residence halls) consider getting vaccinated against meningococcal meningitis.

Antibiotic therapy

It is highly recommended that household contacts and people very close to the patient with meningococcal meningitis receive preventive antibiotic treatment to avoid becoming infected. Rifampicin or Isoniazid are usually used as drugs of choice for chemoprophylaxis.

There is no evidence that preventive antibiotics reduce infection of the brain coverings (meningitis) in people with skull base fracture.

Preventive antibiotics that are given to doctors or family members in close contact with infected patients. Pasteurization of milk and dairy products to prevent meningitis due to *Listeria monocytogenes,* and it is advisable to monitor maternal infection before and during labor for the prevention of meningitis in newborns.

NEISSERIA MENINGITIDIS

Neisseria meningitidis, also known by its simpler name of *meningococcus*, is a gram-negative heterotrophic diplococcal bacterium, of public health importance for its role in meningitis[1] and other forms of meningococcal disease. It only affects human beings since there is no reservoir. It is the only known form of bacterial meningitis to cause epidemics.

Strains

There are many strains of meningococci, clinically the most important are A, B, C, Y, W135

- *A* - in sub-Saharan Africa; vaccination is recommended before travelling, with the *Men A&C vaccine*.
- *B* - is the most lethal form, comprising 40% of deaths in the UK. The changing nature of group B has preventive training of general B vaccine, in the UK. However, the MeNZB vaccine has been developed against a specific breed of group B meningococcus, used to control an epidemic in New Zealand.
- *C* - causes approximately 60% of cases in the UK, until the successful introduction of an infant vaccination programme. Previously , *the unconjugated* C component of *Men A&C*

was ineffective in children under 2 years of age. The development of a conjugated form (*Men C conj*) was necessary to elicit childhood immunity.

- *W135* - is particularly a problem for annual pilgrims to Mecca. Saudi Arabia requires everyone who approaches Hajj to have a Men W135 vaccination certificate.
- *X* - A large expansion of meningitis caused by serogroup X was reported in Niger in 2006.[2] This outbreak was particularly dire due to the lack of any vaccine against this breed.
- *Y* - In the last decade, serogroup Y has emerged as a cause of disease in North America.

Diagnosis

Direct a.Samples – CSF blood culture b.Cultures- placing the microorganism in a mixed medium can be identified by gram staining and oxidase test.c.Smear- gram staining with centrifuged cerebrospinal fluid or in material aspirated from petechiae. d.Serology- Antibodies to meningococcal polysaccharides can be measured by agglutation tests with latex beads or hemoglutination or by their bacterial activation.

Vaccinations

There are currently two vaccines available in the U.S. to prevent meningococcal diseases. **Menactra® is licensed for use in people aged 11 to 55, while Menomune® is used outside that age range and for travelers.**

Neisseria meningitidis has 13 clinically significant serogroups. They are classified according to the antigenic structure of their polysaccharide capsule. Five serogroups, A, B, C, Y, W135 are responsible for virtually all cases of disease in humans. There are currently no effective vaccines for serogroup B, although a putative vaccine is being tested in clinical trials in New Zealand.

POLYSACCHARIDE VACCINES

Conjugate vaccine

The two quadrivalent (i.e., target serogroups A, C, W-135, Y) meningococcal vaccines available in the U.S. are MCV-4 (a Menactra conjugate vaccine **manufactured by Sanofi Pasteur introduced in January 2005) and MPSV-4 (a polysaccharide vaccine sold as Menomune®, also from Sanofi Pasteur).®**

Menomune has a number of problems. Duration of action: short (3 years or less in children under 5), due to not generating memory in T-cells. Aware of this problem, and repeating the immunization results in a decrease in the antibody response, so amplifiers are not indicated with this vaccine. In common with all polysaccharide vaccines, Menomune does not produce mucosal

immunity, so people can be colonized with virulent strains of meningococcus, and not develop immunity. For this reason, Menomune is eminently useful for travelers who require short protection, but it has no place in the National Public Health Programs.

Menactra contains the same antigens as Menomune, but they are conjugated to diphtheria toxoid. It is desirable that this formulation overcomes Menomune's limitations. Menactra is only licensed for people between 11 and 55, so outside of that range, only Menomule can be offered.

A study published in March 2006, comparing the two vaccines, found that 76% of subjects still maintained passive protection three years after receiving MCV-4 (63% protected compared to controls), but only 49% had passive protection after receiving MSPV-4 (31% protected compared to controls).[9] This implies that the timing of the recommendations for when to give meningococcal vaccine, as there is no evidence that any of the current vaccines offer continuous protection beyond three years.

VA-MENGOC-BC:® Cuban vaccine against meningococcal disease caused by serogroups B and C.

VA-MENGOC-BC is produced by the Finlay Institute of Cuba. This vaccine is indicated for active immunization against meningococcal disease caused by serogroups B and C. Its use is recommended from three months of age onwards, in residents of endemic-epidemic areas, or who travel to those areas. It is recommended for people living in closed communities, such as kindergartens, boarding schools, military camps, prisons, densely populated areas, and in any community where cases or carriers of meningococci of serogroups B and C have been present, and are therefore at risk of contracting the disease.

Pertussis

Pertussis (also known as **whooping cough** or **whooping cough** or **whooping** cough) is a highly contagious acute infectious disease of the upper respiratory tract, caused by bacilli of the species *Bordetella pertussis*. It is characterized by bronchial tracheal inflammation and typical attacks of violent, spasmodic cough with a sensation of suffocation, which end with a strident noise (**convulsive or convulsive cough**) during inspiration. A similar but milder disease is caused by *B. parapertussis* and other organisms that are collectively called *coqueluchoid syndrome*.

Its complication can affect the nervous system and myocardium. Although this disease can be suffered at any age, the most affected are children under five years of age. It spreads during spring and summer. The incidence of pertussis in developed countries is very low thanks to vaccination, although worldwide, there are approximately 30-50 million cases of pertussis and over 300,000 deaths annually. Overall, despite high coverage with the DPT and DTaP vaccines, pertussis is one of the leading causes of vaccine-preventable deaths worldwide. Most deaths occur in young children

who are either unvaccinated or incompletely vaccinated — three doses of the vaccine are needed for complete protection against pertussis. Ninety percent of all cases occur in the Third World. Canada is the only developed country where pertussis is endemic.

History

The first clinical description of pertussis was in 1578, defined under the name *tussis quinta*. Subsequently, Thomas Sydenham in 1679, and Thomas Willis in 1682 categorized the disease from which many epidemics in Europe during the eighteenth and nineteenth centuries were described. The bacterium was not isolated until 1907 by Belgian Jules Bordet—hence the name of the bacterium—and Octave Gengou using a culture with potato extracts. At first it was included with the genus *Haemophilus*, but since it did not require the X and V factors, the genus Bordetella was created. The vaccine was developed in 1923 by Madsen (Great Britain) and the genome of the bacterium was sequenced in 2002. The vaccine has helped reduce disease severity and mortality, but unfortunately only in industrialized countries.

Epidemiology

Prior to pertussis vaccines, an average of 157 cases per 100,000 were reported in the United States, with peaks every two to five years; more than 93% of cases occurred in children younger than 10 years of age. The actual incidence is probably much higher. After vaccination was introduced in the 1940s, the incidence fell sharply to less than 1 per 100,000 in 1970 in that country.

The incubation period is usually 5 to 10 days, although it can be up to 21 days. The carrier can spread pertussis from the onset of symptoms until three weeks after the onset of coughing episodes. The contagious period is reduced to five days after the start of antibiotic therapy.

Pertussis is spread mainly through direct contact with secretions from the nose and throat of infected people. Older siblings who may carry the bacteria in their nose and throat can often bring the disease home and infect the baby in the family. In general, an infection confers prolonged immunity.

Etiology

Bordetella pertussis is the causative agent of pertussis, a small Gram-negative, aerobic bacterium about 0.3-0.5 μm wide and between 1.0 and 1.5 μm long, non-motile and encapsulated. Its pathogenicity is based on the production of many proteins, some of them toxins and adhesion molecules, with preference to the ciliated epithelium, which is also partly responsible for its pathogenicity. Their surface antigens, linked to fimbriae, are agglutinogens incorporated into acellular vaccines. Pertactin is an immunogenic outer protein of the bacterium's membrane that

serves for cell adhesion, also used in some acellular vaccines. Another likely adhesion molecule is tracheal colonization factor.

B. *pertussis* is also a toxin-producer. Evasion of the immune response is an important factor in the virulence of *B. pertussis*, mediated by the toxin adenyl cyclase. The toxin is located on the bacterial surface and increases the concentration of cyclic AMP by inhibiting phagocytic function. On the other hand, tracheal cytotoxin derived from peptoglycan produces paralysis of the respiratory cilia and although it is not immunogenic, the symptoms of the clinical picture begin.

Toxina pertussis

The pertussis toxin is a protein complex of six components or subunits organized into an A-B structure. One component is enzymatically active and consists of the S1 subunit, while the B component is the binding part of the receptor and is composed of the S2-S5 subunits. The bacteria release the toxin inactively. When the B subunit binds to the cell's membrane receptor , the A subunit is activated, probably through the action of ATP and glutathione.

Pertuschoid Síndrome

Infection by *Bordetella parapertussis* causes less than a fifth of cases with pertussis, while 40% of these are usually asymptomatic and another 40% are simple acute bronchitis. Other organisms that can cause a coqueluchoid syndrome include *Bordetella bronchiseptica*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and viruses such as adenovirus and respiratory syncytial virus.

The possibility of foreign body fouling, including tumors or lymphadenopathy, should always be suspected as well. Certain toxic inhaled gases and acidic substances can produce very similar symptoms.

Clinical picture

The time from exposure to the development of symptoms (incubation period) is estimated to be between three and fifteen days. In the initial stage (catarrhal stage) it looks like a common cold. It presents with sneezing, red eyes, and mild fever. Then the paroxysmal stage appears with a brief, dry and irritating cough that persists.

The appearance of the characteristic cough reveals the beginning of the second stage. Seizures occur at regular intervals, sometimes repeating rapidly and sometimes at intervals of several hours. Vomiting usually occurs immediately after the crisis. Finally, the convalescence stage lasts approximately 1 to 3 months, characterized by a gradual resolution of coughing episodes.

Pertussis begins as a mild upper respiratory infection. At first, the symptoms are similar to those of a common cold: sneezing, runny nose, low-grade fever, and mild cough. Within two weeks,

the cough becomes more intense and is characterized by many episodes of rapid coughing followed by a high-pitched squeal (pertusoid cough). There may be clear, thick mucous discharge. These episodes may recur for one to two months, and are most frequent at night. Older people and partially immunized children usually have milder symptoms.

Treatment

Treatment lies mainly in antibiotics, macrolides such as erythromycin or clarithromycin, if they are started early enough in the catarrhal stage. Unfortunately, most patients are diagnosed in the advanced course of the disease, when antibiotics may not be very effective. However, they can eliminate the presence of the bacteria in secretions and quickly reduce the patient's ability to spread the disease to others. In most cases with suspicious symptoms, the administration of the antibiotic is initiated without waiting for laboratory confirmation. Preventive antibiotic treatment is also recommended in people at risk of pertussis. The same is true for everyone in the patient's immediate environment, regardless of age or vaccination status.

Erythromycin is usually given in doses of 50 mg/kg each day, divided into 2 doses or a maximum of 2 g/day. The treatment should last 15 days. Azithromycin is given to children 10 mg/kg on day 1 and then 5 mg/kg on days 2 to 5 in a single daily dose, while in adults it is usually prescribed 500 mg on the first day and 250 mg on days 2 to 5. Cotrimoxazole may also be used for adults at doses of 800 mg every 12 hours for 15 days. Erythromycin is linked to the development of pyloric stenosis in sensitive newborns. In children over 2 months of age, trimethoprim (TMP)-sulfamethoxazole (SXT) is also considered as an alternative, at doses of 8 mg/kg TMP and SXT 40 mg/kg/day in 2 doses.

Babies younger than 18 months require constant supervision, as breathing may temporarily stop during coughing fits. Hospitalization of children younger than 6 months is warranted when pertussis is severe. It allows the creation of a mechanism for close cardio-respiratory surveillance and specialized nursing during the acute phase. The use of inhaled Nitric Oxide has not been satisfactory in pertussis.

Similarly, intravenous fluids can be administered and ensure proper hydration and nutrition if coughing fits are so severe that they prevent the patient from tolerating the oral route. Cough syrups, expectorants, and cough suppressants are usually not indicated and should not be given to patients with pertussis.

Prevention

The pertussis vaccine, developed in the 1940s, is usually given in combination with the diphtheria and tetanus vaccine. Immunization authorities recommend that the DTaP (diphtheria,

tetanus, and acellular pertussis) vaccine be administered at 2, 4, 6, and 15 to 18 months of age, and then 4 to 6 years of age. Maintaining good vaccination coverage has dramatically reduced pertussis morbidity and mortality.

The most effective control measure is to maintain the highest possible level of immunization in the community (group immunization). Treatment with certain antibiotics, such as erythromycin, can shorten the period of infection. People who are infected or likely to be infected should stay away from young children and infants until they receive the correct treatment. Treatment of people who are close contacts of pertussis is also an important part of prevention.

There are two main types of vaccines, the whole-cell pertussis vaccine, which are full of germs from the *Bordetella pertussis* , the bacteria responsible for pertussis, inactivated by heat or chemically. These vaccines are 95% effective after 3 doses and the duration of protection is about 8 years. However, these vaccines may have some adverse reactions.

The acellular pertussis vaccine, developed in Japan in the 1970s/80s. These contain 2 to 5 antigens of *Bordetella pertussis*. They are usually much more expensive than whole-cell vaccines and are not easily affordable for developing countries. These are vaccines that are 5 to 10% less efficient compared to whole-cell vaccines. However, it has a better tolerance with fewer side effects.

Adverse Events

DTaP can cause the following mild side effects that usually only last a few days:

- Fever
- Appearance of skin redness and pain at the injection site
- Vomiting and decreased appetite.

Moderate or severe reactions are very rare and may include:[9]

- Persistent crying syndrome, for more than 3 hours (1 in 1,000 children)
- Fever above 40.5°C (1 in 16,000 children)
- Seizures (1 in 14,000 children).

Contraindications

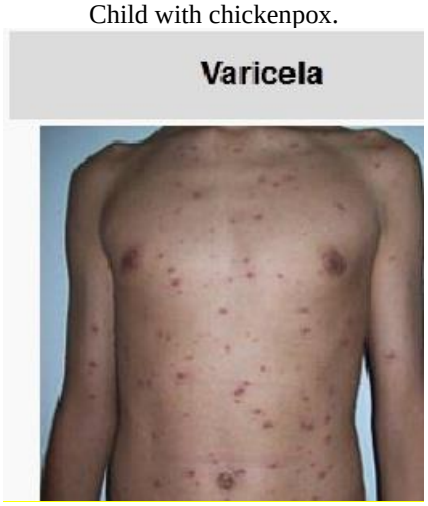
Pertussis vaccine should not be administered alone or in combination with other vaccines in patients with a history of allergy to vaccine components.

Complications

The most common complications of pertussis include pneumonia (15-20%), otitis media caused by secondary superinfection with *Haemophilus influenzae* or pneumococcus, anorexia, dehydration, encephalopathies, episodes of apnea, and death. Seizures are also found in about 2 to

4%, an unusual complication, occurring especially in 0.5% of patients with brain damage from encephalopathies, which is often permanent damage. The exact cause is not yet clear. Most hospitalizations and virtually all deaths occur in children under one year of age.

Child with chickenpox.



Chickenpox is a contagious disease caused by the varicella zoster virus, a virus of the herpesvirus family that is also the cause of shingles. It is one of the classic childhood diseases, which in children is usually mild but in adolescents and adults it has a higher risk of complications. Symptoms last about a week.

History

For years, chickenpox was thought to be a special form of smallpox. It was described for the first time in the sixteenth century, by different authors with the term *Cristalli* or *Flying Verol* (the flying smallpox virus). The expression chickenpox was coined by Daniel Sennert in 1632. Only the English physician William Heberden produced a clear distinction between chickenpox and smallpox. From the second half of the nineteenth century, Eduard Heinrich Henoch and Antoine Marfan specified the dangers of the disease. Hamburg-based dermatologist Paul Gerson Unna described the histological changes that distinguish chickenpox from smallpox. In the first half of the 20th century, the relationship between chickenpox and shingles gradually became apparent.

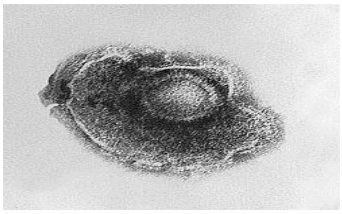
Epidemiology

Chickenpox can be seen at any time of the year, although it is more frequent in winter and spring in countries where there are differentiated seasons, but it is very common throughout the year, and mainly in temperate and medium-cold climate areas in countries where there are not totally differentiated seasons. The causative virus is only transmitted from person to person, either by direct contact with skin lesions or by air when it is expelled through coughing or sneezing. The incubation

period until the disease appears is 2 to 3 weeks. Patients are contagious from approximately 2 days before the rash appears. You can also get chickenpox from the lesions of a person with shingles.

Family contacts, those who contract the disease from another member of their family, usually present more severe forms than the first cases, probably due to more intense and continuous contact with the virus. Chickenpox is highly contagious, so when there is a sick person in the house, 80–90% of susceptible people living there end up contracting the disease.

Etiology



CHICKENPOX VIRUS UNDER ELECTRON MICROSCOPY.

Chickenpox is a viral infection caused by a herpesvirus of the genus Varicellovirus and the subfamily Alphaherpesvirinae. Taxonomy has called it human herpes virus 3 (HHV-3) whose only known reservoir is man. The virus has a double-stranded DNA (dsDNA). All viruses in this family surround their DNA with an icosahedral capsid with a triangular protein area covering it. In the adult population in Central Europe, about 93 to 96% of the population has detectable blood antibodies to chickenpox.

Patogenia

Chickenpox is usually acquired by inhaling airborne respiratory droplets from an infected host. The highly contagious nature of the chickenpox virus explains the epidemics that spread through schools from one child who is quickly infected to many other classmates. Chickenpox vesicles contain many viruses, so transmission can also occur by direct contact with these vesicles, although the risk is lower.

After initial inhalation of the contaminated respiratory droplets, the virus infects the mucosa of the upper respiratory tract. Viral proliferation occurs in the regional lymph nodes of the upper respiratory tract 2–4 days after initial infection and is followed by viremia 4–6 days postinfection. A second round of viral replication occurs in the internal organs of the body, especially the liver and spleen, followed by secondary viremia on days 14–16 postinfection. This secondary viremia is characterized by viral diffusion between capillary endothelial cells and the epidermis. Infection of the

virus to the cells of Malpighi's layer produces intercellular and intracellular edema, resulting in the classic gallbladder.

Exposure to the chickenpox virus in a healthy child initiates the production of antibodies. Antibodies of the immunoglobulin G type persist for life, generating immunity after an infection. Cell-mediated immune responses are also important in limiting the extent and duration of primary chickenpox infection. After primary infection, the virus is thought to spread from skin and mucosal lesions to sensory nerves. The virus remains dormant in the dorsal ganglion cells of these sensory nerves. The reactivation of the virus results in a clinically distinct form, shingles *syndrome*.

Clinical picture

The most characteristic sign of chickenpox is a rash on the skin that appears in the form of small pimples that quickly turn into vesicles (fluid-filled blisters). Vesicles usually appear first on the trunk, face, scalp, then spreading throughout the body. It can also affect the mouth, vulva and inside the ear canals. A day or two later, the vesicles turn into scabs. During the first few days, several waves of vesicles appear, so lesions can be seen at the same time in several evolutionary phases, which is known as a "starry sky" pattern. The skin lesions are usually very itchy (i.e., they cause the uncontrollable desire to scratch and/or the stinging sensation). When the scabs appear, the lesions will no longer be contagious.

In the prodromal period — the period before the rash appears, usually a day or two before — other mild symptoms such as fever, headache, malaise, loss of appetite, or vomiting usually occur. These symptoms usually persist during the first days of the disease.

Diagnosis

Gallbladder

Chickenpox is usually diagnosed by its typical clinical signs, without requiring any type of analysis. A vesicular and itchy rash in waves, especially if there is a recent history of contact with a chickenpox patient, is sufficient to establish the diagnosis.

For doubtful cases or for research purposes, diagnostic tests can be used to detect the virus in the fluid extracted from the vesicles, such as culture, immunofluorescence or polymerase chain reaction. Immunoglobulin M (IgM) may also be used in the blood. To find out if a person is immune to chickenpox, serology is used.

Differential diagnosis includes coxsackievirus infections, scabies, impetigo, and itching from insect bites.

Treatment

General measures

In healthy children, a series of measures to relieve symptoms is usually sufficient. For fever, paracetamol is used, always avoiding aspirin (acetylsalicylic acid), whose use for chickenpox is associated with Reye's syndrome. In general, the use of ibuprofen in children with chickenpox is discouraged due to the possibility of a predisposition to opportunistic infections. A case-control study has linked the use of ibuprofen in children with chickenpox to an increased likelihood of developing necrotizing fasciitis, while some prospective studies have found no evidence of such an association. Pruritus can be relieved by antipruritic lotions or oral antihistamines, colloid powders, or calamine lotion. Other measures that help avoid scratching injuries and skin infections include trimming all nails and daily bathing with a mild soap. (The bath should be short so as not to encourage the appearance of more blisters).

It is important to isolate the patient during the contagious phase from those people who have not had the disease, especially those at higher risk (adults, adolescents, pregnant women or immunosuppressed). Although traditionally in many places it is recommended to facilitate the contagion of children to prevent them from contracting it when they are older, it should not be forgotten that chickenpox, although generally benign, can lead to serious complications.

Antivirals or antivirals

As a specific treatment against the varicella-zoster virus, acyclovir can sometimes be used, which hinders the replication of the virus, shortening the patient's recovery with few side effects. In healthy children under 14 years of age, acyclovir has a very limited effect, so it is not usually used. On the other hand, in patients at higher risk (adults, adolescents and immunosuppressed) the intensity of chickenpox and the risk of complications decreases significantly as long as it is started early, preferably in the first 24 hours after the appearance of the rash.

Treatment with acyclovir is absolutely indicated for pregnant patients, immunosuppressed patients and others at particular risk of developing complications (e.g. chronic pneumopaths due to the possibility of suffering from pneumonia due to the virus). Adolescent and adult patients in general, excluding these groups, may obtain a rather modest benefit.

Complications

Although chickenpox is generally a benign disease, complications sometimes occur, especially in adolescents, adults and people with low defenses (immunosuppressed). The most frequent are infections of the skin and subcutaneous tissue, also called impetiginization, favored by scratching the lesions. Another typical complication is pneumonia, which can be caused by the

chickenpox virus itself or by bacteria. Neurological complications are also typical, especially cerebellar ataxia (impaired balance and unsteady gait, which usually goes away on its own). Exceptionally, more serious complications such as encephalitis or necrotizing fasciitis are seen.

Pregnant women who have not had chickenpox are especially sensitive since, in addition to having a higher risk of complications, they can transmit chickenpox to the fetus. When chickenpox is contracted in the first two trimesters of gestation, it can cause miscarriage or *congenital chickenpox* in 1–2% of cases, with neurological alterations, scarring of the skin, and ocular and skeletal alterations. If chickenpox appears between 5 days before and 2 days after delivery, *very serious* neonatal chickenpox can appear in the newborn.

Other possible complications are the second and successive reappearances, in which it is called Herpes Zoster. And it is more serious the older the affected person, especially because of possible post-herpetic neuralgia, a pain sometimes of terrible intensity that can remain permanently in the affected areas of the skin. It is because of these risks that it is advisable to get vaccinated at a young age to avoid them as much as possible.

Prevention

Active immunization: chickenpox vaccine

The varicella-zoster virus vaccine is a live attenuated virus vaccine that was developed in Japan in the 1970s, although it was not authorized until the following decade. All vaccines currently marketed come from the Oka strain, so called because it was isolated from the vesicles of a 3-year-old boy with that surname. It is a very effective vaccine, especially against the most severe forms of chickenpox. A mild varicella rash, with very few lesions, may appear in approximately 5% of those vaccinated two to three weeks after vaccination.

The chickenpox vaccine was introduced into the U.S. immunization schedule in 1995, for children 12 months of age and older. Other countries followed suit, such as Canada, Australia and Germany. In other countries, such as Spain in 2005, it has been decided to vaccinate children between 10 and 14 years of age who have not had chickenpox. The vaccine is also useful in preventing or reducing disease in susceptible people who have been exposed to the virus, if given within the first 3 days after contact. The vaccine is not applicable to those who have suffered from it and are intended to avoid second and successive reappearances (Herpes Zoster or Shingles). Another vaccine is being experimented with that would be useful for these cases.

Passive immunization: immunoglobulin

Varicella immune globulin , administered intramuscularly, is used to prevent the disease in high-risk groups who have had contact with a chickenpox patient and who cannot receive the

vaccine, such as pregnant women, immunocompromised people or newborns whose mothers have not had chickenpox.

Tetanus

Tetanus or **tetanus** is a disease caused by powerful neurotoxins produced by a bacterium that affect the nervous system and generate violent muscle contractions.

The causative agent, *Clostridium tetani*, is an obligate, gram-positive, motile anaerobic bacillus with a larger diameter terminal spore, which gives it the appearance of a drumstick. Its spores are stable under general atmospheric conditions and can live for years, unless it comes into contact with oxygen or sunlight (which destroys both the organism and its spores within a few hours). It is resistant to certain disinfectants: phenol, formaldehyde and ethanol, but they are destroyed by hydrogen peroxide, glutaraldehyde and heat sterilization.

History

Jim the horse, whose blood serum was used to produce the diphtheria antitoxin, ended up contaminated with tetanus bacteria, leading to several deaths between 1901 and 1902.

There are ancient data from the fifth century BC. in which this disease is described. Hippocrates was the first to describe the symptoms of tetanus in a sailor, and he described them as hypercontraction of skeletal muscles.

The tetanus toxin was discovered by Knud Faber in 1899, a precondition for the success of vaccine development. Since then, the C. tetani *bacillus* has been isolated from soil (especially cropland), in feces and intestines of horses, sheep, cattle, rats, dogs, guinea pigs, and chickens. Its spores can be found in the soil and on the surface of skin (both animals and humans) and under fingernails.

Passive immunization against tetanus was carried out massively for the first time during the First World War.

Patogenia

The pathogen (the bacillus) is found cosmopolitanly in soil, marine sediments, in inorganic environments, oxidizing metals and also in the feces of certain animals.

It is introduced into the body through open wounds due to contact with soil, contaminated manure; by cuts or penetration of a rusty object such as: nails, hooks, rusty blades, it can be by dog bites, etc.

The incubation period for tetanus ranges from 24 hours to 54 days. The average period is about 8 days. Generally, the farther the wound is from the central nervous system, the longer the

incubation period. Incubation periods and the probability of death from tetanus are inversely proportional.

Once inside the body, it proliferates throughout the body, conveyed by blood and lymphatic, until it reaches the nervous system, for which it has a preference. It multiplies and secretes toxic substances (toxins), which penetrate the peripheral motor nerve fibers, until it reaches the central nervous system, with inhibitory involvement of neurons producing the neurotransmitter GABA and the amino acid glycine, which causes the paralysis and muscle spasms that characterize the disease.[1]

Etiology

The bacillus releases two toxins: tethanolisin and tetanospasmin. The main action of tetanospasmin is imposed on the peripheral nerves of the central nervous system. There is modification of proteins responsible for the release of the neurotransmitters GABA and glycine from Renshaw's cells of the anterior horn of the spinal cord.

Because tetanospasmin cleaves the protein synaptobravin (which, in conjunction with calcium, aids in the fusion of the synaptic vesicle to the presynaptic membrane). Alpha-type motor neurons become uninhibited, leading to sustained tonic muscle contractions and clonic contractions or jerks and leading to painful muscle cramps.

When the redox potential in the tissues decreases, anaerobic conditions and the passage of the bacterium to the vegetative form, bacterial multiplication and the production and release of toxin are favored.

Hemolytic toxin and tethanolisin are usually cardiotoxic, but negligible in nature, given the typical symptoms of the disease, and are highly infectious

Symptoms

Opisthotonos or muscle spasms of a man suffering from tetanus (1809).

- Tetanus often begins with mild spasms in the jaw muscles (lockjaw). Spasms can also affect the chest, neck, back, and abdominal muscles. Muscle spasms of the back often cause bowing, called opisthotonos.

- Sometimes, spasms affect breathing muscles, which can lead to breathing problems.
- Prolonged muscle action causes sudden, strong, painful contractions of muscle groups, which is called tetany. These episodes can lead to fractures and muscle tears.
- Drooling
- excessive sweating
- fever
- hand or foot spasms or both
- irritability
- difficulty swallowing
- uncontrollable urination or bowel movements

Classification

Depending on the intensity of the contractions, the following forms of tetanus appear:

- mild: muscle stiffness with few muscle contractions;
- moderate: rigid jaw closure, difficulty swallowing (dysphagia), and contractions of the neck, back, and abdomen muscles; tetanic fascias and sardonic laughter;
- Severe: respiratory involvement.

Based on the pathogenesis of the disease, the following can be distinguished:

- Local tetanus: is a rare form of the disease, in which patients have persistent contraction of the muscles in the same anatomical area of the injury. Contractions may persist for several weeks before the eventual and gradual decrease in symptoms. Local tetanus is generally mild, and only about 1 percent of cases are fatal, although it can be preceded by the onset of widespread tetanus.
- Cephalic tetanus: is a rare form of the disease, sometimes associated with otitis media, in which *C. tetani* is present in the flora of the middle ear, or after traumatic head injuries. The cranial nerves are involved, especially those in the facial area.
- Generalized tetanus: This is the most common type of tetanus, accounting for about 80 percent of cases. The generalized form usually presents with a descending pattern. The first sign is lockjaw and so-called *facial spasm* or *sardonic laughter*, followed by stiff neck, difficulty swallowing, and stiffness of the pectoral and calf muscles. Other symptoms include an elevated temperature, sweating, elevated blood pressure, and a rapid heart rate, which occurs episodically. Spasms can occur frequently and last for several minutes with the body in the characteristic arched shape, called *opisthotonos*. Spasms may continue for 3-4 weeks, and full recovery may take up to months.

- Neonatal tetanus: is a generalized form of tetanus that occurs in newborns, in children who have not acquired passive immunity because the mother has never been vaccinated. Infection usually occurs through the infected umbilical stump, particularly when the cord is cut with a non-sterile instrument. Neonatal tetanus is common in many developing countries and is responsible for about 14 percent of neonatal deaths, but it is very rare in developed countries.

Clinical picture

Spasmodic backward curvature of the body: opisthotonus. The same phenomenon with forward curvature is called *emprostotone*.

Some of the characteristic symptoms of tetanus are:

- muscle stiffness and muscle spasms (jaw, whose stiffness is also known as trismus, face, abdomen, upper and lower limbs);
- fever and rapid pulse;
- difficulty swallowing;
- apnea;
- contraction of the entire body in such a way that it remains hunched over: backwards (opisthotonos) or forwards (emprostotones).

Differential diagnosis

Tetanus has clinical elements that can confuse it with other pathologies, including:

- Hypocalcemic tetany
- Dystonic reactions of phenothiazines
- hyperventilation from hysterical attacks
- engraved encephalitis
- Anger
- Strychnine poisoning

Treatment

The wound should be cleaned thoroughly and the source of the toxin removed, dead tissue removed, and left exposed to air, as oxygen kills anaerobic bacteria. Penicillin (or tetracycline for allergy sufferers) helps reduce the number of bacteria, but it has no effect on the neurotoxin they produce. Nowadays, the use of metronidazole is recommended to replace penicillin, since the latter has an anti-GABA effect, which could have synergistic activity with tetanus toxin. Human tetanus

immunoglobulin to neutralize circulating toxin that has not yet bound to nerve endings[3] or tetanus serum should also be administered.

Prevention

Tetanus can be prevented by vaccination. A vaccine booster is recommended every 10 years. A vaccine is usually given every time a patient suffers a puncture or wound when vaccination is not certain.

Following the 3-dose schedule during breastfeeding, one booster in childhood, one in adolescence and one in adulthood, protection can last a lifetime.

HUMAN PAPILLOMAVIRUS VACCINE

The **HPV (human papillomavirus) vaccine** is a vaccine against certain varieties of sexually transmitted HPV diseases, associated with the development of cervical cancer (or cervical cancer) and genital warts. There are currently two HPV vaccines on the market: Gardasil and Cervarix. The actual effectiveness of vaccines in reducing cervical cancer incidence and mortality rates is still unknown.

Human papillomavirus **(**HPV*) is a group of* DNA viruses belonging to the Papillomaviridae family and represents one of the most sexually transmitted infections more than 100 viral types are known, and in relation to their oncological pathogenesis, they are classified into types of high and low oncological risk. The International Agency for Research on Cancer (IARC) considers HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 to be carcinogens to humans – types of high cancer risk – and that other types, including HPV 6 and HPV 11, are possible carcinogens to humans – types of low cancer risk. Like all viruses in this family, HPVs only establish productive infections in the stratified epithelium of the skin and mucous membranes of humans, as well as a variety of animals. Most of the HPVs described do not cause any symptoms in most people. Some types of HPV can cause warts or condylomas, while others can lead to subclinical infections, which can (in a minority of cases) lead to cervical, vulvar, vaginal, and anal cancer in women, or cancer of the anus and penis in men. Most people infected with HPV are unaware that they are infected. All HPVs are transmitted by skin-to-skin contact.

Treatment of infections

The treatment of HPV infections is currently based on the use of some available topical creams, whose antiviral activity is not well known or which act by activating a local immune response against the virus. In the case of precancerous lesions caused by HPV, the most appropriate

treatment is the removal of the affected areas by surgery. In large part, this treatment is effective because HPV produces well-localized superficial lesions, and HPVs do not cause systemic infections.

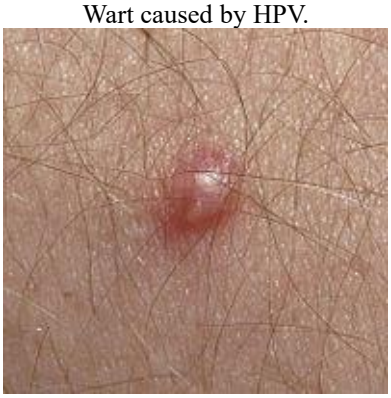
HPV-induced diseases

More than 100 different types of HPV have been identified, which are named with a number. A persistent infection by the sub-group known as "high risk", which includes about 13 types of sexually transmitted HPV viruses including types other than those that cause warts, can promote the development of:

- CIN (neoplasia cervical intraepitelial),
- VIN (neoplasia intraepitelial vulvar),
- PIN (neoplasia intraepitelial de pene), o
- AIN (neoplasia intraepitelial anal)

These are precancerous lesions and can progress to invasive cancer

Wart caused by HPV.



- Common warts: Some "cutaneous" types of HPV, such as HPV-1 and HPV-2, cause common warts; frequently found on hands and feet, but can appear in other areas, such as the knee and elbow. These warts have a characteristic cauliflower surface, and typically raised slightly above the surrounding skin. Cutaneous HPV types do not usually cause genital warts and are not associated with the development of cancer.
- Plantar warts: they are located at the base of the foot; and grow inward, usually causing pain when walking.
- Subungual or periungual warts: they form under the nail (subungual), around the nail or in the cuticle (periungual). They may be more difficult to treat than other warts from different places.
- Flat warts: These are commonly located on the arms, face, or nape of the neck. Like common warts, these flats occur more in children and teens. In people with normal immune function, these flat warts are not associated with the development of cancer.

Genital warts

Anal wart Vaginal warts Warts on the penis

Genital or anal warts (*Condylomata acuminata* or venereal warts) are the most recognized signs of this genital HPV infection. Although there are a wide variety of HPV types that can cause genital warts, types 6 and 11 account for about 90% of all cases.

Many people who acquire HPV types associated with genital warts resolve the infection quickly without even developing warts or other symptoms. You can spread the virus to others even if none of the symptoms of infection have unfolded. However, in the vast majority of cases, this is not the cause of not having adequate tests routinely administered.

The types of HPV that tend to cause genital warts are not the same as those that cause cervical cancer. However, since an individual can be infected with multiple types of HPV, the presence of warts is not a rule that the possibility of the presence of high-risk types of the virus is absent.

Cancer

HPV-induced cancers. The graph shows the number of annual cases of different types of cancer in the world. The fraction of cancer cases estimated to be HPV-induced is shown in red. For example, almost all cases of cervical cancer are thought to be caused by HPV.

An HPV infection is a necessary factor in the development of almost all cases of cervical cancer.

About a dozen types of HPV (including types 16, 18, 31, 45) are called "high-risk" types because they can trigger cervical canceror also anal cancer, vulvar cancer, penile cancer. From the point of view of cervical cancer, the two most important types are HPV 16 and 18: HPV 16 is associated with almost 60% of cervical cancer cases, and HPV 18 for another 10% of cases.

Risk factors for cervical cancer are related to both virus and host characteristics, and include:

- multiple sexual partners;
- a male partner with many present or past sexual partners;
- in young women, persistent urinary tract infections;
- early age at first sexual intercourse;

- high number of births;
- persistent infection with a high-risk HPV (such as HPV 16 or 18);
- immunosuppression;
- certain subtypes of HLA (human leukocyte antigens);
- use of oral contraceptives;
- nicotine use.

Respiratory papillomatosis

HPV types 6 and 11 can cause a rare condition known as recurrent laryngeal papillomatosis (a respiratory papillomatosis), where warts form in the larynx or other areas of the respiratory tract.

These warts can recur frequently, require repeated surgeries, interfere with breathing, and in extremely rare cases progress to cancer.

It is necessary to take into account that if the mother is affected by the human papillomavirus genotype 6 or 11, at the time of delivery the baby could inhale it; this would trigger recurrent respiratory papillomatosis in him.

Epidemiology

HPV infections occur worldwide. There are no countries, races, ages or sexes that are not attacked. Most HPV primary infections occur in infancy and childhood, but are not discovered except by very sophisticated techniques. The vast majority are subclinical. This is as much as in skin infections such as genital (vaginal, balanoposthitis) or orodigestive infections. A primary factor that can be a cause associated with wounds and injuries caused in unhealthy areas subjected to repeated trauma such as maceration of mucous membranes or skin

Cutaneous HPV

Infection with cutaneous HPV is ubiquitous. Some types of HPV, such as HPV-5, can establish infections that persist throughout the life of individuals, without even manifesting any clinical symptoms. Like the remora that doesn't harm the shark, those HPV types can be thought of as human commensals. Other cutaneous HPVs, such as HPV types 1 or 2, can cause common warts in some infected individuals. Cutaneous warts are very common in childhood, and typically appear and remit spontaneously over the course of weeks to months. About 10% of adults also suffer from recurrent skin warts. All HPVs are thought to be capable of establishing long-term "latent" infections in a small number of stem cells present in the skin. Although these latent infections may never be completely eradicated, immune control is designed to block the appearance of symptoms such as

warts. The immune control of HPV is of the specific type, meaning that an individual can become immunologically resistant to one type of HPV while remaining susceptible to other types

VPH genitales

A large increase in the incidence of genital HPV infection occurs at the age when individuals begin to have sexual intercourse. The vast majority of genital HPV infections never cause overt symptoms, and are cleared up by the immune system within months.

As with cutaneous HPVs, HPV immunity is thought to be of a specific type. A subset of infected individuals may fail to produce genital HPV infection under immune control. Pairing the infection with high-risk HPV types, such as HPV 16, 18, 31, and 45, can trigger the development of cervical cancer or other cancers.

High-risk HPV types 16 and 18 are together responsible for 65% of cervical cancer cases.

Type 16 causes 41 to 54% of cervical cancers, and adds even more HPV-induced vaginal/vulvar cancers, penile, anal, and head and neck cancers.

Public Health and Genital HPV

According to the U.S. Centers for Disease Control and Prevention, by age 50 or older, 80 percent of U.S. women will contract at least one type of genital HPV. Women are given an annual Pap scan to detect cellular abnormalities caused by HPV

The HPV vaccine, Gardasil, protects against the two types of HPV that cause 70% of cervical cancer cases, and the two types of HPV that cause 90% of genital warts.

The CDC recommends vaccination between ages 11 and 26.

Perinatal transmission

Although genital types of HPV are sometimes passed from mother to child during birth, the occurrence of disease-related genital HPV in newborns is rare. Perinatal transmission of HPV types 6 and 11 may result in the development of juvenile recurrent respiratory papillomatosis (JORRP). JORRP is very rare, with rates of about 2 cases per 100,000 children in the United States. Although the rate of JORRP is substantially higher if the woman has genital warts at the time of delivery, the risk of JORRP in such cases is less than 1%.

Cervical Cancer Screening and Prevention

Many people become infected with several skin types of HPV during their childhood. Papillomaviruses have a protective protein coat or capsid, which may then be able to survive in the environment for long periods of time. Contact with contaminated surfaces, such as communal shower

floors or overhead lines, should be avoided, reducing the risk of cutaneous HPV infection. Also treating common warts early can reduce the spread of the infection to additional sites.

Genital HPV infections can be widely distributed over genital skin and mucosal surfaces, and transmission can occur even if you don't have visible symptoms. Several strategies should be employed to minimize the risk of developing diseases caused by genital HPV:

Pap Iiloma campaign

Slim preparation with a cluster of normal cervical cells on the left, and HPV-infected cells on the right. HPV cells show typical forms of koilocytes: enlarged nuclei x2 or x3, and hyperchromasia.

Certain types of sexually transmitted HPV can cause cervical cancer. Persistent infection with one or more of about a dozen of these "high-risk" HPV types is a major factor in most all cases of cervical cancer. The development of HP-induced cervical cancer is a slow process that usually takes many years. During the developmental phase, precancerous cells can be detected by an annual or semiannual Pap smear (colloquially "pap"). **Pap** is an effective strategy to reduce the risk of cervical cancer. The Pap test involves taking tissue from the cervix, placing it on a glass plate, and examining it under a microscope to look for abnormal cells. It is 70 to 80% effective in detecting cellular abnormalities caused by HPV. A more sensitive method is the "thin preparation," where the tissue of the cervix is put into a liquid solution, and is 85% to 95% effective in detecting cellular abnormalities caused by HPV. This last Pap test is mostly used in women over 30 years of age. It is a combination of HPV pap-DNA test. If this test is negative, you can wait three years before doing it again. A close inspection of the cervix by colposcopy may be indicated if abnormal cells are detected by routine pap test. A frequent example of occurrence of abnormal cells found in association with HPV are koilocytes

The U.S. Centers for Disease Control and Prevention (CDC) recommends that women get a Pap stool no later than 3 years after their first sexual intercourse and no more than 21 years of age. Women should have a Pap smear every year until they are 30. And afterward, they should discuss risk factors with their doctor to determine if Pap smearing should be done annually. If risk factors are low and previous Pap smears have been negative, many women only need to be tested every 2 to 3 years until age 65 (CDC, 2005).

Since these control tools were developed, deaths from cervical cancer have decreased by 70% in the last 50 years. The pap test has proven to be one of the most successful control tests in the history of medicine, although the American College of Obstetricians and Gynecologists says that the new tests based on cytology (Thinprep and Surepath) will reduce cases of CIN3 (cervical intraepithelial neoplasia) and cancer by 15 to 35%.

A study published in April 2007 suggested that the removal of tissue with pap produces a cytokine inflammatory response that may initiate an immune clearance of HPV, although it reduces the risk of cervical cancer.

A woman who has tested positive for only one Pap smear in her history has a lower incidence of cancer. "A statistically significant decline in HPV is positively correlated with the amount of pap in human lifetime."

It has been suggested that pap may be beneficial for anal cancer control in some gay subpopulations.

HPV Testing

An HPV test detects certain types of human papillomaviruses (HPVs), depending on the test. A method for detecting the DNA of high-risk HPVs has recently been added to the range of clinical options for cervical cancer screening.

In March 2003, the U.S. Food and Drug Administration (FDA) approved a hybrid trapping test, marketed by Digene, as a primary trapping tool for detecting high-risk HPV infections that can lead to cervical cancer. This test was also approved for use in conjunction with the pap test and should be performed routinely at a gynecological checkup.

Adding HPV testing to all women over 30 years of age improves the sensitivity of isolated cytology to almost 100% and gives the physician the option to increase the interval between Pap smears to 3 years.

The experimental study of the different molecular pathways involved in the development of cervical cancer has allowed the development of new biological markers that could considerably improve the cytological and histological diagnosis of cervical lesions. The detection of E6 and E7 messenger RNA (HPV OncoTect®) and the study of the p16 cell cycle protein are two of these new markers. The first published results indicate that these markers are highly sensitive and specific, and allow the identification of cells in the process of cancerous transformation, which means a great advance from a clinical point of view.

In the case of men, according to the CDC, there is no test to determine HPV infection. Genital "abnormalities" are the only visible sign of HPV in men, and can be identified by visual inspection of the genital area. These visible "abnormalities," however, are the result of noncancerous HPV types. Vinegar solutions have been useful in identifying "abnormalities" by making them more noticeable, but these tests have been found to be more favorable in moist areas, such as the female genital tract

The CDC says on its *STD Facts-HPV Vaccine* website that "An HPV test or a pap test can detect whether a woman has HPV, but cannot specify the type of HPV the woman has."

Vaccines

On June 8, 2006, the FDA approved Gardasil, a prophylactic HPV vaccine marketed by Merck & Co., Inc. Clinical trials of the vaccine, conducted among adult women with a median age of 23, showed protection against initial infection with serotypes 16 and 18, which together cause about 70% of cervical cancers. These HPV serotypes also cause anorectal tumors in both women and men.

The trial also showed 100% efficacy against peristic infections, not just acute infections. The vaccine also protects against serotypes 6 and 11, which cause 90% of genital warts. Women can be vaccinated in the age range of 9 to 26 years, although younger women were not part of the clinical trial.

Currently, in addition to Gardasil, GlaxoSmithKline has marketed the Cervarix vaccine. Both Gardasil and Cervarix protect against initial infections against HPV types 16 and 18, which cause most cases of cervical cancer. Gardasil also protects against HPV types 6 and 11: these four types combined (16, 18, 6, 11) account for 90% of cervical cancer cases.

The vaccine provides little benefit to women who are already infected with HPV types 16 and 18, i.e. to most sexually active women, as the vaccines have no therapeutic effect on existing infection or cervical lesions. For this reason, the vaccine is mainly recommended for women who have not yet initiated sexual intercourse. The vaccine (both Gardasil and Cervarix) is administered in 3 doses over 6 months at a cost of about 300 euros. The CDC recommends women between the ages of 11 and 26 get vaccinated, although girls as young as 9 may benefit. The actual effectiveness of vaccines in reducing cervical cancer incidence and mortality rates is still unknown.

Because current vaccines do not protect women against all HPV serotypes that cause cervical cancer, it is important for women to continue Pap smears and Pap smears, even after they have received the vaccine.

Although administrations and companies assure that the vaccine has no side effects, except for pain around the injection site, the truth is that to date in the United States 18 girls have already died after being vaccinated and more than 8000 have suffered adverse events. In Spain, 103 alerts have been issued, with 35 cases of serious adverse reactions with diarrhoea, pain, syncope or seizures. Merck, as well as the FDA and CDC consider the vaccine to be completely safe and that there is no cause-and-effect relationship. It does not contain mercury, thimerosal, or attenuated viruses (killed virus only). Merck & Co., Inc., the manufacturer of Gardasil, is continuing to test women who have received the vaccine to determine its effectiveness over a lifetime period.

Both men and women are carriers of HPV. To eradicate the disease, eventually men would have to be vaccinated. Studies are currently underway to determine the efficiency of vaccinating boys with the current vaccine. In most countries, vaccines have been approved for female use only, but in

countries such as the United States and the United Kingdom they have been approved for male use as well.

Condoms

Female condom Male condom

The Centers for Disease Control and Prevention states that "although the effect of condoms in preventing HPV infection is not exactly known, condom use has been associated with a lower rate of cervical cancer, a disease directly related to HPV."

According to Marcus Steiner and Willard Cates in the *New England Journal of Medicine*, "the protection offered by condoms cannot be quantified exactly." However, in a study in the same issue, of 82 university women followed in routine clinical practice for 8 months, the incidence of genital HPV was 37.8 per 100 patients/year among women whose partners used condoms in all their sexual relations, compared to 89.3 per 100 patients/years in those whose partners used condoms in less than 5% of relationships. The researchers concluded that "among women who are beginning to be sexually active, consistent condom use in their relationships by their partners appears to reduce the risk of cervical and vulvovaginal HPV infection."

Other studies have suggested that regular condom use can effectively limit the persistence and spread of HPV to other genital areas in already infected individuals.

Condom use can reduce the risk that infected individuals will develop toward cervical cancer or the development of genital "abnormalities." Planned Parenthood recommends the use of condoms in order to prevent the risk of HPV infection.

Clinical picture

Some of the most important symptoms that suggest the presence of human papillomavirus are:

- Constant irritations at the entrance to the vagina with burning and burning sensation during sexual intercourse (called vulvodynia).
- Small warts in the ano-genital area: cervix, vagina, vulva and urethra (in women) and penis, urethra and scrotum (in men).

They can vary in appearance (flat warts not visible or acuminate if visible), number and size, so the assistance of a specialist is needed for their diagnosis. Pap smear alterations that tell us that there are squamous intraepithelial lesions in the cervix (areas infected by HPV, which can cause cancer).

Prevention

The safest method of prevention is having only one sexual partner (mutual monogamy), avoiding having sex with more than one partner, or abstinence.

The use of condoms protects against HPV infection in 70% of cases. The remaining 30% where it does not protect is due to the existence of injuries in areas not covered by the condom and its misuse.[67]

History of the discovery of the relationship between the virus and cancer

The key fact that led the researchers to link sexually transmitted HPV infection to cervical cancer was the higher rates of cervical cancer recorded in prostitutes compared to rates recorded in nuns. Nowadays many studies have clearly shown that HPV is mainly transmitted by sexual contact.

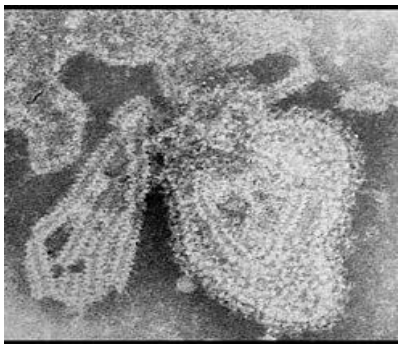
Some of the contraindications may be temporary, such as for live vaccines (pregnancy and immunosuppression), and one type of transitory precaution is for all vaccines, acute, moderate, or severe disease, and recent administration of a blood product containing antibodies to the PRS vaccine.

Care should be taken such as the availability of epinephrine, whenever immunization is administered, waiting for the evaporation of the alcohol used to clean the injection site, because it could inactivate the live vaccine, not using the I.M route in patients with hematological alterations, such as hemophilia or thrombocytopenia, storage between 2 and 5 ^{0C}

In general, mild adverse reactions are the most common and include local reactions at the injection site (erythema, edema, pain), systemic reactions (fever, chills, irritability and malaise), occasionally more serious adverse reactions and anaphylaxis rarely occurs.

The possibility of being administered simultaneously, 2 live virus vaccines (when required and not available in a combined preparation), the need to move immunization with live viruses away from the administration of immunoglobulins, avoiding the co-administration of vaccines and interferons, the probable decrease in the response generated by them, before the administration of immunosuppressive agents (corticosteroids, cytostatics) are elements to be taken into account during immunization.

LA TUBERCULOSIS



Mumps virus

Tuberculosis (abbreviated **TB** or **TB**), formerly called **consumption** (from the Greek *φθίσις*, via the Latin *phthisis*) is a contagious bacterial infection that mainly involves the lungs, but can spread to other organs. The most important and representative species of bacteria that causes tuberculosis is *Mycobacterium tuberculosis* or Koch's bacillus, belonging to the Mycobacterium tuberculosis complex. TB is arguably the most prevalent infectious disease in the world. Other mycobacteria, such as *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium canetti* and *Mycobacterium microti* can also cause tuberculosis, but all these species do not usually do so in the healthy individual. Although tuberculosis is a predominantly lung disease, it can also affect the central nervous system, lymphatic system, circulatory system, genitourinary system, digestive system, bones, joints, and even the skin.

The classic symptoms of tuberculosis are:

1. Chronic cough, with bloody sputum,
2. Fever, night sweats
3. Weight loss.

Infection of other organs causes a wide variety of symptoms. Diagnosis is based on radiology (usually chest x-rays), a skin tuberculin test and blood tests, as well as a microscopic examination and a microbiological culture of body fluids such as expectorations.

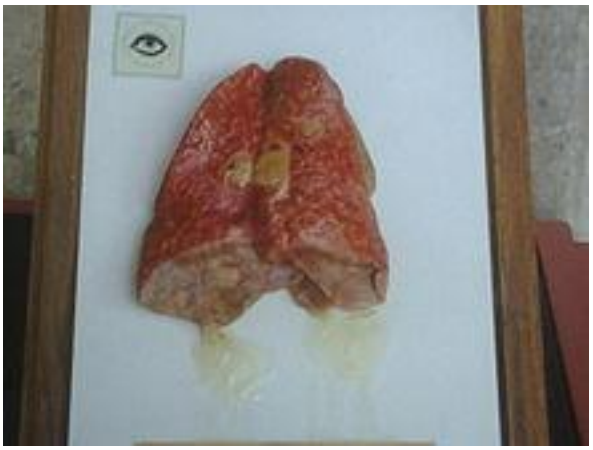
Treatment of tuberculosis is complicated and requires long periods of exposure to various antibiotics. The patient's relatives, if necessary, are also analyzed and treated. In recent years, tuberculosis has shown a growing resistance to multiple antibiotics and for this purpose, vaccination campaigns have been chosen, as a preventive measure, generally with the Bacillus Calmette-Guérin (BCG) vaccine.

TB is spread through the air, when infected people cough, sneeze, or spit. In addition, a growing number of people around the world are contracting tuberculosis because their immune

systems are compromised by immunosuppressive drugs, drug abuse or AIDS. The distribution of tuberculosis is not uniform throughout the world; approximately 80% of the population in many Asian and African countries test positive for tuberculin, while only 5-10% of the U.S . population tests positive.

According to data published in 2014 by the WHO, approximately 9 million people fell ill with tuberculosis and 1.5 million died from this cause in 2013, of which 510,000 were women. The WHO estimates that early diagnosis and effective treatment saved 37 million people between 2000 and 2013, but considers the number of deaths "still unacceptably high" because their deaths are preventable.

Lungs with tuberculosis at the Museum of Mexican Medicine in Mexico City



History of tuberculosis

Tuberculosis is one of the oldest diseases affecting humans. Although it is estimated to be between 15,000 and 22,000 years old, it is more widely accepted that this species evolved from other more primitive microorganisms within the genus *Mycobacterium* itself. It can be thought that at some point in evolution, some species of mycobacteria crossed the biological barrier, by selective pressure, and began to have a reservoir in animals. This possibly gave rise to an elderly progenitor of *Mycobacterium bovis*, which is accepted by many as the oldest of the species that currently make up the so-called *Mycobacterium tuberculosis complex*, which includes *M. tuberculosis*, *M. bovis*, *M. africanum* and *M. microti*. The next "step" would be the passage from *M. bovis* to the human species, coinciding with the domestication of animals by man. Thus, possibly, it could have emerged as a pathogen for the dog.

Progression

It will progress from tuberculosis infection to tuberculosis disease. It can occur early (primary tuberculosis, about 1-5%) or several years after infection (post-primary tuberculosis, secondary,

tuberculous reactivation in about 5-9%). The risk of reactivation is increased with alterations in the immune system, such as those caused by HIV. In patients co-infected with HIV and TB, the risk of reactivation increases by 10% per year, while in an immunocompetent person the risk is 5 to 10% throughout life.

Some drugs, including treatments currently used in rheumatoid arthritis that act by blocking tumor necrosis factor, increase the risk of activation of latent TB due to the important action of this cytokine on the immune response against TB.

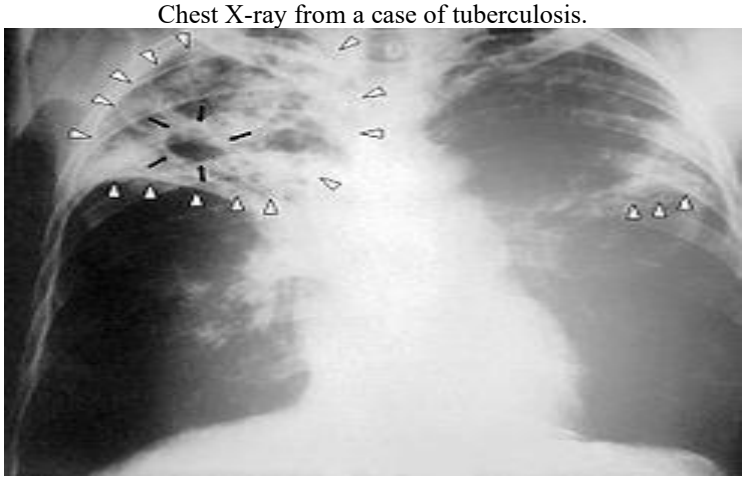
Diagnosis

Auto fluorescence

The Autonomous University of Madrid published a study in the *Journal of Clinical Microbiology* where it is described for the first time that mycobacteria are capable of emitting fluorescence, which allows them to be seen under a fluorescence microscope without the need for prior staining. This characteristic is of interest for the diagnosis of tuberculosis since before it was necessary to resort to specific stains to be able to observe most bacteria since very few present autofluorescence. However, the self-fluorescence emitted by sky-blue mycobacteria is as intense and bright as when they are stained green with the old method. In addition, it has been found that the phenomenon is permanent, with no decrease in autofluorescence over time, so special conservation of the samples is not necessary for their maintenance.

Chest X-ray

Chest X-ray from a case of tuberculosis.



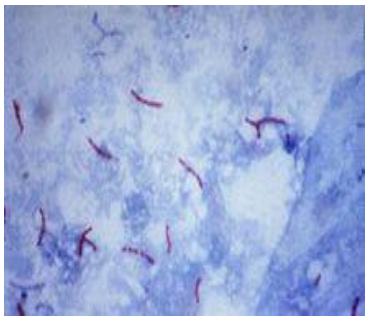
X-rays are essential in diagnosing the disease. Typical radiological lesions are apical lesions, in the right hemithorax, in posterior segments and generally forming cavities.

The fundamental tool for diagnosing a tuberculosis case is bacteriology (smear smear and culture) due to its high specificity, sensitivity and predictive value. In those situations where bacteriological studies are inconclusive, it will be necessary to carry out diagnostic follow-up in accordance with the organization of the health services network, using other criteria: clinical, epidemiological, diagnostic imaging, immunological, anatomopathological.

Any person diagnosed with tuberculosis after counseling and acceptance must be tested for HIV.

Sputum smear smear

Mycobacterium tuberculosis visualization with the use of Ziehl Neelsen staining.



It consists of a serious test (three consecutive days), where a sample of sputum is taken to see what bacteria are present. This test does not require fasting or brushing. With a low cost and quick execution, smear smear is a technique that allows the identification of 70-80% of positive lung cases.

The bacterium *Mycobacterium tuberculosis* has a different wall structure from those that are capable of being typed by Gram staining as it has a very abundant amount of lipids. It is called acid-fast alcohol and this characteristic is what allows its observation by Ziehl Neelsen staining.

Biological sample culture

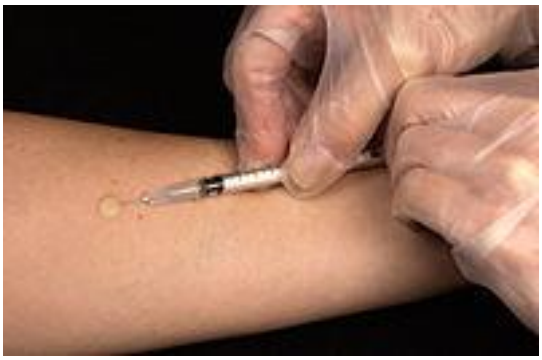
The culture can be done in Löwenstein-Jensen medium, which is made up of:

- egg (albumin, lipids) (coagulates and gives solidity)
- Malachite green (inhibits other bacteria)
- glycerol (carbon source)
- asparagines (source of nitrogen)

It grows very slowly (30 to 90 days) at 37 °C in an atmosphere with carbon dioxide (in culture they grow better despite being strictly aerobic), giving colonies that look like breadcrumbs (or spider eggs), dry yellowish and rough.

Tuberculin test using the Mantoux technique

Test de Mantoux



Intradermal injection of PPD for the Mantoux test.

This is a skin test (intradermal reaction) to check for TB infection. PPD (Purified Protein Derivative) is used as a reagent. It should be noted that the Mantoux tuberculin test only involves contact, not infection.

MODS (Microscopic observation drug susceptibility)

Microscopic observation of drug susceptibility (MODS) is a newly developed method that has very high sensitivity and specificity, as well as a great reduction in the time to diagnosis of *Mycobacterium tuberculosis* infection, while evaluating the resistance of first-line antibiotics, such as isoniazid and rifampicin for MDR-TB (multidrug-resistant) patients.

Treatment

The treatment of tuberculosis is carried out with combinations of anti-tuberculosis drugs, making effective the guidelines of six months of treatment, two months in the first phase of treatment and four months in the second phase.

Tuberculosis is curable, but early diagnosis is necessary (go to the doctor immediately), as it is a serious disease if the appropriate treatment is not followed. Next, it is essential not to abandon the treatment given by the doctor because, when the treatment is stopped, this disease worsens rapidly and the proliferation of drug-resistant bacilli is favored .

Pharmacological treatment of tuberculosis

The history of tuberculosis changes dramatically after the introduction of antimicrobial agents. The treatment of tuberculosis is essential for its control since it breaks the chain of transmission when the treatment is correct and complete.

Drug treatment began in 1944 with streptomycin (SM) and para-aminosalicylic acid (PAS). In 1950, the first clinical trial was carried out comparing the efficacy of MS and SBP together or as monotherapy. The study showed that the combination therapy was more effective. In 1952, a third drug, isoniazid (INH), was added to the combination, dramatically improving the efficacy of the treatment, although still lasting 18-24 months. Ethambutol was introduced in 1960, replacing PAS in treatment schedules and reducing the duration to 18 months. In the 1970s with the introduction of rifampicin (ADR) in the combination, treatment was shortened to nine months. Finally, in 1980, pyrazinamide (PZA) was introduced into the therapeutic scheme, and the duration could be reduced to six months.[14]

Two biological facts explain why combination therapy is more effective in the treatment of TB than monotherapy. The first is that treatment with a single drug induces the selection of resistant bacilli and consequently the failure to eliminate the disease. The second is that different bacillary populations can coexist in the same patient.

Prevention

It is prevented through a healthy and hygienic life, identifying the sick in a timely manner and ensuring their cure so as not to infect other people, mainly through vaccination with BCG vaccine.

Preventive measures

- The infected person should protect themselves whenever they cough with tissues.
- Washing hands after coughing.
- Adequate ventilation of the place of residence.
- Clean the home with damp cloths.
- Use a mask in common areas.
- Restrict visits to people not exposed to the disease.
- Ensure adherence to treatment.
- Do not smoke. Smoking does not cause tuberculosis, but it does promote the development of the disease.

Vaccinations

In many countries, the BCG vaccine is used as part of TB control programmes, especially in children. This vaccine was developed at the Pasteur Institute, France between 1905 and 1921. However, mass vaccinations did not begin until after World War II. The efficacy in protecting BCG in severe forms of tuberculosis (e.g., meningitis) in children under 4 years of age is large, and is around 80%; its efficacy in adolescents and adults is more variable, ranging from 0 to 80%

RUTI is a therapeutic vaccine currently being developed at the Experimental Tuberculosis Unit in Badalona, Spain, to decrease the treatment of latent TB infection[22] from 9 to 1 month of isoniazid administration. Heads of Archivel Farma and the Germans Trias i Pujol Hospital in Badalona, popularly known as Can Ruti, which has given the vaccine its name.

Curiosity

World TB Day

The WHO stipulated that March 24 would be World Tuberculosis Day. It commemorates that on March 24, 1882, Dr. Robert Koch announced the discovery of the tuberculosis bacillus.

In 1982, the first World Tuberculosis Day was held, sponsored by the World Health Organization (WHO) and the International Union Against Tuberculosis and Respiratory Diseases (IUCTER). This event sought to educate the public about the devastating health and economic consequences caused by TB, its effect on developing countries, and its ongoing tragic impact on global health.

CONCLUSIONS

GENERAL IMMUNIZATION

When administering a vaccine, contraindications and precautions for these must be taken into account, which are circumstances in which the vaccine should not be administered.

Few real contraindications and precautions are permanent, such as severe allergy to one of the components of the vaccine or following a previous dose of the vaccine and encephalopathy within 7 days of immunization against B pertussis. There are precautions considered permanent for subsequent doses of vaccines containing pertussis (temperature greater than 400 C, collapse, shock-like state, inconsolable and persistent crying for more than 3 hours within 48 hours of administering the vaccine, seizures with or without fever within 3 days of dosing).

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