**Dr.Maryam Virology**

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| **Paramyxoviruses:**  The paramyxovirus family contains four important human pathogens: measles virus, mumps virus, respiratory syncytial virus (RSV), and parainfluenza viruses. They differ from orthomyxoviruses in that their **genomes are not segmented,** they have a larger diameter, and their surface spikes are different Paramyxoviruses are composed of **one piece** of single-stranded RNA, a helical nucleocapsid, and an outer lipoprotein envelope. The virion contains an RNA-dependent **RNA polymerase,** which transcribes the **negative-polarity** genome into mRNA. The genome is therefore not infectious. The envelope is covered with spikes, which contain hemagglutinin, neuraminidase, or a fusion protein that causes cell fusion and, in some cases, hemolysis (Table –1).   |  |  | | --- | --- | | |  | | --- | | Table–1 Envelope Spikes of Paramyxoviruses | | | | **Virus** | **Hemagglutinin** | **Neuraminidase** | **Fusion Protein1** | | --- | --- | --- | --- | | Measles virus | + | – | + | | Mumps virus2 | + | + | + | | Respiratory syncytial virus | – | – | + | | Parainfluenza virus2 | + | + | + | | | 1The measles and mumps fusion proteins are hemolysins also.  2In mumps and parainfluenza viruses, the hemagglutinin and neuraminidase are on the same spike and the fusion protein is on a different spike. | |

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| **Measles Virus**  This virus causes measles, a disease characterized by a maculopapular rash. It occurs primarily in childhood. The genome RNA and nucleocapsid of measles virus are those of a typical paramyxovirus (see above). The virion has two types of envelope spikes, one with hemagglutinating activity and the other with cell-fusing and hemolytic activities (Table-1). It has a single serotype, and the hemagglutinin is the antigen against which neutralizing antibody is directed. Humans are the natural host.  **Summary of Replicative Cycle**  After adsorption to the cell surface via its hemagglutinin, the virus penetrates and uncoats and the virion RNA polymerase transcribes the negative-strand genome into mRNA. Multiple mRNAs are synthesized, each of which is translated into the specific viral proteins; no polyprotein analogous to that synthesized by poliovirus is made. The helical nucleocapsid is assembled, the matrix protein mediates the interaction with the envelope, and the virus is released by budding from the cell membrane.  **Transmission & Epidemiology**  Measles virus is transmitted via **respiratory droplets** produced by coughing and sneezing both during the prodromal period and for a few days after the rash appears. Measles occurs worldwide, usually in outbreaks every 2 to 3 years, when the number of susceptible children reaches a high level. The attack rate is one of the highest of viral diseases; most children contract the clinical disease on exposure. When this virus is introduced into a population that has not experienced measles, such as the inhabitants of the Hawaiian Islands in the 1800s, devastating epidemics occurs. In malnourished children, especially those in developing countries, measles is a much more serious disease than in well-nourished children. Vitamin A deficiency is especially important in this regard, and supplementation of this vitamin greatly reduces the severity of measles. Patients with deficient cell-mediated immunity, e.g., AIDS patients, have a severe, life-threatening disease when they contract measles.  **Pathogenesis & Immunity**  After infecting the cells lining the upper respiratory tract, the virus enters the blood and infects reticuloendothelial cells, where it replicates again. It then spreads via the blood to the skin. The **rash** is caused primarily by cytotoxic T cells attacking the measles virus–infected vascular endothelial cells in the skin. Antibody-mediated vasculitis may also play a role. Shortly after the rash appears, the virus can no longer be recovered and the patient can no longer spread the virus to others. **Multinucleated giant cells,** which form as a result of the fusion protein in the spikes, are characteristic of the lesions.  **Lifelong immunity** occurs in individuals who have had the disease. Although IgG antibody may play a role in neutralizing the virus during the viremic stage, cell-mediated immunity is more important. The importance of cell-mediated immunity is illustrated by the fact that agammaglobulinemic children have a normal course of disease, are subsequently immune, and are protected by immunization. Maternal antibody passes the placenta, and infants are protected during the first 6 months of life.  Infection with measles virus can **transiently depress cell-mediated immunity** against other intracellular microorganisms, such as *Mycobacterium tuberculosis*, leading to a loss of PPD skin test reactivity, reactivation of dormant organisms, and clinical disease. The proposed mechanism for this unusual finding is that when measles virus binds to its receptor (called CD46) on the surface of human macrophages, the production of IL-12, which is necessary for cell-mediated immunity to occur, is suppressed.  **Clinical Findings**  After an incubation period of 10 to 14 days, a prodromal phase characterized by fever, conjunctivitis (causing photophobia), running nose, and coughing occurs. **Koplik's spots** are bright red lesions with a white, central dot that are located on the buccal mucosa and are virtually diagnostic. A few days later, a maculopapular rash appears on the face and proceeds gradually down the body to the lower extremities, including the palms and soles. The rash develops a brownish hue several days later.  The complications of measles can be quite severe. Encephalitis occurs at a rate of 1 per 1000 cases of measles. The mortality rate of encephalitis is 10%, and there are permanent sequelae, such as deafness and mental retardation, in 40% of cases. In addition, both primary measles (giant cell) pneumonia and secondary bacterial pneumonia occur. Bacterial otitis media is quite common. Subacute sclerosing panencephalitis (SSPE) is a rare, fatal disease of the central nervous system that occurs several years after measles.  Measles in a pregnant woman leads to an increased risk of stillbirth rather than congenital abnormalities. Measles virus infection of the fetus is more severe than rubella virus infection, so the former typically causes fetal death, whereas the latter causes congenital abnormalities.  Atypical measles occurs in some people who were given the killed vaccine and were subsequently infected with measles virus. It is characterized by an atypical rash without Koplik's spots. Because the killed vaccine has not been used for many years, atypical measles occurs only in adults and is infrequent.  **Laboratory Diagnosis**  Most diagnoses are made on clinical grounds, but the virus can be isolated in cell culture; a rise in antibody titer of greater than fourfold can be used to diagnose difficult cases.    **Treatment:** There is no antiviral therapy available.  **Prevention**  Prevention rests on immunization with the **live, attenuated vaccine.** The vaccine is effective and causes few side effects. It is given subcutaneously to children at 15 months of age, usually in combination with rubella and mumps vaccines. The vaccine should not be given to children prior to **15 months of age, because maternal antibody in the child can neutralize the virus** and reduce the immune response. Because immunity can wane, a **booster dose** is recommended. The vaccine contains live virus, so it should not be given to immunocompromised persons or pregnant women. However, outbreaks still occur among unimmunized individuals, e.g., children in inner cities and in developing countries.  The killed vaccine should not be used. Immune globulin can be used to modify the disease if given to unimmunized individuals early in the incubation period. This is especially necessary if the unimmunized individuals are immunocompromised. |

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| **Mumps Virus**  This virus causes mumps, a disease characterized by parotid gland swelling. It occurs primarily in childhood.  **Important Properties:**The genome RNA and nucleocapsid are those of a typical paramyxovirus. The virion has two types of envelope spikes: one with both hemagglutinin and neuraminidase activities and the other with cell-fusing and hemolytic activities (Table -1).  The virus has a single serotype. Neutralizing antibody is directed against the hemagglutinin. The internal nucleocapsid protein is the S (soluble) antigen detected in the complement fixation test used for diagnosis. Humans are the natural host.  **Summary of Replicative Cycle:**Replication is similar to that of measles virus (see Measles Virus).  **Transmission & Epidemiology;**Mumps virus is transmitted via respiratory droplets. Mumps occurs worldwide, with a peak incidence in the winter. About 30% of children have a subclinical (inapparent) infection, which confers immunity. There were only 683 reported cases of mumps in the United States in 1997—a finding attributed to the widespread use of the vaccine. However, in 2006, a resurgence of mumps occurred with 6584 cases being recorded despite a high (87%) coverage rate for the vaccine.  **Pathogenesis & Immunity;**The virus infects the upper respiratory tract and then spreads through the blood to infect the parotid glands, testes, ovaries, pancreas, and, in some cases, meninges. Alternatively, the virus may ascend from the buccal mucosa up Stensen's duct to the parotid gland.  **Lifelong immunity** occurs in persons who have had the disease. There is a popular misconception that unilateral mumps can be followed by mumps on the other side. Mumps occurs only once; subsequent cases of parotitis can be caused by other viruses such as parainfluenza viruses, by bacteria, and by duct stones. Maternal antibody passes the placenta and provides protection during the first 6 months of life.  **Clinical Findings**  After an incubation period of 18 to 21 days, a prodromal stage of fever, malaise, and anorexia is followed by tender swelling of the parotid glands, either unilateral or bilateral. There is a characteristic increase in parotid pain when drinking citrus juices. The disease is typically benign and resolves spontaneously within 1 week.  Two complications are of significance. One is orchitis in postpubertal males, which, if bilateral, can result in sterility. Postpubertal males have a fibrous tunica albuginea, which resists expansion, thereby causing pressure necrosis of the spermatocytes. Unilateral orchitis, although quite painful, does not lead to sterility. The other complication is meningitis, which is usually benign, self-limited, and without sequelae. Mumps virus, Coxsackie virus, and echovirus are the three most frequent causes of viral (aseptic) meningitis. The widespread use of the vaccine in the United States has led to a marked decrease in the incidence of mumps meningitis.  **Laboratory Diagnosis**  The diagnosis of mumps is usually made clinically, but laboratory tests are available for confirmation. The virus can be isolated in cell culture from saliva, spinal fluid, or urine. In addition, a fourfold rise in antibody titer in either the hemagglutination inhibition or the CF test is diagnostic. A single CF test that assays both the S and the V (viral) antigens can also be used. Because antibody to S antigen appears early and is short-lived, it indicates current infection. If only V antibody is found, the patient has had mumps in the past.  A mumps skin test based on delayed hypersensitivity can be used to detect previous infection, but serologic tests are preferred. The mumps skin test is widely used to determine whether a patient's cell-mediated immunity is competent.  **Treatment;**There is no antiviral therapy for mumps.  **Prevention**  Prevention consists of immunization with the **live, attenuated vaccine.** The vaccine is effective and long-lasting (at least 10 years) and causes few side effects. Two immunizations are recommended, one at 15 months and a booster dose at 4 to 6 years, usually in combination with measles and rubella vaccines. Because it is a live vaccine, it should not be given to immunocompromised persons or pregnant women. Immune globulin is not useful for preventing or mitigating mumps orchitis.  In the late 1980s, outbreaks of mumps occurred in both immunized and unimmunized people. This led to the recommendation in 1989 that a second course of MMR (measles, mumps, and rubella) vaccine be administered. The incidence of mumps fell and outbreaks did not occur until 2006 when 6584 cases occurred, primarily in college-age individuals who, surprisingly, had received two doses of the vaccine. Waning immunity after the second dose and immunization with a different genotype from the genotype that caused the outbreak are suggested explanations. |

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| **Respiratory Syncytial Virus**  Respiratory syncytial virus (RSV) is the most important cause of pneumonia and bronchiolitis in infants. It is also an important cause of otitis media in children and of pneumonia in the elderly and in patients with chronic cardiopulmonary diseases.  **Important Properties;**The genome RNA and nucleocapsid are those of a typical paramyxovirus. Its surface spikes are **fusion proteins,** not hemagglutinins or neuraminidases (Table -1). The fusion protein causes cells to fuse, forming **multinucleated giant cells (syncytia),** which give rise to the name of the virus.  Humans are the natural hosts of RSV. For many years, RSV was thought to have one serotype; however, two serotypes, designated subgroup A and subgroup B, have been detected by monoclonal antibody tests. Antibody against the fusion protein neutralizes infectivity.  **Summary of Replicative Cycle;**Replication is similar to that of measles virus (see Measles Virus).  **Transmission & Epidemiology**  Transmission occurs via **respiratory droplets** and by direct contact of contaminated hands with the nose or mouth. RSV causes **outbreaks** of respiratory infections every winter, in contrast to many other "cold" viruses, which reenter the community every few years. It occurs worldwide, and virtually everyone has been infected by the age of 3 years. RSV also causes outbreaks of respiratory infections in **hospitalized infants;** these outbreaks can be controlled by handwashing and use of gloves, which interrupt transmission by hospital personnel.  **Pathogenesis & Immunity**  RSV infection in **infants is more severe** and more often involves the lower respiratory tract than in older children and adults. The infection is localized to the respiratory tract; viremia does not occur.  The severe disease in infants may have an **immunopathogenic** mechanism. Maternal antibody passed to the infant may react with the virus, form immune complexes, and damage the respiratory tract cells. Trials with a killed vaccine resulted in more severe disease, an unexpected finding that supports such a mechanism.  Most individuals have multiple infections caused by RSV, indicating that immunity is incomplete. The reason for this is unknown, but it is not due to antigenic variation of the virus. IgA respiratory antibody reduces the frequency of RSV infection as a person ages.  **Clinical Findings**  In infants, RSV is an important cause of lower respiratory tract diseases such as bronchiolitis and pneumonia. RSV is also an important cause of otitis media in young children. In older children and young, healthy adults, RSV cause respiratory tract infections such as the common cold and bronchitis. However, in the elderly (people older than 65 years of age) and in adults with chronic cardiopulmonary diseases, RSV causes severe lower respiratory tract disease, including pneumonia.  **Laboratory Diagnosis**  An enzyme immunoassay ("rapid antigen test") that detects the presence of RSV antigens in respiratory secretions is commonly used. The presence of the virus can be detected by immunofluorescence on smears of respiratory epithelium or by isolation in cell culture. The cytopathic effect in cell culture is characterized by the formation of multinucleated giant cells. A rise in antibody titer of at least four fold is also diagnostic. A reverse transcriptase polymerase chain reaction (RRT-PCR) test is also available.  **Treatment**  Aerosolized ribavirin (Virazole) is recommended for severely ill-hospitalized infants, but there is uncertainty regarding its effectiveness. A combination of ribavirin and hyperimmune globulins against RSV may be more effective.    **Prevention**  There is no vaccine. Previous attempts to protect with a killed vaccine resulted in an increase in severity of symptoms. Passive immunization with a monoclonal antibody directed against the fusion protein of RSV (palivizumab, Synagis) can be used for prophylaxis in premature or immunocompromised infants. Hyperimmune globulins (RespiGam) are also available for prophylaxis in these infants and in children with chronic lung disease. Nosocomial outbreaks can be limited by handwashing and use of gloves. |

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| **Parainfluenza Viruses**  These viruses cause croup (acute laryngotracheobronchitis), laryngitis, bronchiolitis, and pneumonia in children and a disease resembling the common cold in adults.  **Important Properties;**The genome RNA and nucleocapsid are those of a typical paramyxovirus. The surface spikes consist of hemagglutinin (H), neuraminidase (N), and fusion (F) proteins (Table -1). The fusion protein mediates the formation of multinucleated giant cells. The H and N proteins are on the same spike; the F protein is on a separate spike. Both humans and animals are infected by parainfluenza viruses, but the animal strains do not infect humans. There are four types, which are distinguished by antigenicity, cytopathic effect, and pathogenicity (see below). Antibody to either the H or the F protein neutralizes infectivity.  **Summary of Replicative Cycle;**Replication is similar to that of measles virus (see Measles Virus).  **Transmission & Epidemiology**  These viruses are transmitted via **respiratory droplets.** They cause disease worldwide, primarily in the winter months.  **Pathogenesis & Immunity**  These viruses cause upper and lower respiratory tract disease without viremia. A large proportion of infections are subclinical. Parainfluenza viruses 1 and 2 are **major causes of croup.** Parainfluenza virus 3 is the most common parainfluenza virus isolated from children with lower respiratory tract infection in the United States. Parainfluenza virus 4 rarely causes disease, except for the common cold.  **Clinical Findings**  Parainfluenza viruses are best known as the main cause of croup in children younger than 5 years of age. Croup is characterized by a harsh cough and hoarseness. In addition to croup, these viruses cause a variety of respiratory diseases such as the common cold, pharyngitis, laryngitis, otitis media, bronchitis, and pneumonia.  **Laboratory Diagnosis**  Most infections are diagnosed clinically. The diagnosis can be made in the laboratory either by isolating the virus in cell culture or by observing a fourfold or greater rise in antibody titer.  **Treatment & Prevention;**There is neither antiviral therapy nor a vaccine available. |

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