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Rubella Virus (German measles)

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INTRODUCTION

A.History of the Disease.

Rubella was at first considered to be a variant of the measles or scarlet fever and was called 3rd disease. The name Rubella comes from the Latin word meaning “little red.” In 1814, it was first discovered to be a separate disease from the measles in German medical literature thus receiving its nickname the “German measles.”

In 1912, measles became a nationally notifiable disease in the United States, requiring U.S. healthcare providers and laboratories to report all diagnosed cases. In the first decade of reporting, an average of 6,000 measles-related deaths were reported each year. In 1914, Hess postulated a viral etiology, and in 1938, Hiro and Tosaka confirmed his etiology by passing the disease to children with nasal washings from an infected person with an acute case.

In 1941, Norman Gregg reported congenital cataracts in 78 infants whose mothers had maternal rubella in early pregnancy. These were the first cases reported of congenital rubella syndrome (CRS). In 1962, rubella was first isolated by Parkman and Weller who then went on to find the general characteristics of the virus.

In the decade before 1963 when a vaccine became available, nearly all children got measles by the time they were 15 years of age. It is estimated 3 to 4 million people in the United States were infected each year. Also each year an estimated 400 to 500 people died, 48,000 were hospitalized, and 4,000 suffered encephalitis (swelling of the brain) from measles.



This baby has blindness due to Rubella cataracts.

Rubella virus

B. Introduction of this virus.

Rubella is caused by RNA virus and has a peak age of 15 years the incubation period is 14-21 days. Rubella Virus is only known to infect humans and is responsible for the common childhood disease known as German Measles or Three Day Measles because of its short duration.

The disease presents primarily as a skin rash, fever, lymphadenopathy with other mild symptoms in adults who contract the disease. Rubella can also cause arthritic symptoms, most commonly in women Rubella Virus can be prevented with the MMR (Measles, Mumps, Rubella) Vaccine which makes the virus uncommon in countries where vaccines are available.

Rubella Virus can cause serious harm to unborn fetuses of mothers who contract Rubella Virus within the first trimester. The virus causes CRS (Congenital Rubella Syndrome) causing birth defects. CRS can cause a variety of birth defects and can lead to miscarriage or stillbirth.



C. The distribution of this disease.

Worldwide. Now rubella is rare in locations where vaccination is standard practice. Countries with standard rubella vaccination are shown in blue color.

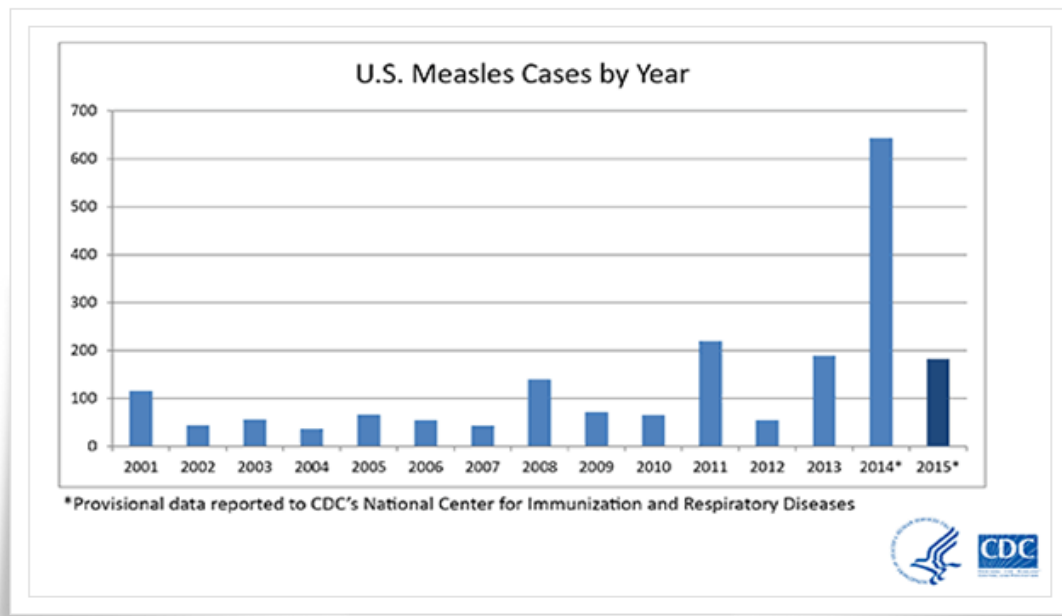


Countries/territories with Rubella vaccine in the national immunization system in 2002.

Rubella virus

D.Epidemic.

Epidemics occurred roughly every 6-9 years but immunization programs have greatly reduced the number of cases in developed countries and the majority of people who got measles were unvaccinated. Infections peaks in late winter and spring. The following figure shows the numbers of rubella cases reported in United States.



CLASSIFICATION OF THE VIRUS

A. Order

Not assigned.

B. Family.

Togaviridae family

C. Genus.

Rubivirus.(Rubella is the sole member of the Rubivirus genus).



Rubella virus under the electron Microscope.

STRUCTURE AND GENOME

A. Shape.

Circular or oval in shape.

B. Size

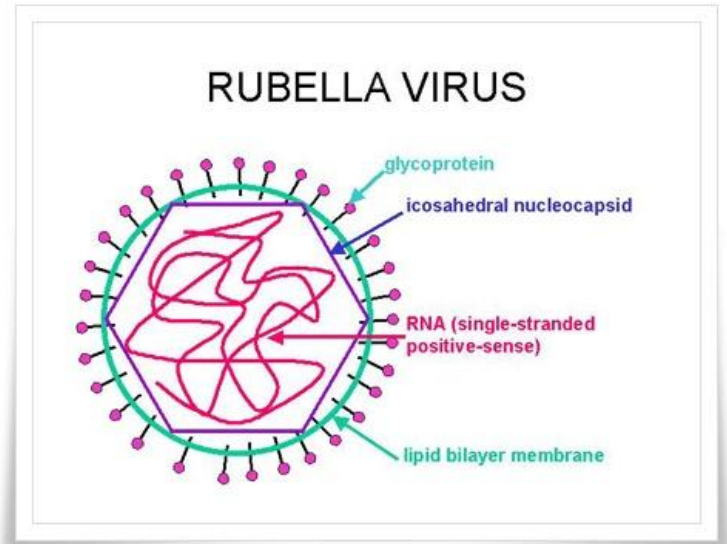
40- to 80-nm in diameter.

C. Enveloped or not.

Enveloped icosahedral virus.

D. Nucleic acid.

Rubella virus is an RNA virus, positive-sense, single-stranded RNA (+ssRNA).



PROTEINS

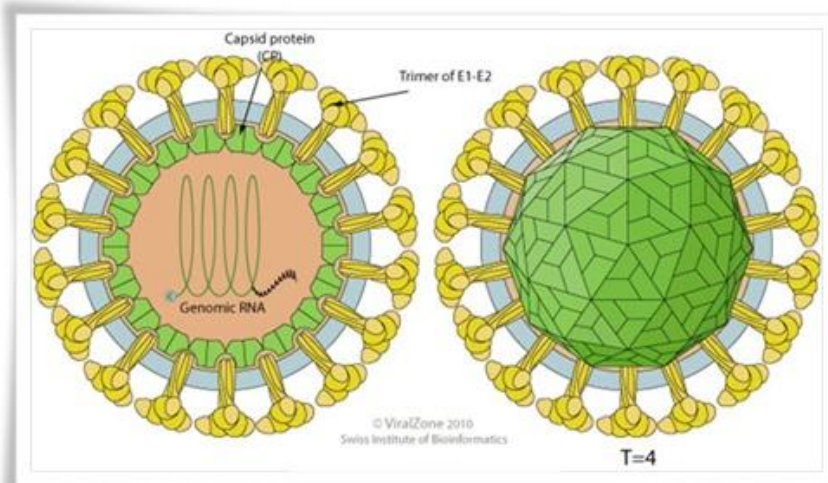
Proteins of Rubella virus:

The genomic RNA of rubella virus contains two long open reading frames (ORF), a 5'-proximal ORF that codes for the nonstructural proteins and a 3'-proximal ORF that encodes the structural proteins.

Rubella virus

A. Structural proteins:

Protein	Function
Capsid protein	Interacts with genomic RNA and assembles into icosaedric core particles. The resulting nucleocapsid eventually associates with the cytoplasmic domain of E2 at the cell membrane, leading to budding and formation of mature virions. Phosphorylation negatively regulates RNA-binding activity, possibly delaying virion assembly during the viral replication phase. Capsid protein dimerizes and becomes disulfide-linked in the virion. Modulates genomic RNA replication. Modulates subgenomic RNA synthesis by interacting with human. Induces both perinuclear clustering of mitochondria and the formation of electron-dense intermitochondrial plaques, both hallmarks of rubella virus infected cells. Induces apoptosis when expressed in transfected cells.
E1 envelope glycoprotein	a class II viral fusion protein. Fusion activity is inactive as long as E1 is bound to E2 in mature virion. After virus attachment to target cell and clathrin-mediated endocytosis, acidification of the endosome would induce dissociation of E1/E2 heterodimer and concomitant trimerization of the E1 subunits. This E1 homotrimer is fusion active, and promotes release of viral nucleocapsid in cytoplasm after endosome and viral membrane fusion. E1 cytoplasmic tail modulates virus release, and the tyrosines residues are critical for this function.
E2 envelope glycoprotein	Responsible for viral attachment to target host cell, by binding to the cell receptor. Its transport to the plasma membrane depends on interaction with E1 protein.

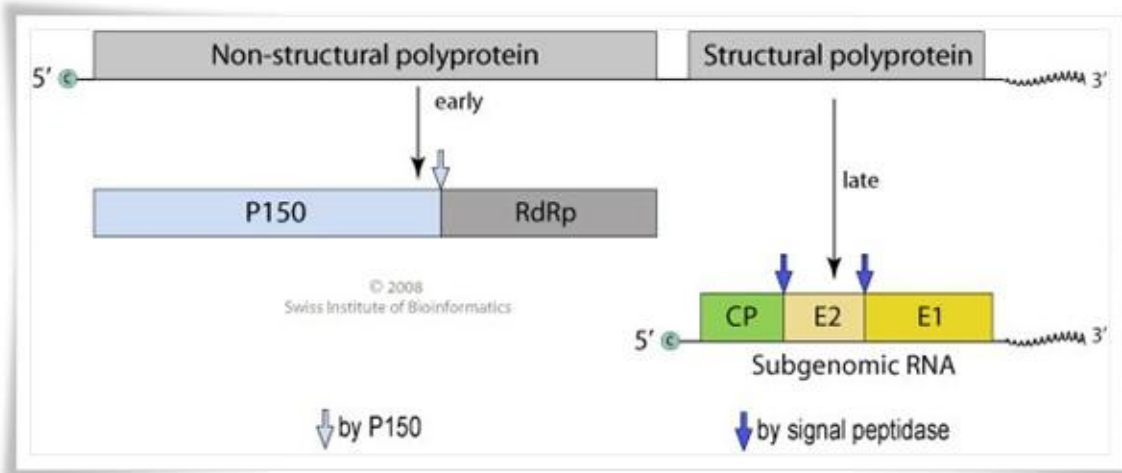


Interaction of capsid protein with genomic RNA gives the nucleocapsid.

B. Nonstructural proteins:

Non-structural polyprotein p200 replicates the 40S (+) genomic RNA into (-) antigenomic RNA. It cannot replicate the (-) into (+) until cleaved in p150 and p90.

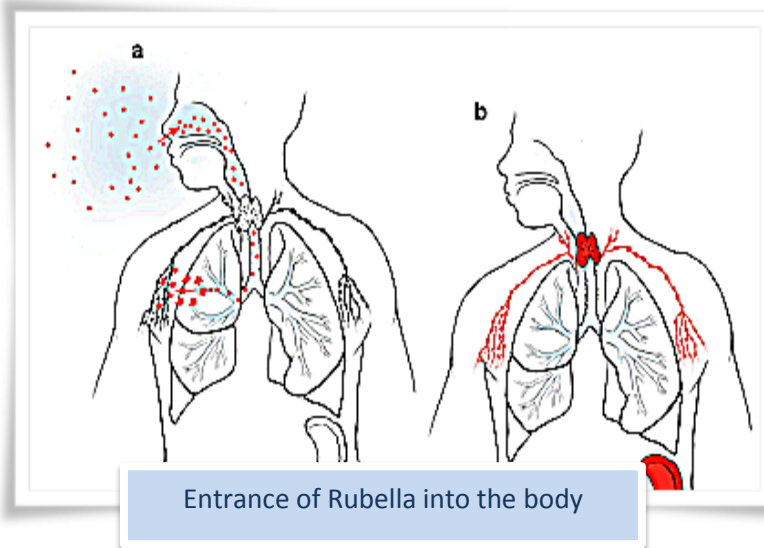
protein	function
p150	Protease p150 has 2 separate domains with different biological activities. The N-terminal section has presumably a cytoplasmic mRNA-capping activity. This function is necessary since all viral RNAs are synthesized in the cytoplasm, and host capping enzymes are restricted to the nucleus. The C-terminal section harbors a protease active in cis or in trans which specifically cleaves and releases the two mature proteins.
p90	RNA-directed RNA polymerase/triphosphatase/helicase p90 replicates the 40S genomic and antigenomic RNA by recognizing replications specific signals. Transcribes also a subgenomic mRNA by initiating RNA synthesis internally on antigenomic RNA. This 24S mRNA codes for structural proteins.



The coding for non-structural protein at 5'-proximal ORF and for structural protein at 3'-proximal ORF

TRANSMISSION OF RUBELLA VIRUS

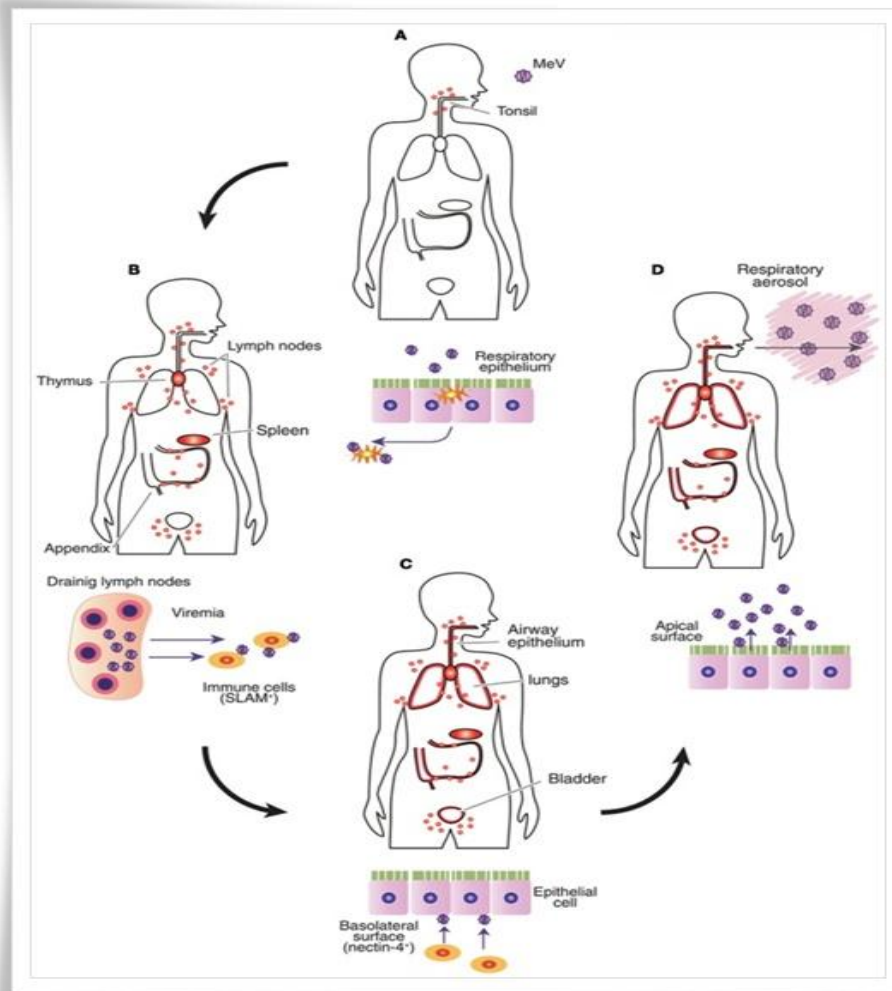
Measles is highly contagious and it lives in the mucus in the nose and throat of infected people. It can be spread by respiratory droplets and by direct contact with secretions from nose and throat of an infected person when they sneeze, cough or talk, droplets spray into the air and the droplets remain active and contagious on infected surfaces for up to two hours.



PENETRATION AND TARGET ORGAN OF RUBELLA VIRUS

The virus enters through the respiratory and almost certainly multiplies the cells of the respiratory tract. Then it extends to local lymph nodes where virus amplification, during the prodromal stage, gives rise to giant multinucleated lymphoid or reticuloendothelial cells (i.e., Warthin–Finkeldy cells). These syncytia, identified in the submucosal areas of tonsils and pharynx, are thought to be a major source of virus spread to other organs and tissues through the blood stream. Subsequent additional replication in selected target organs, such as the spleen and lymph nodes, leads to a secondary viremia with wide distribution of rubella virus. A secondary viraemia follows whereby the virus is further spread to involve the skin, the viscera, kidney and bladder. At this time the virus can be detected in the blood and respiratory secretions.

Rubella virus



This figure shows the penetration and multiplication of rubella in the respiratory tract and Lymph nodes.

THE LIFE CYCLE OF THE VIRUS

1. Transmission

The first step of the viral life cycle is transmission to a host cell. Viruses completely rely on the host organism to carry out the means of transmission. In many situations, some activity of the host organism directly transfers the virus to another organism. Certain viruses are transmitted to a new host by a vector. In complex animals and plants, viruses are transmitted from cell to cell within the body as well as transferred to a new host. Successful transmission means that the virus must make contact with uninfected host cell. For most viruses, this means that the virus must enter the body and be transferred to the particular cells that they infect.

2. Adsorption

Following the transmission step is the adsorption step, which involves the virus's attachment to the host cell's surface. Attachment typically occurs on particular cells of the host. Attachment takes place when viruses come across a cell that has cell membrane receptors that match the viral attachment proteins. Many types of receptors are found on the outer surface of the cell membrane. Receptors carry out many functions for a cell, including the detection of certain chemicals such as hormones. Viruses cannot seek out a particular receptor. They are transmitted randomly to host cells and by chance may reach a cell that matches their attachment proteins.

3. Penetration

After adsorption, the viral infection progresses to the third stage, which is called penetration. Viruses without an envelope stimulate the cell to engulf the virus. These viruses attach to a specific cell receptor that causes the cell to take in the virus. Cells engulf viruses by covering the virus with a bubble of cell membrane. The cell then moves the bubble into the cell, swallowing up the virus. Enveloped viruses enter a cell by fusing with the cell membrane. Upon fusion, the virus either blends with the cell or is engulfed in a bubble of cell membrane. The virus is not yet active at this point of infection.

4. Uncoating

Stage four of infection is the uncoating event. At this stage the envelope and capsid break apart, releasing the viral genome into the intracellular fluids. Viral replication cannot take place without this stage. Researchers have discovered that once the virus is uncoated, it is very difficult to find the viral genome in the host cell. Thus, scientists call this the eclipse phase because the virus is apparently hiding in the cell. At this stage it is possible for the cell to destroy the virus using enzymes and other molecules designed to ward off viral attack. Cells attack viruses using proteins and nucleic acids that digest viral genetic material.

5. Synthesis

The next stage is called synthesis; at this stage the cell is being directed by the virus to replicate the viral genome and capsomeres. This stage varies greatly. Each virus has a specific synthesis stage based on its genome composition and type of capsid. The viral genome serves as the blueprint for building the viral components. Overall, many viruses start the synthesis stage by first producing repressor proteins that control certain host cell functions. At this point, the cell is now diseased and does not carry out many of its vital functions. Some cells die prematurely at this stage and in turn stop viral replication. In humans, infected cells usually release signaling proteins that initiate an immune response targeted at controlling viral replication.

6. Assembly (maturation phase)

Viral assembly is the sixth stage of infection. It is some-times called the maturation phase. This is when the viral parts come together inside the infected cell to form new viruses. Mul-tiple copies of new genomes are made using the cell's chemistry for making DNA and RNA from nucleic acid building blocks in the cell. These copies then bind to viral proteins to combine the genome copies with capsomeres. The replicated capsomere proteins self-assemble around the genome or the nucleocapsid. Other proteins are also made by the host cell and self-assembled into the capsid structure. Many of the mature viruses contain defects, including incomplete genomes and abnormal capsids. The number of defective viruses is insignificant compared to the number of normal viruses that will move along successfully to the last stage of infection.

7. Releasing

The release phase is the final stage of viral infection. Like the synthesis stage, this stage varies greatly among the different types of viruses. Some viruses are released from the cell by programming the cell to undergo lysis, which causes the cell to break down and die. The cell can be induced into lysis by specific viral proteins. In many cases, a cell undergoes lysis as it slowly dies over the course of the viral infection. Other viruses remain in the cell for long periods of time without reaching the release phase. **In certain cases, these delayed viruses can cause a cell to replicate rapidly and produce a tumor. It is possible for some tumors to develop into cancer.**

Certain enveloped viruses bud from the cell. The virus forms a bud by being pushed against the inner surface of the cell until it becomes enveloped in a bubble of cell membrane. The bud is then released, and this produces a viral capsid surrounded by an envelope that is composed of cell membrane and viral proteins. Enveloped viruses usually bud slowly, which keeps the cell alive for the natural lifetime of the cell and produces a persistent infection that results in a long illness. Much of the illness associated with a viral infection is due to a loss of cell function. Viral replication prevents the cell from carrying out its functions. Some of these cell functions may affect the rest of the body. Viruses that infect cells of critical body organs can produce severe effects on the body and can lead to death. The time it takes to feel ill from a viral infection depends on the replication speed of the virus. A certain number of cells must be infected before the body is affected by the nonfunctioning cells.

REPLICATION OF RUBELLA VIRUS

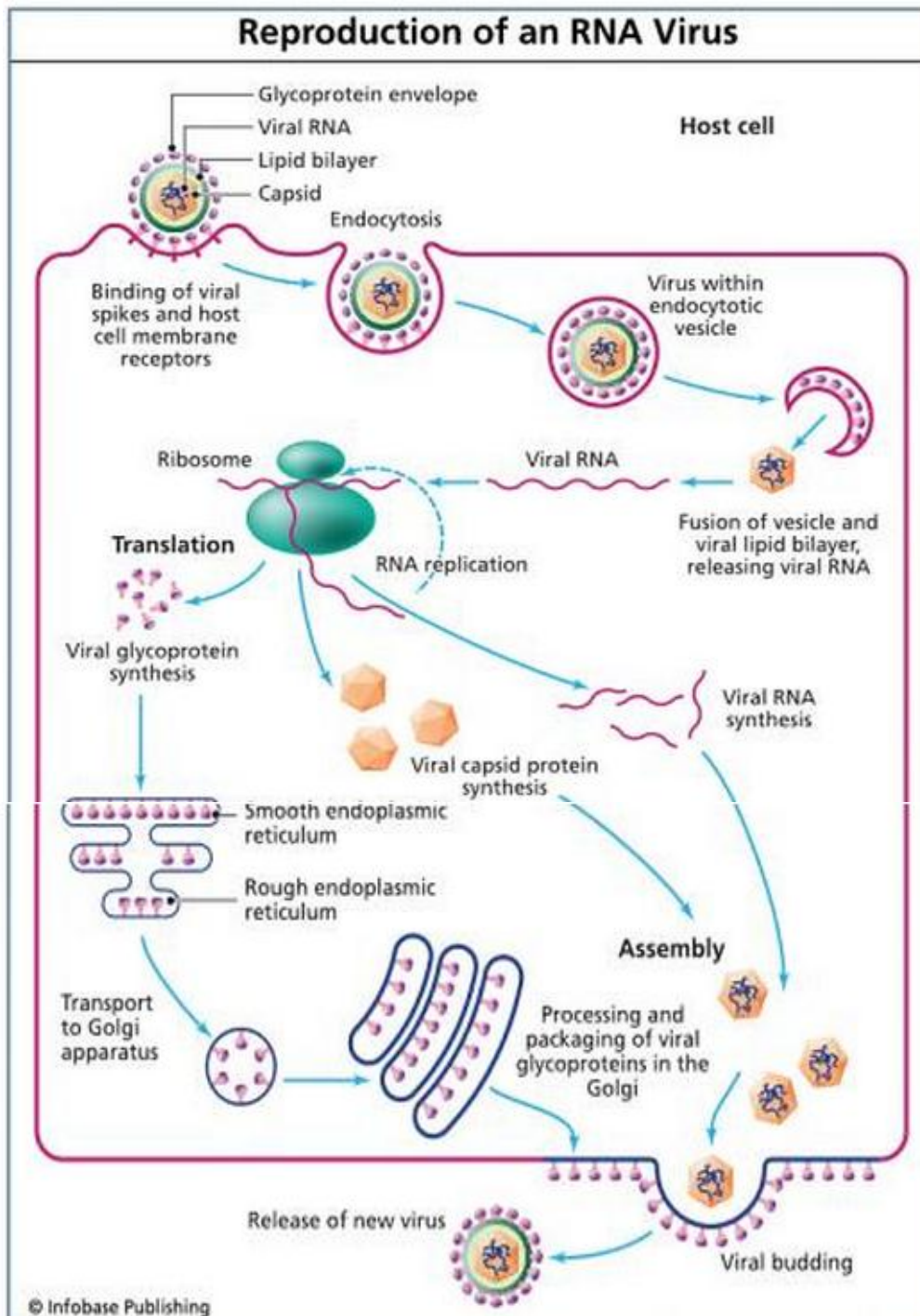


Figure 1.5 This illustration shows the viral replication process. First, the virus enters a host cell. The virus then sheds its protein coat to begin replication using the host cell's genetic material. After the new copies of the virus have been put together, they are released from the cell.

SYMPTOMS

The signs and symptoms of viral infections are caused by the immune system's reaction to the infection. Many viruses cause the immune system to release chemicals that produce :



Fever



a runny nose



rashes



tiredness

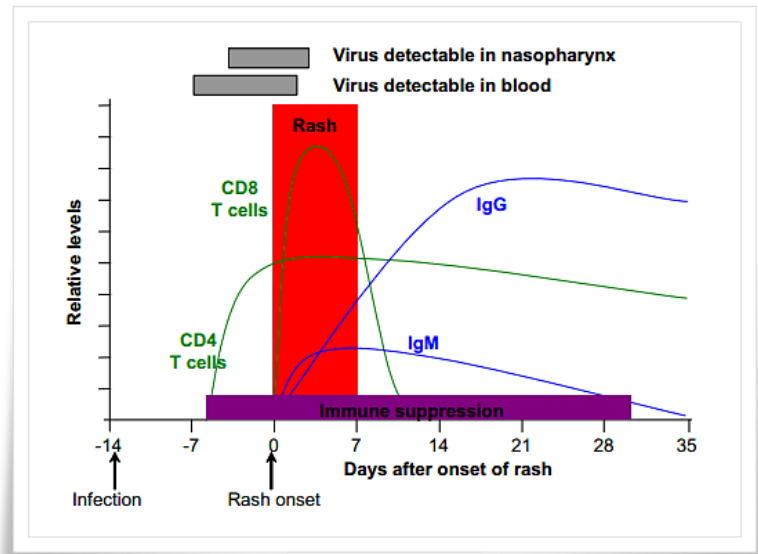


watery eyes

DIAGNOSIS:

❖ Isolation and identification of virus:

Nasopharyngeal and conjunctival swabs, blood samples, respiratory secretions, and urine collected from a patient during the febrile period are appropriate sources for viral isolation. Monkey or human kidney cells or a lymphoblastoid cell line (B95-a) are optimal for isolation attempts. Measles virus grows slowly using fluorescent antibody staining to detect measles antigens in the inoculated cultures.



❖ Serology

Serologic confirmation of measles infection depends on a **fourfold rise in antibody titer between acute phase and convalescent phase sera** (where the second serum sample is collected at least 10 days after the first, acute sample) or on **demonstration of measles specific IgM antibody** in a single serum specimen drawn between 1 and 2 weeks after the onset of rash. IgM antibody levels peak after about 7-10 days and then decline rapidly, being rarely detectable after 6-8 weeks.

❖ ELISA

used to measure measles antibodies, IgG antibody levels peak within about 4 weeks and persist long after infection. The major part of the immune response is directed against the viral nucleoprotein. The virus has been isolated from respiratory tract secretions and rarely from urine or circulating lymphocytes during the prodromal phase of illness or within a few days after the rash onset.

❖ RT-PCR

The most important role of RT-PCR in measles and rubella control lies in the genetic characterization of wild measles and rubella viruses and detecting genomic variation at different times and regions of the world. As RT-PCR can detect inactivated virus particles, the period of time when virus can be detected after rash onset is often several days to weeks longer than for virus isolation. However, RT-PCR presents a number of technical problems related to sensitivity and reproducibility that can invalidate the assay. In addition, cross-contamination during the RT-PCR process is a significant problem unless the strictest laboratory standards are established and maintained. (World Health Organization. 2007).

❖ **Diagnosis in pregnant women:**

One of the routine blood tests which is taken in early pregnancy checks for rubella (German measles) antibodies. You will be offered this test in subsequent pregnancies also:

- In most women the test is positive for antibodies, which means that you are immune.
- If your test is negative (no antibodies), you are at risk if you come into contact with rubella. You should keep away from people who might have rubella. Once your baby is born, you should be immunized to protect against rubella in future pregnancies.

CYTOPATHIC EFFECTS:

Virus replication is often detected by the morphological changes, or cytopathic effects (CPE), that are seen in infected cell cultures. (Fig. 1) illustrate the CPE typical of measles virus infection of the human HeLa cell line. The large syncytia, or multinucleated giant cells, result from fusion of cell membranes bearing viral glycoproteins. Also visible in this culture (Fig. 2) are inclusion bodies, which are seen as eosinophilic areas of altered staining in the cytoplasm. For comparison, (Fig. 3) show the uninfected Vero cell. several nucleoli are visible inside each nucleus. Note the eosinophilic cytoplasm (pink) and basophilic nuclei (purple).

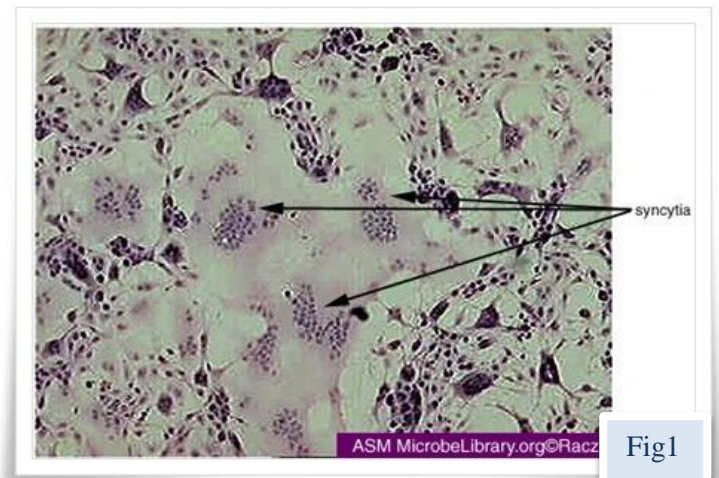


Fig1

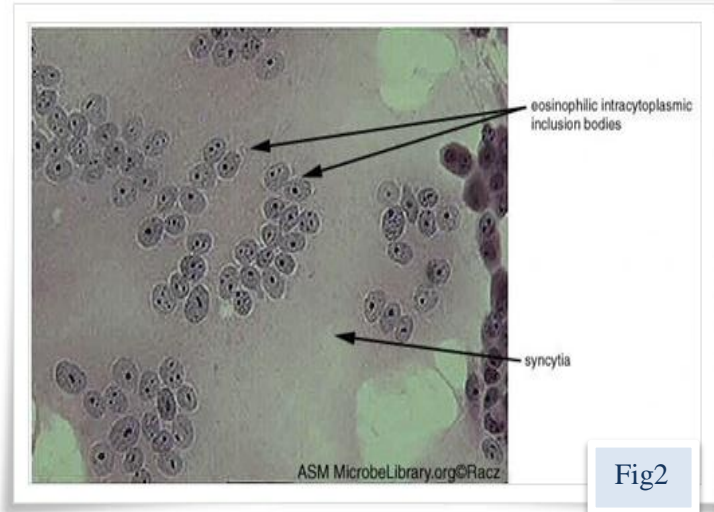
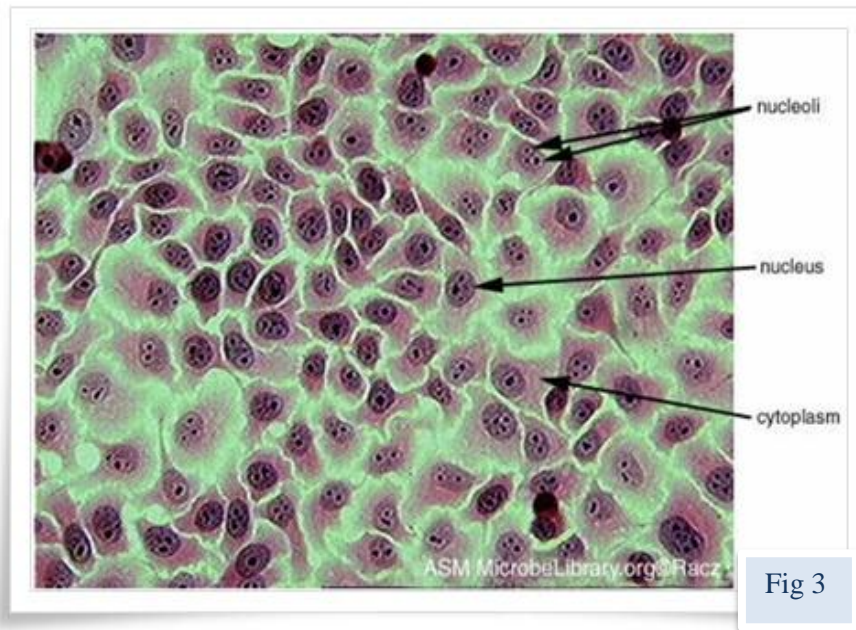


Fig2



PREVENTION

There is a safe and effective vaccine to prevent rubella. The rubella vaccine is recommended for all children. It is routinely given when children are 12 to 15 months old, but is sometimes given earlier during epidemics. A second vaccination (booster) is routinely given to children ages 4 to 6. MMR is a combination vaccine that protects against measles, mumps, and rubella. Women of childbearing age usually have a blood test to see if they have immunity to rubella. If they are not immune, women should avoid getting pregnant for 28 days after receiving the vaccine. Those who should not get vaccinated include: Women who are pregnant and Anyone whose immune system is affected by cancer, corticosteroid medications, or radiation treatment (Coonrod, Jack et al. 2008).

TREATING RUBELLA

There is no specific treatment for rubella, but symptoms will normally pass within seven to 10 days. If the child are finding the symptoms uncomfortable, can treat some of these at home while wait for the infection to pass For example, paracetamol or ibuprofen can be used to reduce the fever and treat any aches or pains. Liquid infant paracetamol can be used for young children. Aspirin should not be given to children under 16 years old. If contract rubella while women pregnant, discuss the risks to your baby with your doctor. If you wish to continue your pregnancy, you may be given antibodies called hyperimmune globulin that can fight off the infection. This can reduce your symptoms, but doesn't eliminate the possibility of your baby developing congenital rubella syndrome

VACCINATION

The rubella vaccine is a live attenuated strain that has been in use for more than 40 years. A single dose gives more than 95% long-lasting immunity, which is similar to that induced by natural infection. Rubella vaccines are available either in monovalent formulation (vaccine directed at only one pathogen) or more commonly in combinations with other vaccines such as with vaccines against measles (MR), measles and mumps (MMR), or measles, mumps and varicella (MMRV). Adverse reactions following vaccination are generally mild. They may include pain and redness at the injection site, low-grade fever, rash and muscle aches. Mass immunization campaigns in the Region of the Americas involving more than 250 million adolescents and adults did not identify any serious adverse reactions associated with the vaccine.



GENETICS (GENE MUTATION):

There is No gene mutation that Cause another disease.

RECENT DISCOVERIES:

There are no recent study on rubella virus latest studies were in the 2016 Congenital rubella syndrome (CRS) was discovered in the 1940s, rubella virus was isolated in the early 1960s, and rubella vaccines became available by the end of the same decade. Systematic vaccination against rubella, usually in combination with measles, has eliminated both the congenital and acquired infection from some developed countries, most recently the United States, as is confirmed by the articles in this supplement. The present article summarizes the clinical syndrome of CRS, the process by which the vaccine was developed, and the history leading up to elimination, as well as the possible extension of elimination on a wider scale.

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