RESPIRATORY VIRUSES

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Orthomyxoviridae: Influenza

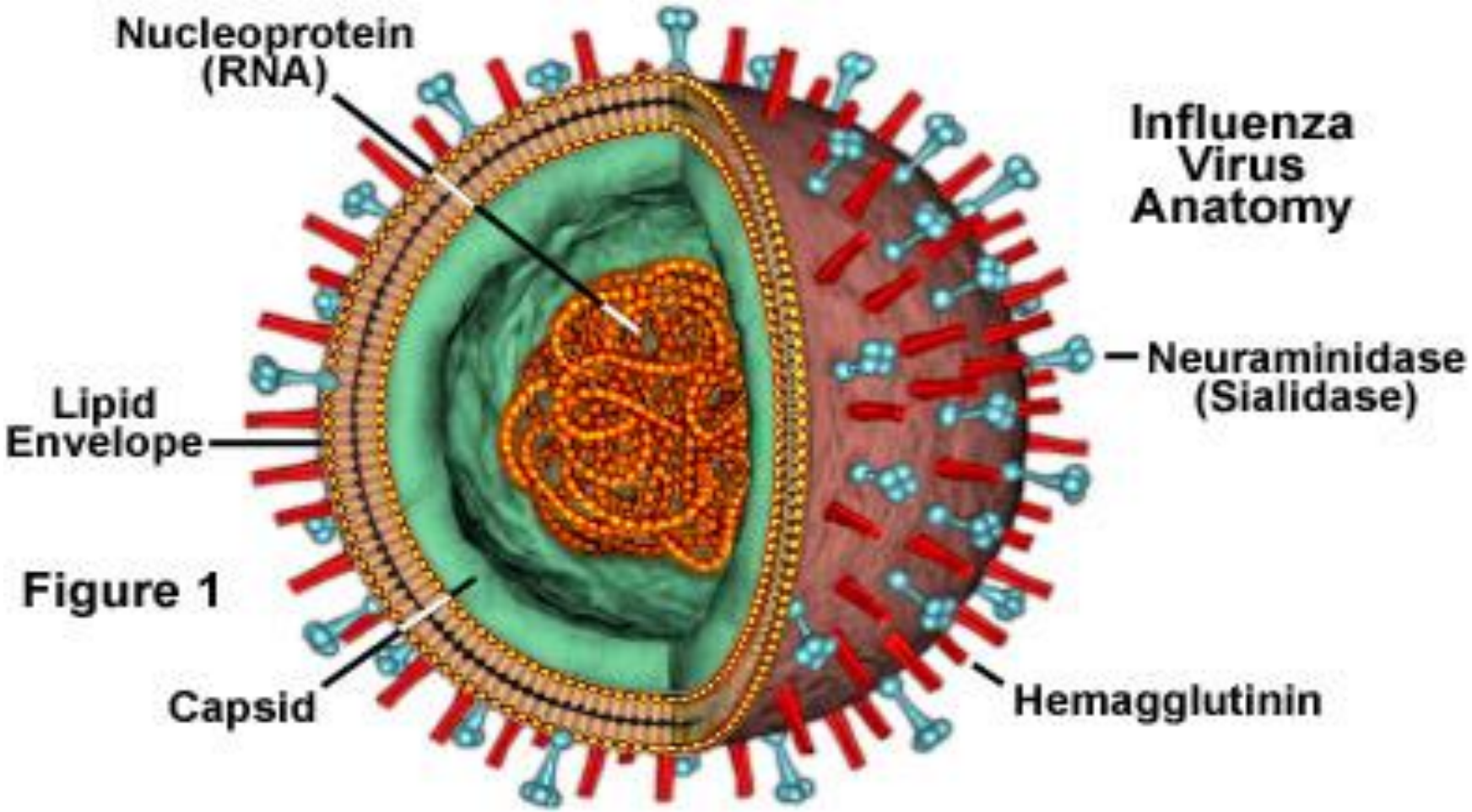
- Orthomyxovirus are Single stranded , negative sense RNA viruses each containing 8 segment code for a single protein.
- They are Helical in shape
- Contain a lipid envelope derived from the host cell
- The envelope contains glycoprotein spikes – the Heamaglutinin (HA) and Neuramidase (NA).

Introduction

- Orthomyxoviruses are divided into three types, Type A, Type B and Type C.
- They cause highly contagious airborne respiratory illness- Influenza

	Influenza A	Influenza B	Influenza C
Genetic structure	8 segments	8 segments	7 segments
Viral proteins	10 total	11 total	9 total
Unique viral protein	M2	NB	HEF
Antigenic determinants	Hemagglutinin and neuroaminidase	Hemagglutinin and neuroaminidase	Hemagglutinin and neuroaminidase
Genetic change	Antigenic shift and drift	Antigenic drift	Antigentic drift
Host range	Avians, humans swine, marine mammals, horses	Humans	Humans and swine
Human epidemiology	Pandemics and seasonal epidemics	Seasonal epidemics	No seasonality

INFLUENZA


Nucleoprotein
(RNA)
Influenza
Virus
Anatomy
Neuraminidase
(Sialidase)
Lipid
Envelope
Figure 1
Capsid
Hemagglutinin

HAEMAGGLUTININ, NEURAMINIDASE

- The two virulence factors are very important to the virus, and they help the virus enter and exit the host cell.
- HA binds to sialic acid residues on target cells to initiate infection.
- NA degrades the mucus layer to expose these residues.
- After replication, NA cleaves sialic acid to facilitate release of the progeny viruses.

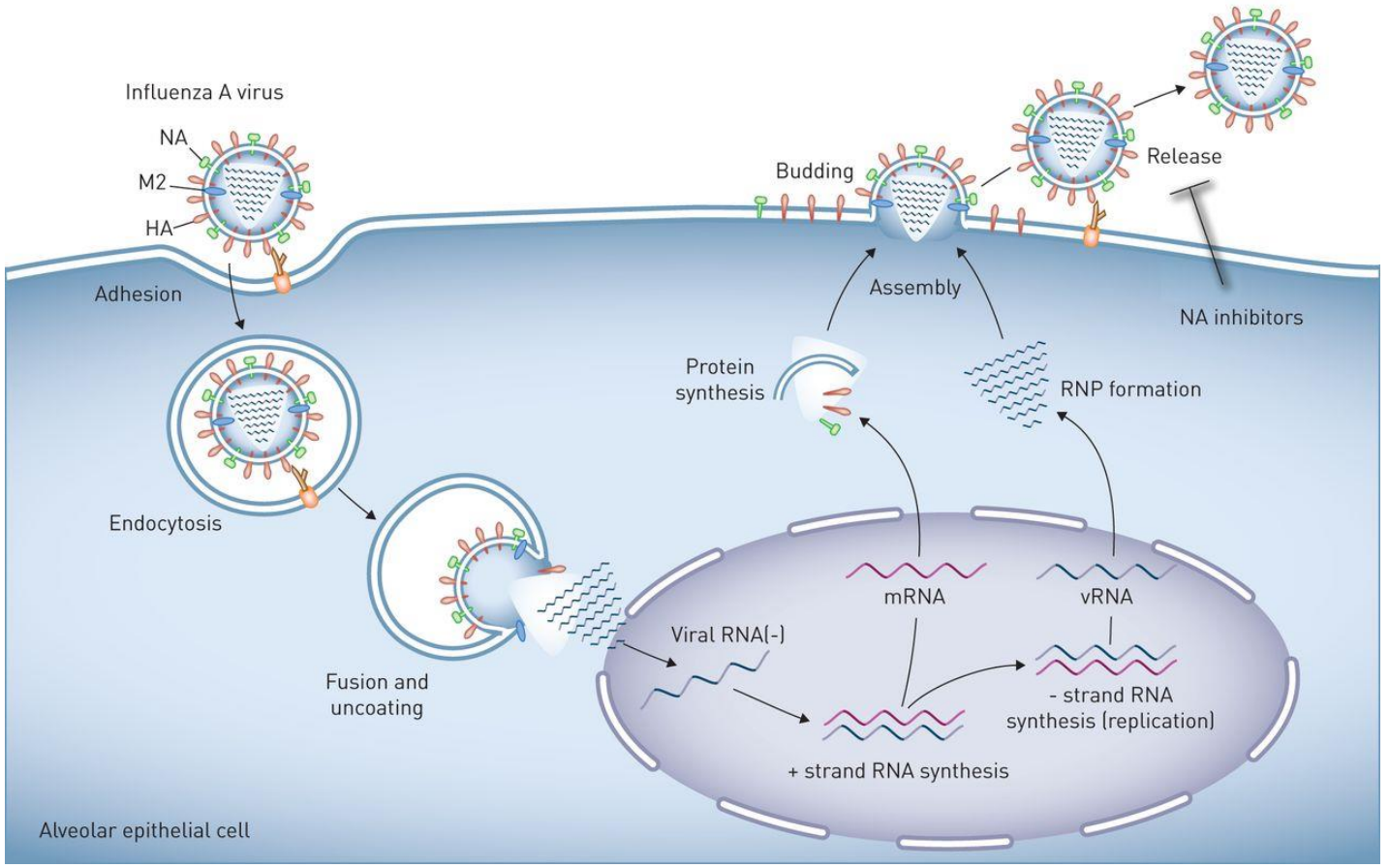
HA, NA continued

- They are key antigenic components – variation in their sequence is the basis of subtyping of influenza viruses.
- HA is the major antigen against which protective neutralizing antibodies are formed.
- NA is an important drug target- inhibitors e.g. Zanamivir, Oseltamivir.

Replication

- Entry – this is facilitated by Haemagglutinin binding to sialic acid.
- Uncoating –this is facilitated by low pH in the endosomes due to the entry of protons via the M2 ion channels.
- Transcription –important steps in the Nucleus – the viral RNA polymerase transcribes all genomic segments to mRNA
- The mRNA then moves to the cytoplasm for the translation to protein.
- Assembly – the assembly of nucleocapsid is the nucleus.
- These are then released by budding through a membrane embedded with the glycoprotein HA, NA.

Image of the process



Antigenic shift and Drift

- Influenza viruses are genetically labile with resulting variations in HA, and NA.
- Antigenic drift- Minor changes resulting from point mutations- these are frequent and a cause of seasonal outbreaks.
- Antigenic shift- these are Major changes based on reassortment of genomic segments between two strains. This is done in the mixing chamber.

Antigenic shift

- The reassortment of the segments involves coinfection with two strains of influenza A Virus in a Host or mixing chamber- pigs.
- This gives rise to a virus that is more virulent than individual strains.
- Causes pandemics – Spanish flu pandemic of 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) etc.

Pathogenesis

- Airborne droplets are transmitted to the upper airway.
- Primary ifxn occurs marked by multiplication in ciliated columnar epithelial cells, impairing ciliary fxn.
- Cytotoxic and immunologic damage results in desquamation.
- Secondary bacterial ifxn may follow.

Clinical features

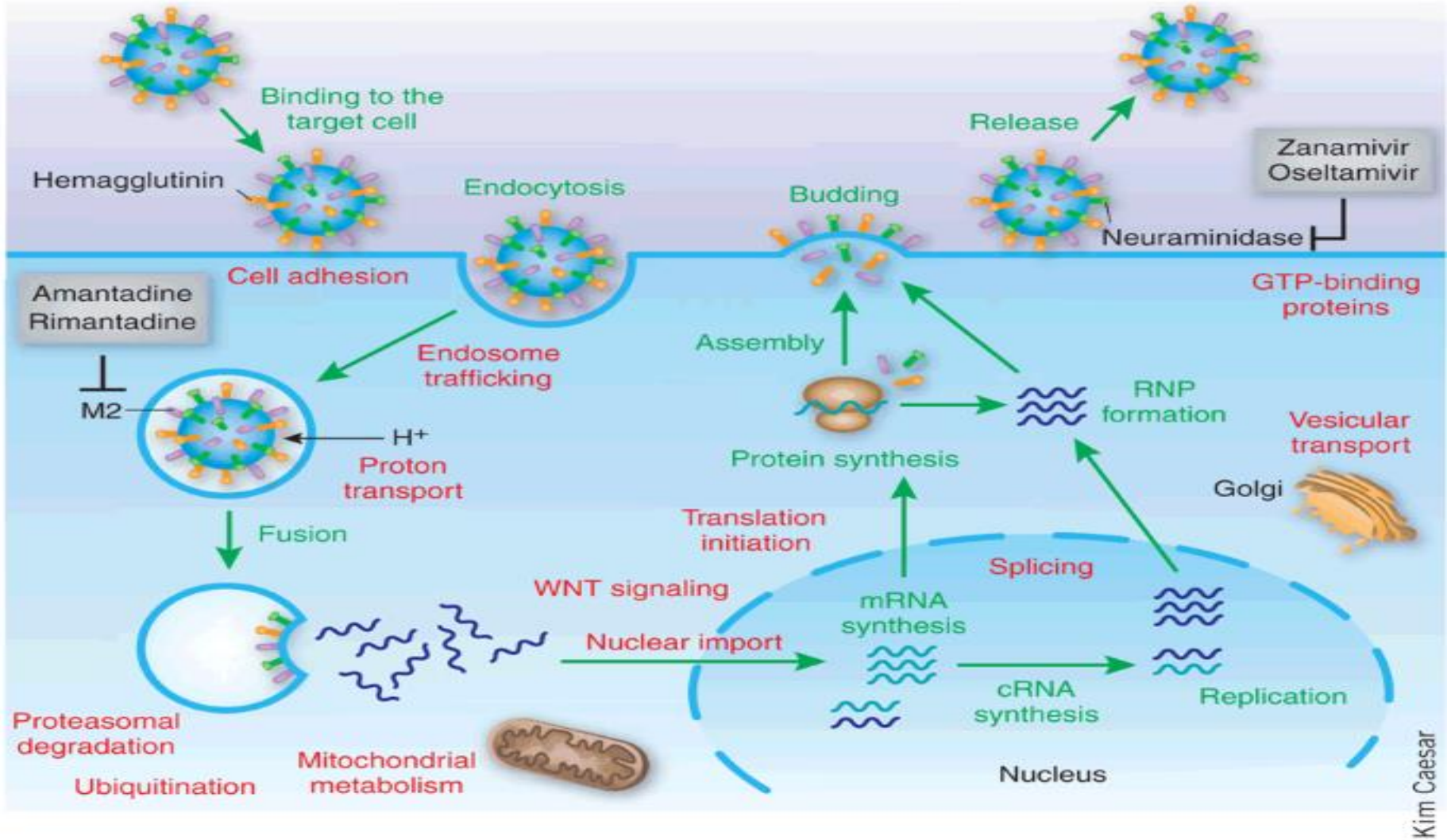
- Incubation period- 24-48hrs
- Cxr by sudden onset of fever, Myalgia, headache, sore throat, cough.
- Symptoms resolve in 7-14 days.
- Complications may occur in immune incompetent individuals e.g. extremes of age, DM, cancer, or other medical conditions.
- Bacterial superimposition can worsen the condition.

Laboratory diagnosis

- Diagnosis is mostly clinical, but lab confirmation is necessary , esp. in outbreaks
- Nasal and throat swabs, sputum is used
- Viral isolation in a cell culture.
- Identification of viral antigens – serology
- RT-PCR to detect viral RNA

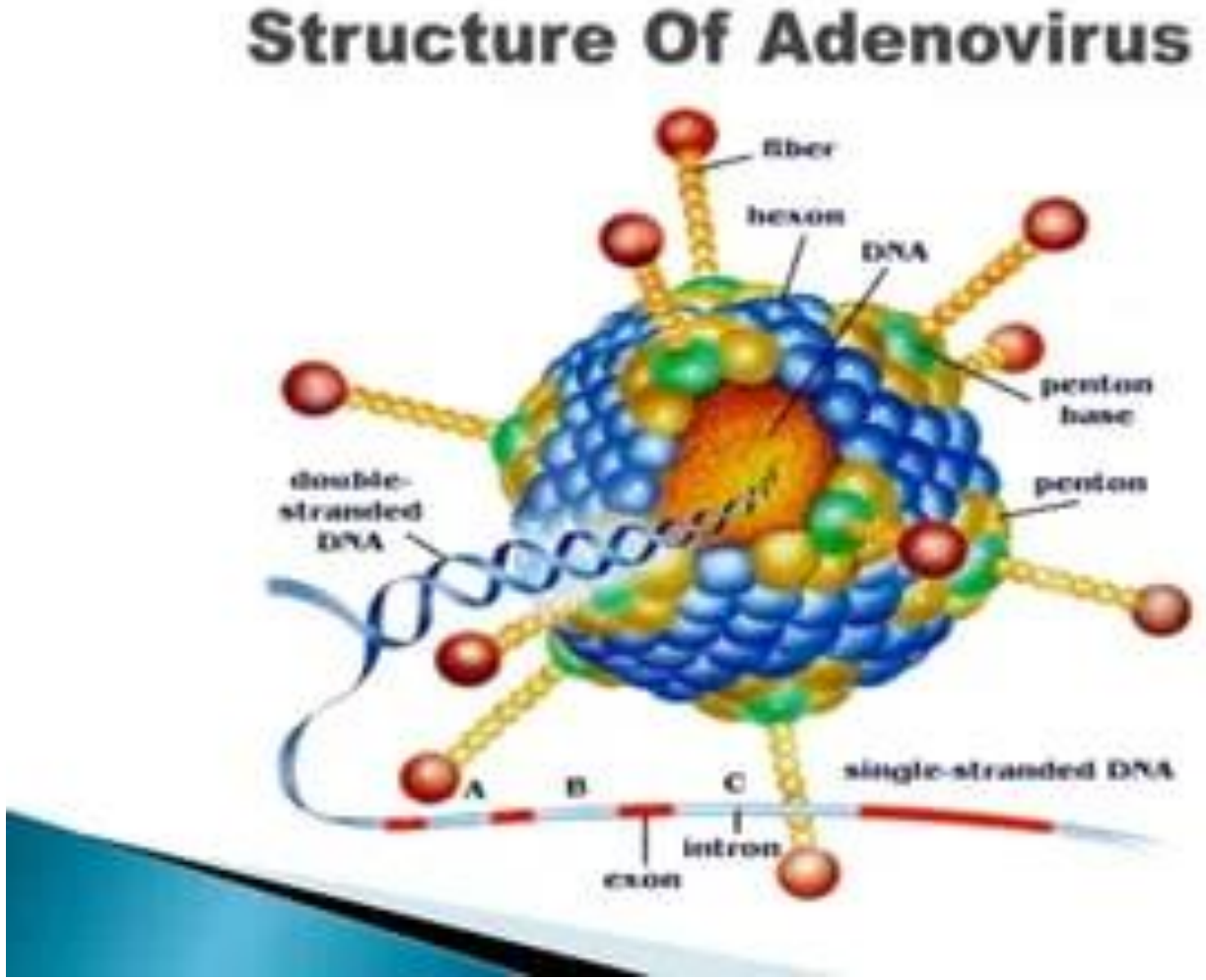
Treatment/ Prevetion

- Symptomatic treatment- Fluids,O2, Pain relief
- the antivirals are only effective when given early- reduce the duration of illness and severity.
- Drugs such as Oseltamivir, Zanamivir- NA inhibitors.
- M2 ion channel blockers- Amantadine, Rimantadine.
- Vaccination- vaccines available for high risk groups eg Health workers, pt with comorbidities.


Binding to the target cell
Hemagglutinin
Endocytosis
Cell adhesion
Amantadine
Rimantadine
M2
Endosome trafficking
H+
Proton transport
Fusion
Proteasomal degradation
Ubiquitination
Mitochondrial metabolism
WNT signaling
Nuclear import
Translation initiation
mRNA synthesis
Splicing
cRNA synthesis
Replication
Nucleus
Protein synthesis
Assembly
Budding
RNP formation
Release
Zanamivir
Oseltamivir
Neuraminidase
GTP-binding proteins
Vesicular transport
Golgi
Kim Caesar

ADENOVIRUSES

- Classification
- Family: Adenoviridae
- Genus: Mastadenovirus
- Species: Human Adenovirus



MORPHOLOGY

- Naked, capsid,Icosahedral, about 80-110nm diameter
- 252 capsomers
- Fibre projects from each of the 12 vertices, these fibers interact with receptors of host cells
- It has a dsDNA
- Replicates in the nucleus

- 57 serotypes of adenovirus infect humans which are classified into 6 subgroups (A-F)
- Adenovirus generally causes respiratory infection and depending on the serotypes, they can even cause gastroenteritis, conjunctivitis, and neurological disease.

Group affected	Syndromes	Adenovirus serotypes
Neonates	Fatal disseminated infection	3,7,21,30
Infants	Coryza, pharyngitis (most asymptomatic)	1,2,5
Children	Upper respiratory disease	1,2,4–6
	Pharyngoconjunctival fever	3,7
	Haemorrhagic cystitis	11,21
	Diarrhoea	2,3,5,40,41
	Intussuception	1,2,4,5
	Meningoencephalitis	2,6,7,12
Young adults	Acute respiratory disease and pneumonia	3,4,7
Adults	Epidemic keritoconjunctivitis	8,19,37
Immunocompromised	Pneumonia with dissemination, urinary tract infection	5,31,34,35,39,42–47
	CNS disease including encephalitis	7,12,32

*Adapted from reference 8

Viral replication

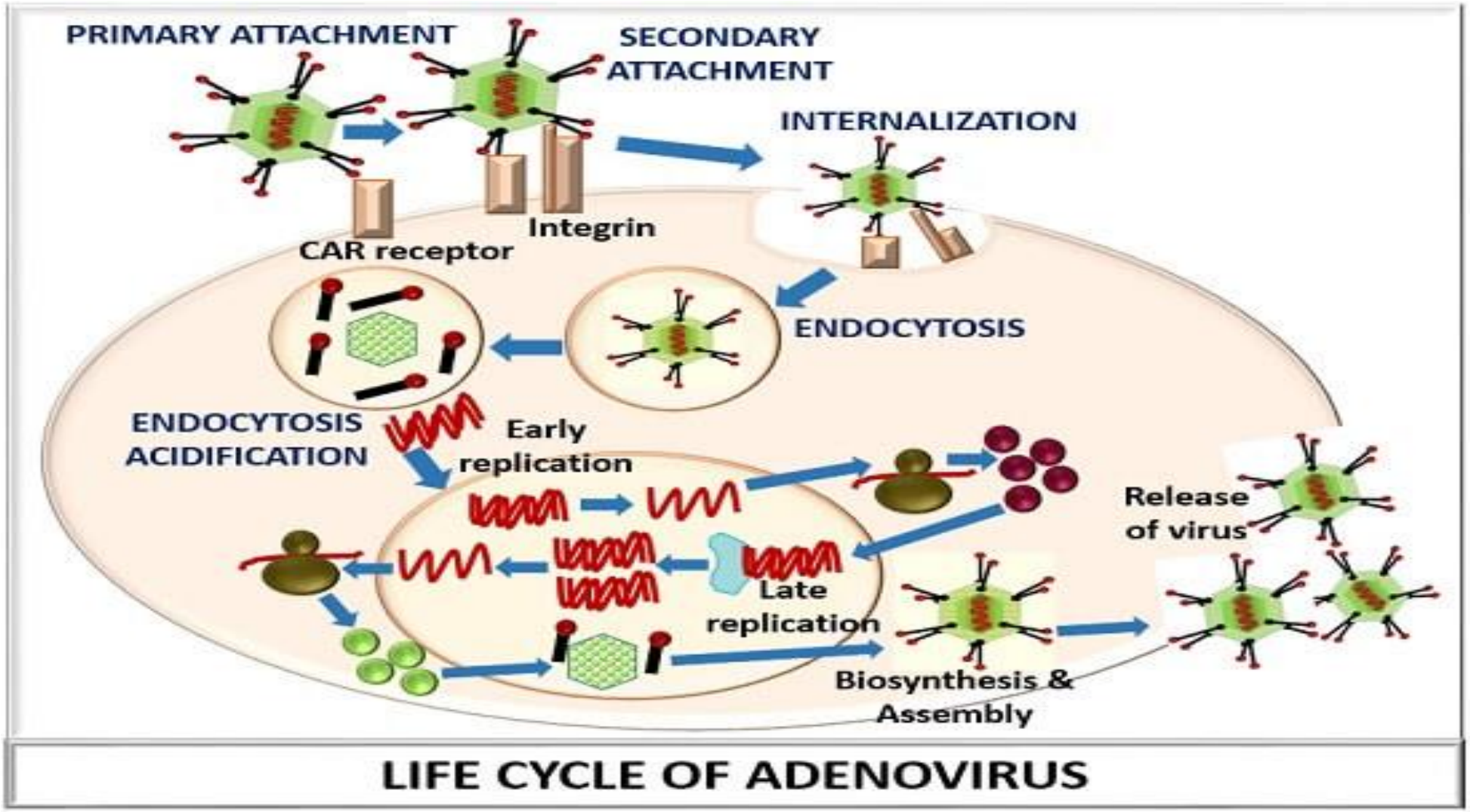
- Adenoviruses attach to the surface of the cells by their fibers, then penetrate the cell via endocytosis
- They uncoat their viral DNA
- The viral DNA is then transported into the nucleus of the cells and initiates the replication cycle
- The host cell DNA-dependent RNA polymerase transcribes the early genes leading to the formation of functional mRNA

- Then in the cytoplasm the early mRNA is translated into nonstructural proteins

- In the nucleus after viral DNA replication, late mRNA is transcribed and then translated into structural virion proteins

- This is then followed by the assembly of virions in the nucleus and the release of virions by lysis of the cells

Viral replication



Pathogenesis

- Enter host cells via respiratory- inhalation of droplet nuclei or fecal oral route
- Direct inoculation of the nasal or conjunctival mucosa by hands, contaminated towels or ophthalmic meds.
- Virus replicates in the epithelium and cause inflammation and necrosis
- After local replication, viremia occurs which follows spread to visceral organs.
- Common in immunocompetent individuals

TABLE 33-5

Clinical Syndromes Associated with Adenovirus Infection

SYNDROME	COMMON SEROTYPES[a]
Childhood febrile illness; pharyngoconjunctival fever	1, 2, **3**, 5, 7, **7a**
Pneumonia and other acute respiratory illnesses	1, 2, **3**, 5, 7, **7a**, **7b** (4 in military recruits)
Pertussis-like illness	1, 2, **3**, 5, **19**, 21
Conjunctivitis	2, 5, 7, 8, **19**, 21
Keratoconjunctivitis	**3**, 8, 9, **19**
Acute hemorrhagic cystitis	11
Acute gastroenteritis	40, 41

[a]Serotypes in **boldface** are those commonly associated with outbreaks.

Diagnosis

- Swabs; throat and eye
- Specimens- urine, feaces
- Isolation – live cell cultures (
- Serology ,Elisa
- Electron Microscopy
- PCR

Treatment and prevention

- No specific treatment
- Symptomatic relief
- No vaccine for general use
- killed and live vaccines used for the control of outbreaks in close communities e.g. military bases.

Respiratory Syncytial Virus

Classification

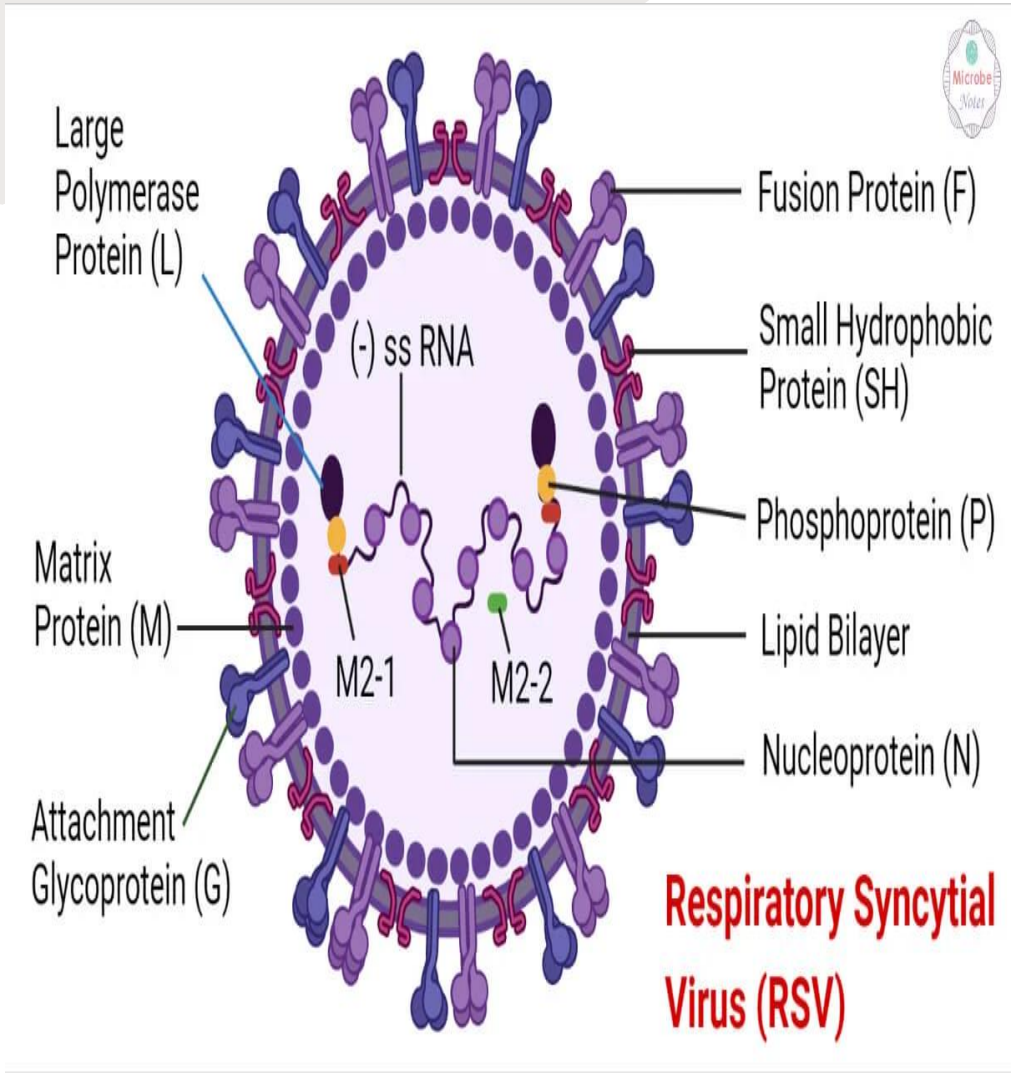
- Family : paramyxoviidae
- Sub family : Pneumovirinae
- Genus: Pneumovirus

Morphology

- Irregular spherical particles
- Diameter range 150-300nm

- Consists of nucleocapsid contained in a lipid envelope

- Non-seg, SS neg sense genome of helical symmetry



- The genome encodes 11 proteins
- 9 structural (L,G,F,N,P,M,M2-1,M2-2,SH)
- And two non-structural (NS1 and NS2)
- RSV is divided into two antigenic subgroups (A and B) on the basis of the G surface glycoprotein

Epidemiology

- Prevalent worldwide
- Highly contagious in nature
- Prevalent in young children with peak incidence in 2-8 months of age
- Most children are infected by RSV by the age of 4 years
- Shed in the respiratory secretions for several days, sometimes weeks
- O/break in neonatology wards are common

Replication

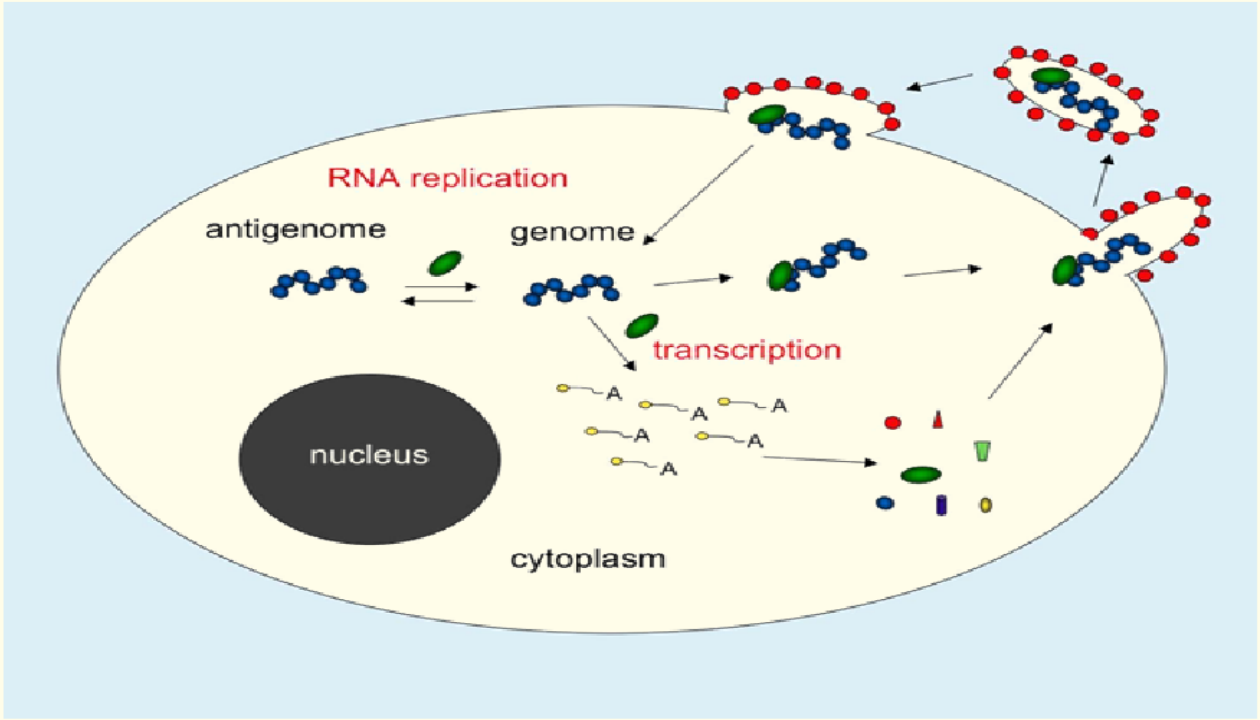


Figure 3: *The RSV replication cycle. The virus enters by direct fusion at the plasma membrane, releasing the encapsidated genome RNA (blue) and RNA dependent RNA polymerase (green) into the cytoplasm. The polymerase uses the genome as a template to produce capped and polyadenylated mRNAs, which are translated into viral proteins, and encapsidated antigenome and genome RNAs. The resulting encapsidated genomes are assembled with other viral proteins and bud from the plasma membrane to produce progeny virus particles. (Courtesy of Rachel Fearns, Ph.D. Associate Professor of Microbiology, School of Medicine, Boston University, USA). ref: http://www.bumc.bu.edu/microbiology/people/faculty-old/rachel-fearns-phd/*

Transmission

- Droplet inhalation
- Direct contact with contaminated hands and formites

Pathogenesis

- RSV is restricted to the respiratory tract
- Innococulation of the virus occurs through the upper resp. tract and initiates infxn in the epi. Cells
- Spreads along the epi. Of the resp. tract mostly by cell-to-cell transfer of the virus along intracytoplasmic bridges (syncytial formation)
- As it spread to the lower respiratory tract it may produce a pneumonia or bronchiolitis

Immunity

- Antibodies of Ig A, IgM, and Ig G classes are produced but plays a minimal role
- Cell-mediated immunity is key to the severity and recovery from RSV infxn
- Reinfection may occur but of low severity

Clinical manifestation

- Incubation period is 2-4days
- Upper resp. symptoms occur- rhinitis, flu like symptoms
- The illness then progresses to peak within 1-3 days
- In infants the peak usually takes the form of a bronchiolitis and pneumonitis with cough, wheezing and respiratory distress
- In older children the dz is mild- croup, tracheobronchitis and URI

Diagnosis

- Use of immunofluorescence or Immunoenzyme detection of the viral antigen
- PCR
- Live cell cultures

Prevention and treatment

- Supportive symptomatic care
- O2 support, ventilation ,
- Monitor for complications such as bacterial superimposition – cover on antibiotics
- No successful vaccine to date.

THANK YOU