RESPIRATORY DISEASE: WHAT IS THE ACTUAL CAUSE AND WHAT CAN WE DO?

APRIL NELSEN, PHD MLS (ASCP)^{CM}, ASSISTANT CLINICAL PROFESSOR/ CLINICAL COORDINATOR
SOUTH DAKOTA STATE UNIVERSITY

1

OBJECTIVES

- Define Respiratory Disease in its entirety.
- Understand significant contributors to respiratory disease, identification of respiratory pathogens, and how pathogen mutation can result in alternative hosts or alternative tissue tropism.
- Formulate methods for early identification and prevention of respiratory pathogens.

2

CONFLICTS OF INTEREST/ DISCLAIMER:

I have no conflicts to disclose.

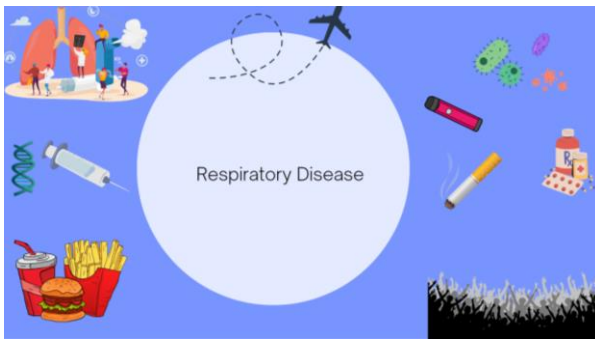
I will mention specific manufacturers and their products during this presentation. My comments should not be interpreted as an endorsement of any manufacturer or their product(s).

3

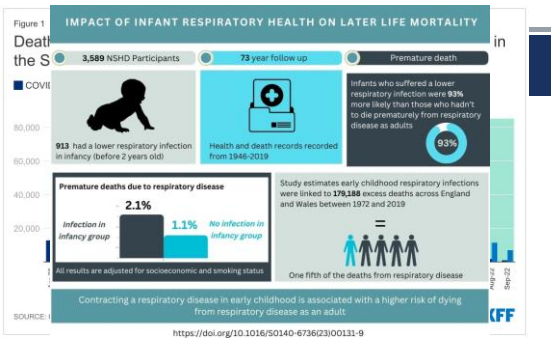
INTRODUCTION

- Respiratory Disease
  - Public Health Concern
  - Economic Concern
  - Pathogens

4



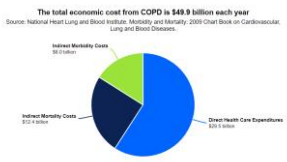
5



https://doi.org/10.1016/S0140-6736(23)00131-9

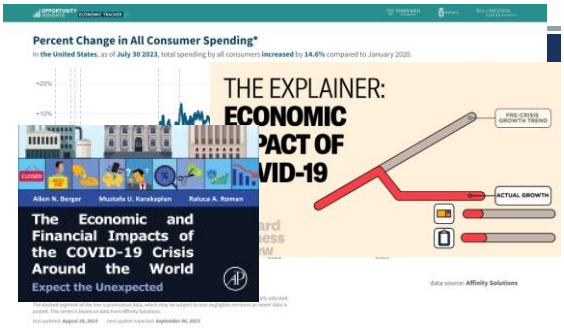
6

ECONOMIC HEALTH CONCERN



American Lung Association

7



8

PATHOGENS

- *Viruses*

Adenovirus
Bocavirus
Coronavirus 229E
Coronavirus HKU1
Coronavirus NL63
Coronavirus OC43
Enterovirus (Pan)
Enterovirus D68
Herpesvirus 6 (HHV6)
HHV3 (varicella zoster virus)
HHV4 (Epstein-Barr virus)
HHV5 (cytomegalovirus)
Metapneumovirus (hMPV)
Influenza A (Pan)
Influenza A/H1-2009
Influenza A/H3
Influenza B
Measles virus
MERS-CoV
Mumps virus
Parainfluenza virus 1
Parainfluenza virus 2
Parainfluenza virus 3
Parainfluenza virus 4
Parechovirus
Respiratory Syncytial Virus A (RSV A)
Rhinovirus
Respiratory Syncytial Virus B (RSV B)
*SARS-CoV (SARS)****
*SARS-CoV-2****

- *Fungus/Bacteria*

P. Jirovecii
Bordetella (Pan)
Bordetella pertussis
*Bordetella holmesii**
Chlamydophila pneumoniae
Clavella haemolyticum
Haemophilus influenzae
Klebsiella pneumoniae complex
Legionella pneumophila
Moraxella catarrhalis
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae

9

VIRUS REVIEW

Virus Classification

- The type of nucleic acid which is found in the virion (RNA or DNA)
- The symmetry and shape of the capsid
- The presence or absence of an envelope
- The size of the virus particle
- **Genome (ICTV)**

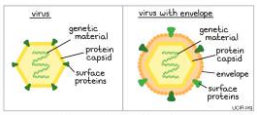
Genome

- DNA
  - Almost all dsDNA
  - Some ssDNA
- RNA
  - Almost all ssRNA
    - Positive (+) sense ssRNA
    - Negative (-) sense ssRNA
  - dsRNA
  - Ambisense- both (+) and (-) strands

10

VIRAL STRUCTURE

Enveloped vs Naked



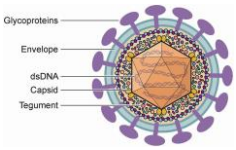
What are oncolytic viruses? (ucsr.org)

Capsids

How a virus forms a protective shell to evade the immune system (news-medical.net)

11

DNA VIRUS BASIC STRUCTURE EXAMPLE

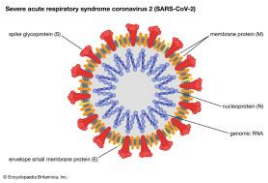


Herpes Simplex Virus Antigens - Creative Diagnostics (creative-diagnostics.com)

- Low mutation rate
- Replication in host nucleus

12

RNA VIRUS BASIC STRUCTURE EXAMPLE



- High mutation rate
- Replication in host cytoplasm

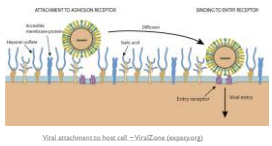
13

VIRUS-CELL INTERACTIONS

- **Attachment**
  - **Viral attachment proteins**
  - **capsid (naked virus)**
  - **Glycoproteins (spikes): enveloped virus**
  - **Cell surface molecules as receptors, or co-receptors (accessory receptors)**
- **Entry**
  - **Receptor mediated endocytosis (most viruses)**
  - **Membrane fusion(some enveloped viruses)**
- **Uncoating**
  - **Plasma membrane**
  - **Cytoplasm (endosome)**
  - **Nuclear membrane**
- **Replication of genome and protein synthesis**
- **Virus assembly and release**

14

ATTACHMENT

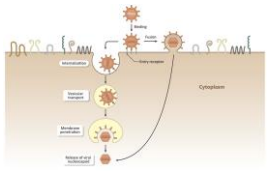


Viral attachment to host cell – ViralZone (expasy.org)

- Attachment (reversible)
  - virus attachment proteins (capsids or glycoproteins)
  - receptors and accessory receptors or co-receptors (cell surface molecules), proteins or carbohydrates
  - virus tropism (spectrum of cells that virus can infect)

15

ENTRY

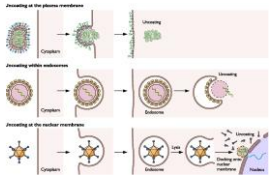


Virus Entry | GeneTex

- Entry (penetration cross the plasma membrane, irreversible)
  - Receptor mediated endocytosis (the most common) into clathrin-coated vesicles and endosomal pathway
  - Cell membrane fusion (usually enveloped virus) plasma membrane or intracellular membrane
  - Translocation: very rare

16

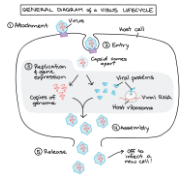
UNCOATING



- Uncoating(release of nucleic acid from its protein coat)
  - uncoating at the plasma membrane (Paramyxovirus)
  - uncoating within endosome triggered by change in pH (Influenza)
  - uncoating at the nuclear membrane

17

REPLICATION

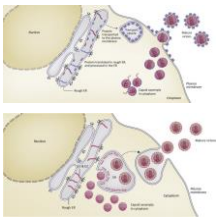


Intro to viruses (article) | Viruses | Khan Academy

- Replication and protein synthesis
  - In general, early proteins (viral enzymes, regulatory proteins) are synthesized first, followed by virus genome replication and late proteins (structural proteins) synthesis

18

ASSEMBLY AND RELEASE



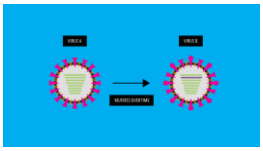
- Assembly and release
  - Non-enveloped virus become mature inside the cell and are released by cell lysis
  - Enveloped viruses mature by budding from the membrane of host cells

Virus Release - an overview | ScienceDirect Topics

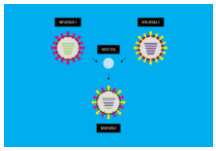
19

VIRAL MUTATIONS

Antigenetic Drift



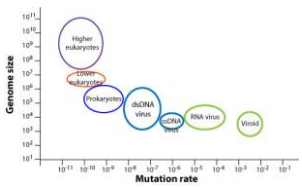
Antigenetic Shift



How Do Viruses Mutate and What it Means for a Vaccine? | Pfizer

20

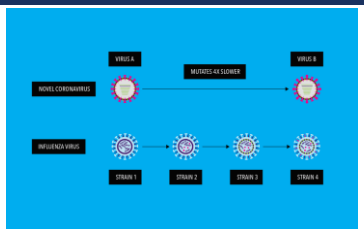
VIRAL MUTATIONS



Viral genome evolution – ViralZone (expasy.org)

21

VIRAL MUTATIONS

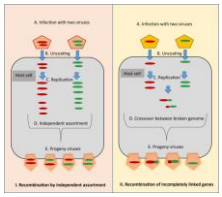


How Do Viruses Mutate and What it Means for a Vaccine? | Pfizer

22

VIRAL MUTATIONS

Recombination and Assortment

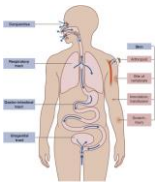


Virus Recombination - an overview | ScienceDirect Topics

23

ROUTES OF VIRAL ENTRY AND TRANSMISSION

- Respiratory
- Gastrointestinal
- Skin
- Genital
- Other



Pathogenesis of Virus Infections - Abstract - Europe PMC

24

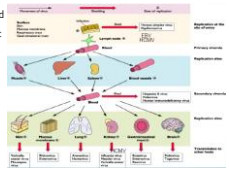
TISSUE TROPISM AND DISEASE

Determinants of Tropism

- Cell receptors for virus (CD4for HIV, sialic acid for Influenza)
- Cellular proteins that regulate viral transcription (papillomavirus in keratinocytes, their enhancers only active in specific cell types)
- Cellular protease: Influenza in respiratory tract (HA is cleaved into HA1 and HA2)
- Site of entry: accessibility of susceptible cells to viruses

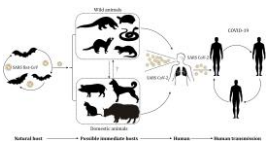
Infection

- Localized
- Systemic

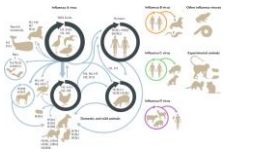


25

ALTERNATIVE HOST



fmicb-11-580137-g001.jpg (4248×2170) (frontiersin.org)



Host and viral determinants of influenza A virus species specificity | Nature Reviews Microbiology

26

SPECIFIC PATHOGENS

- SARS CoV-2
- Astroviruses
- Rotavirus A
- Influenza
- Adenoviruses
- Human metapneumovirus
- Enterovirus
- Seasonal Coronaviruses
- Rhinovirus

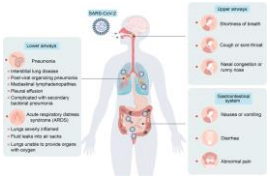


Fig. 1 | Signal Transduction and Targeted Therapy (nature.com)

27

SARS COV-2

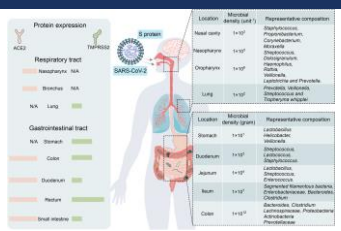
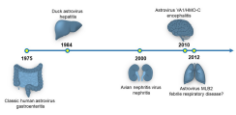


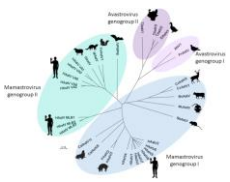
Fig. 2 | Signal Transduction and Targeted Therapy (nature.com)

28

ASTROVIRUSES



Viruses | Free Full-Text | Beyond the Gastrointestinal Tract: The Emerging and Diverse Tissue Tropisms of Astroviruses (mdpi.com)

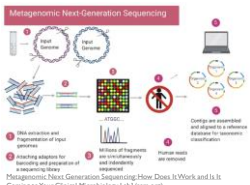


Avastrovirus - an overview | ScienceDirect Topics

29

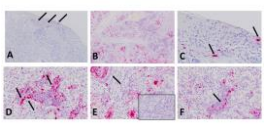
DISCOVERY AND CHARACTERIZATION OF EMERGING VIRUSES

Metagenomic Sequencing



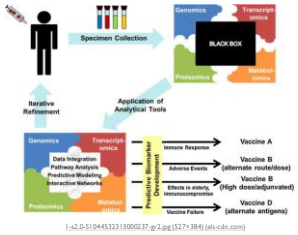
Metagenomic Next-Generation Sequencing: How Does It Work and Is It Coming to Your Clinical Microbiology Lab? (asm.org)

RNAScope® ISH



30

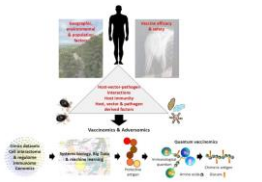
DEVELOPMENT OF DIAGNOSTIC ASSAYS AND VACCINES



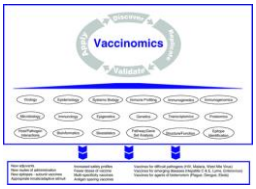
[-s2.0-51044532331000037-gr2.jpg (527×384) (els-cdn.com)

31

VACCINOMICS



Yacunomics for the development of vaccines against emerging pathogens (rec.es)



Vaccinomics approach to new vaccine development.Vaccinomics is the... | Download Scientific Diagram (researchgate.net)

32

SUMMARY

- Respiratory Disease
- Public Health Concerns
- Economic Impact
- Viral mutations, alternative tissue tropism, and alternative transmission
- Rapid Identification and Diagnosis
  - Metagenomic Sequencing
- Viral Culture Unavailable
  - *In Situ* Hybridization
- Future of NGS/ Vaccines

33

34

35