

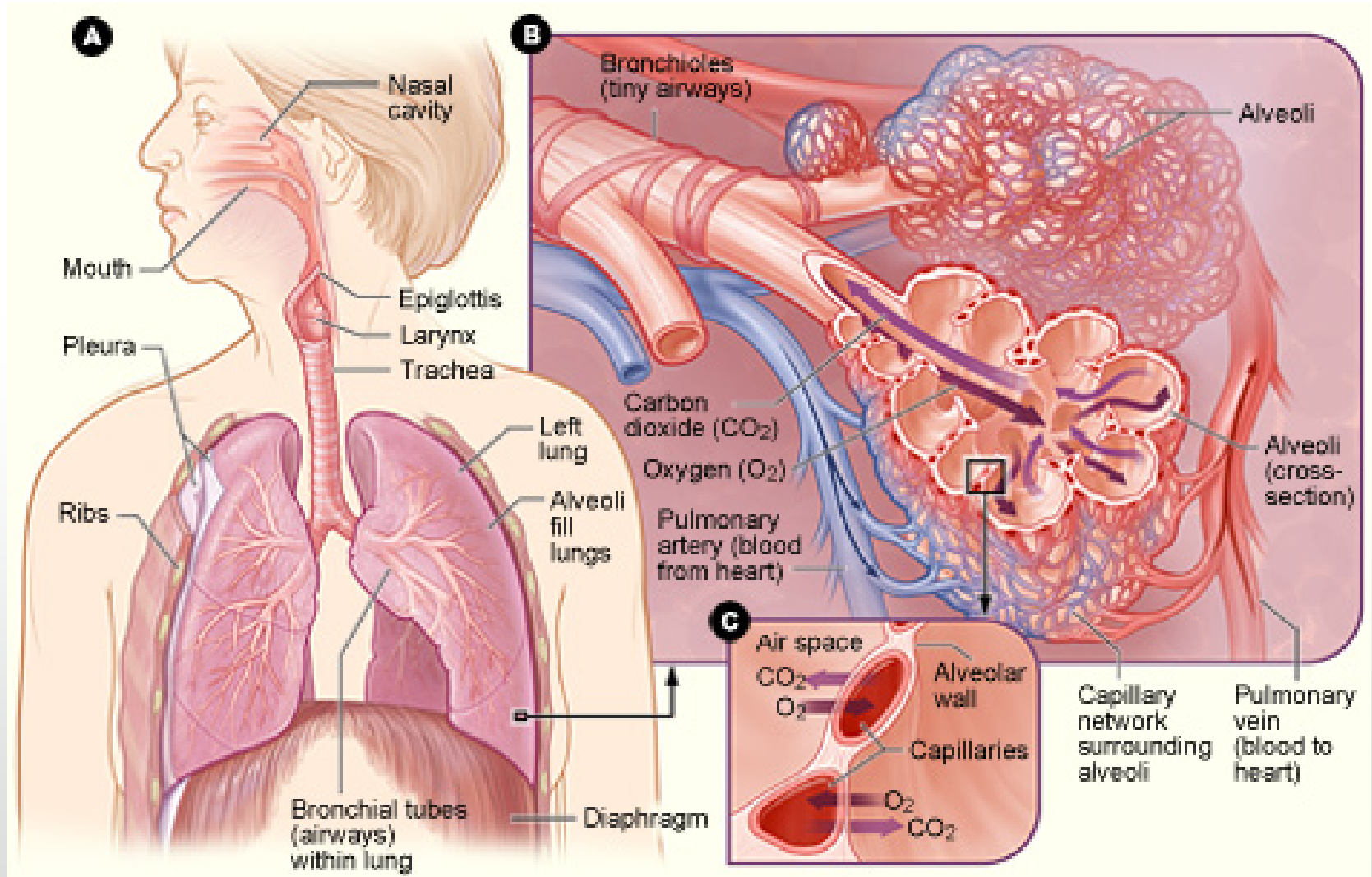
Every Breath You Take

How the lung defends itself against
infection

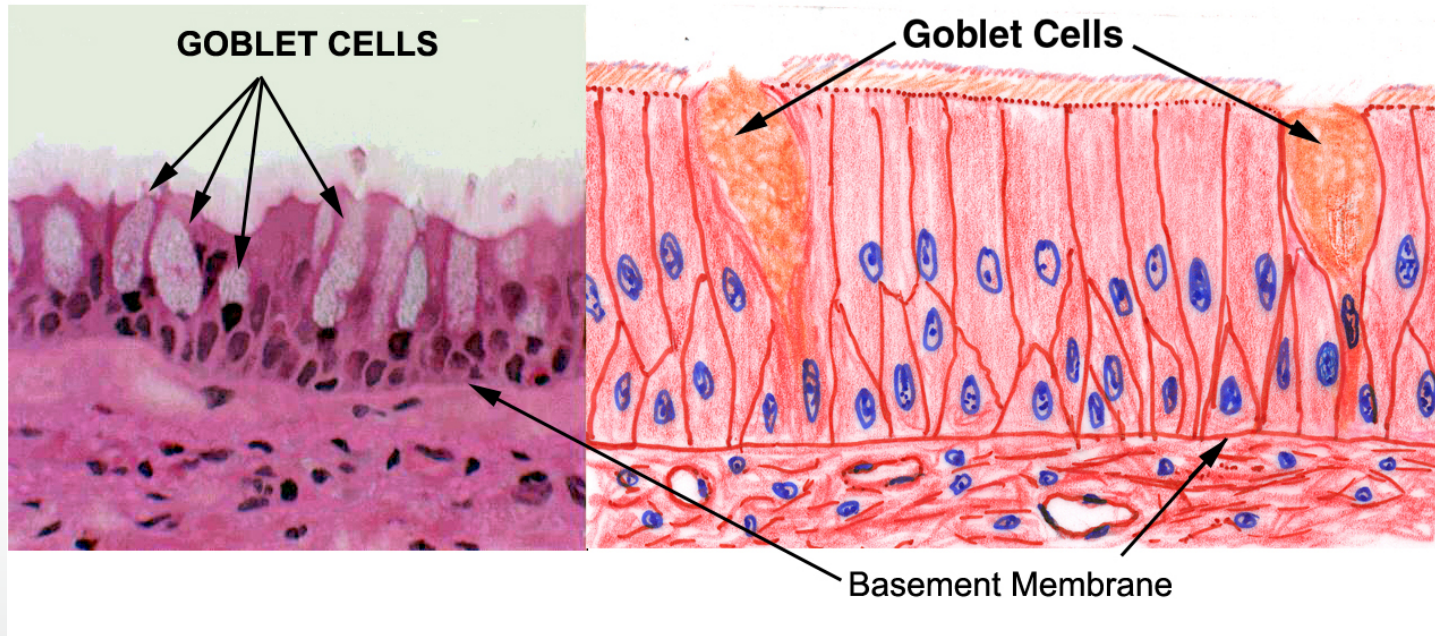
Karl J Staples
26th October 2020



Lung structure relates to function

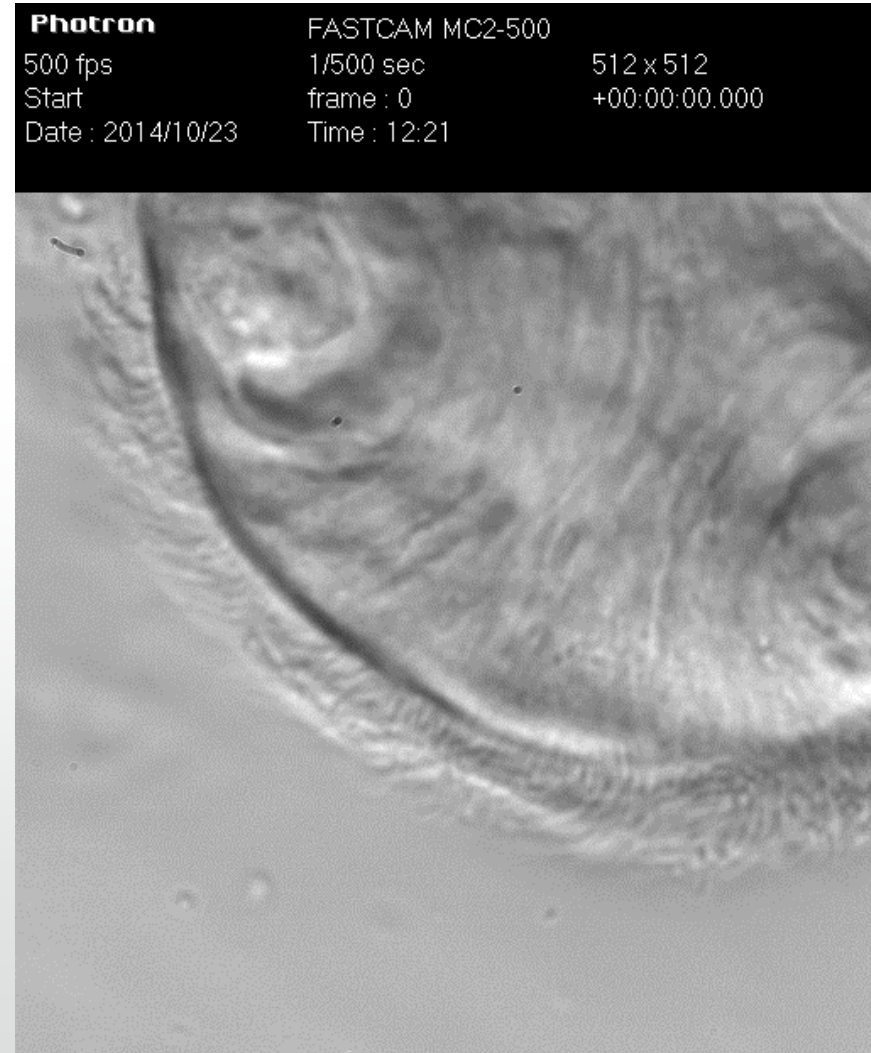
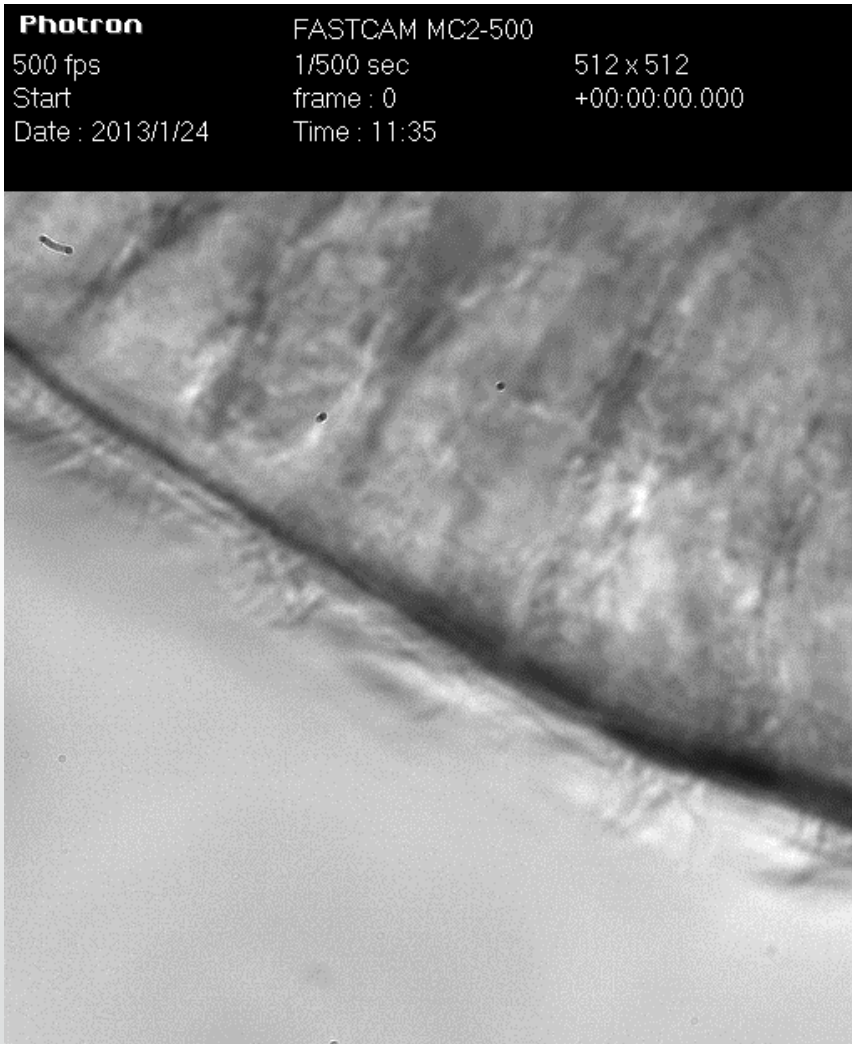


Large airways (bronchus)

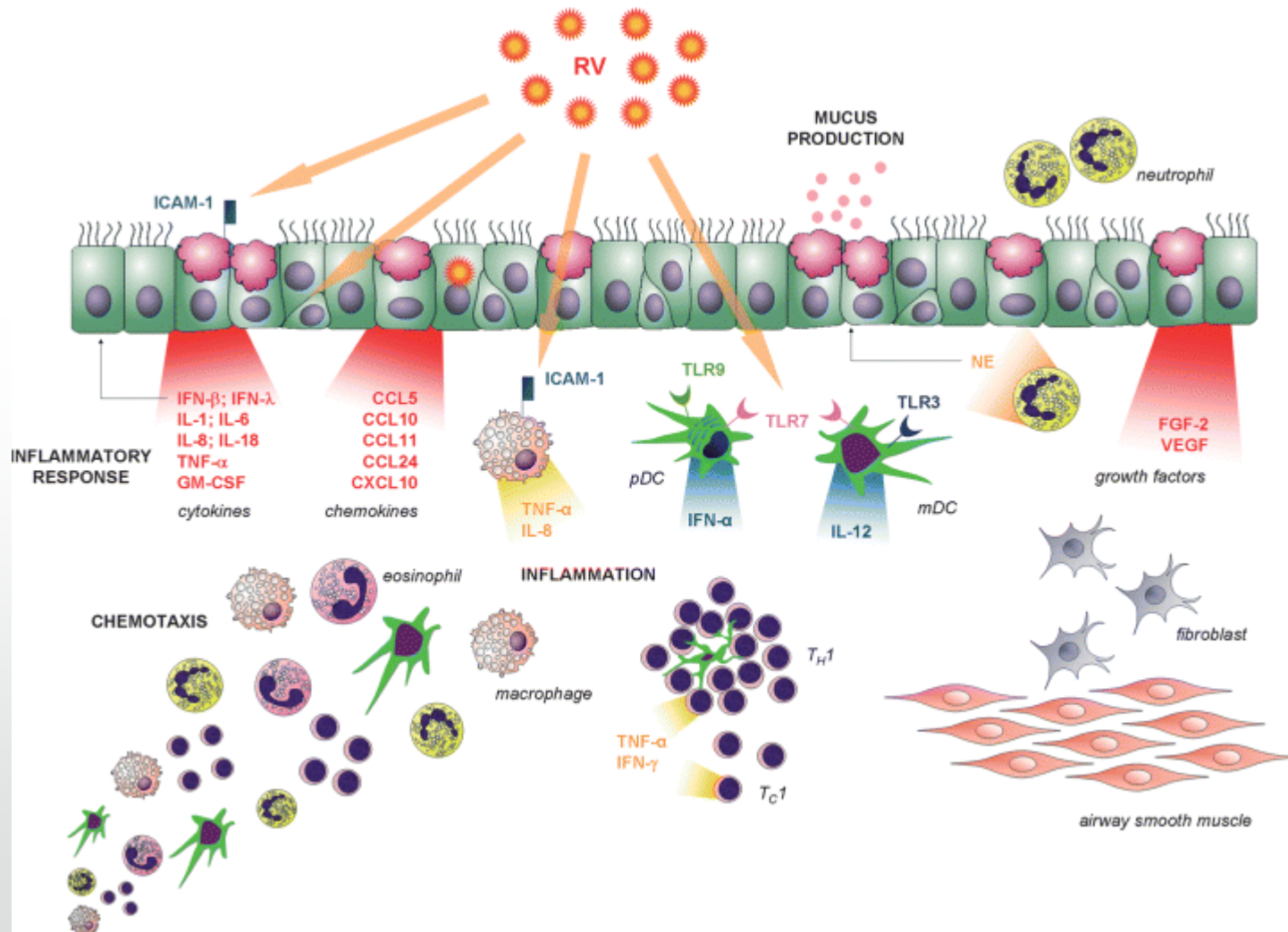


Pseudostratified: Cells appear to be in layers, but in actuality most cells adjoin the basement membrane.

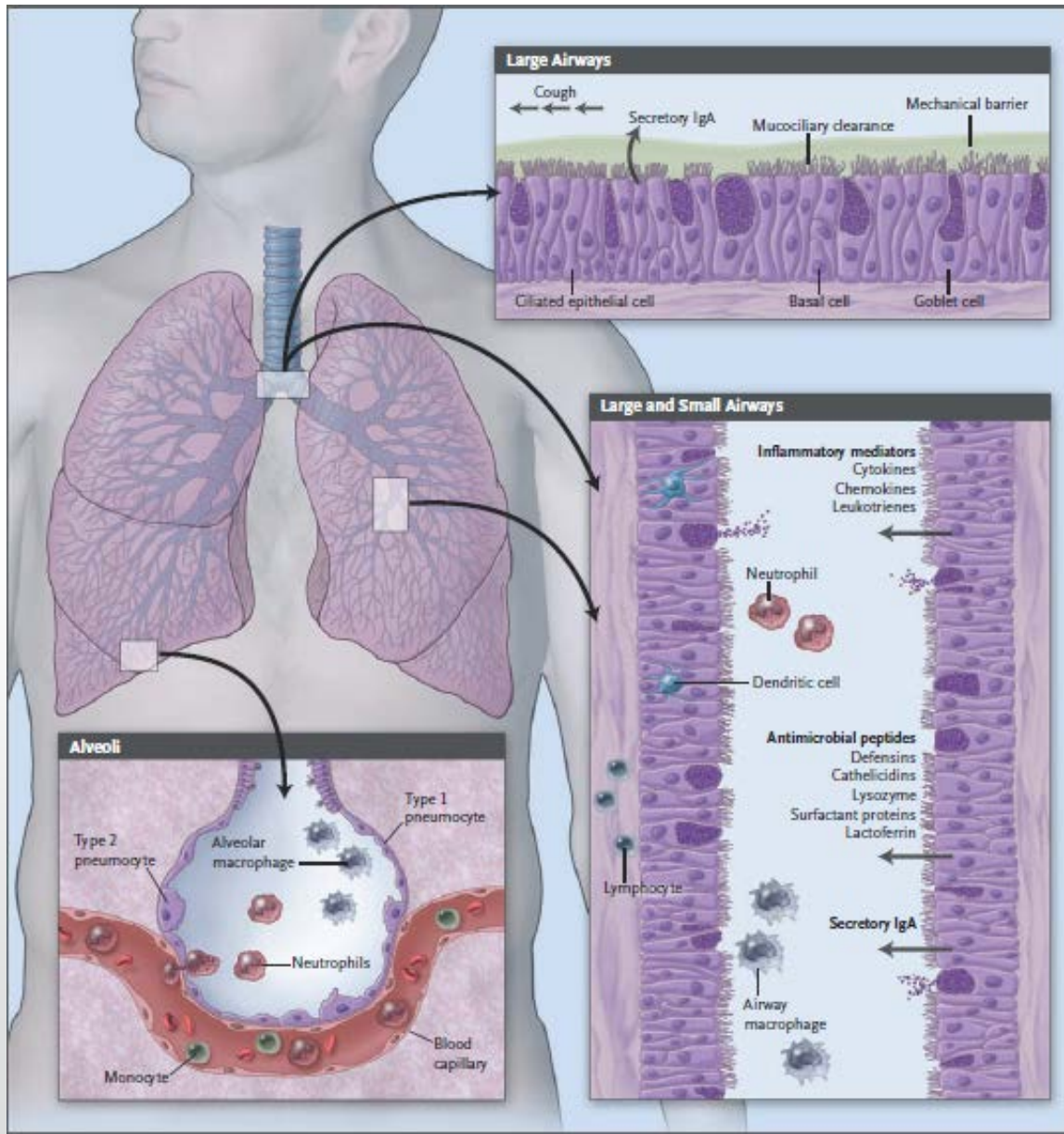
Mucocilliary escalator



Epithelium is not a passive barrier

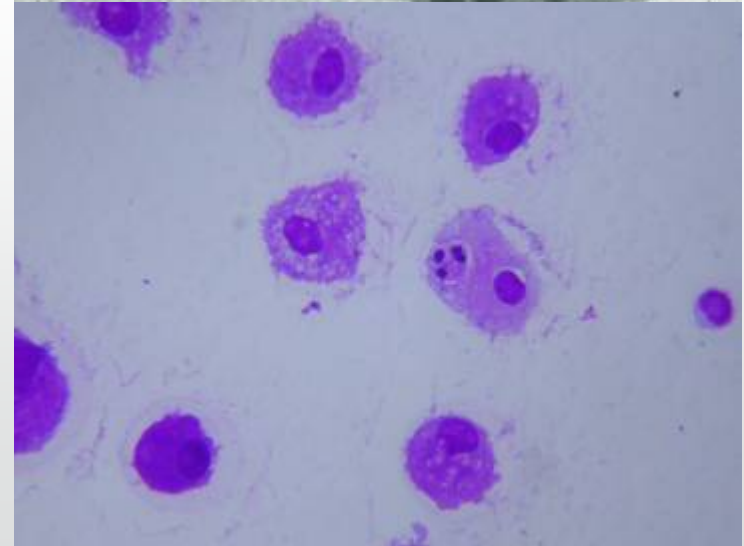
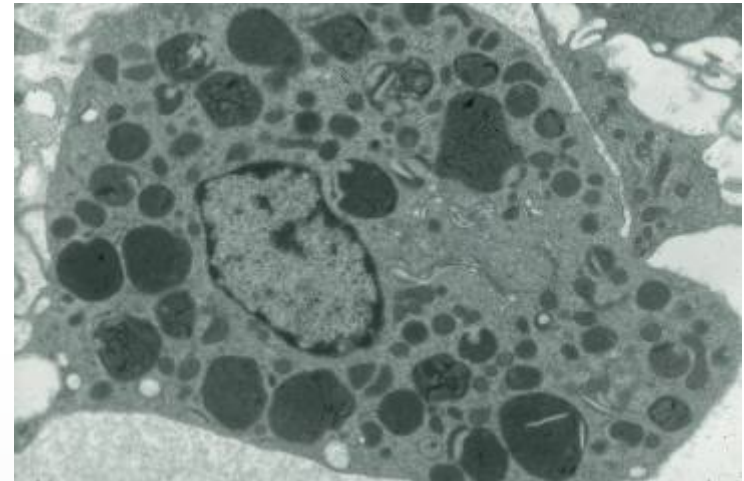


Innate defence in the lung



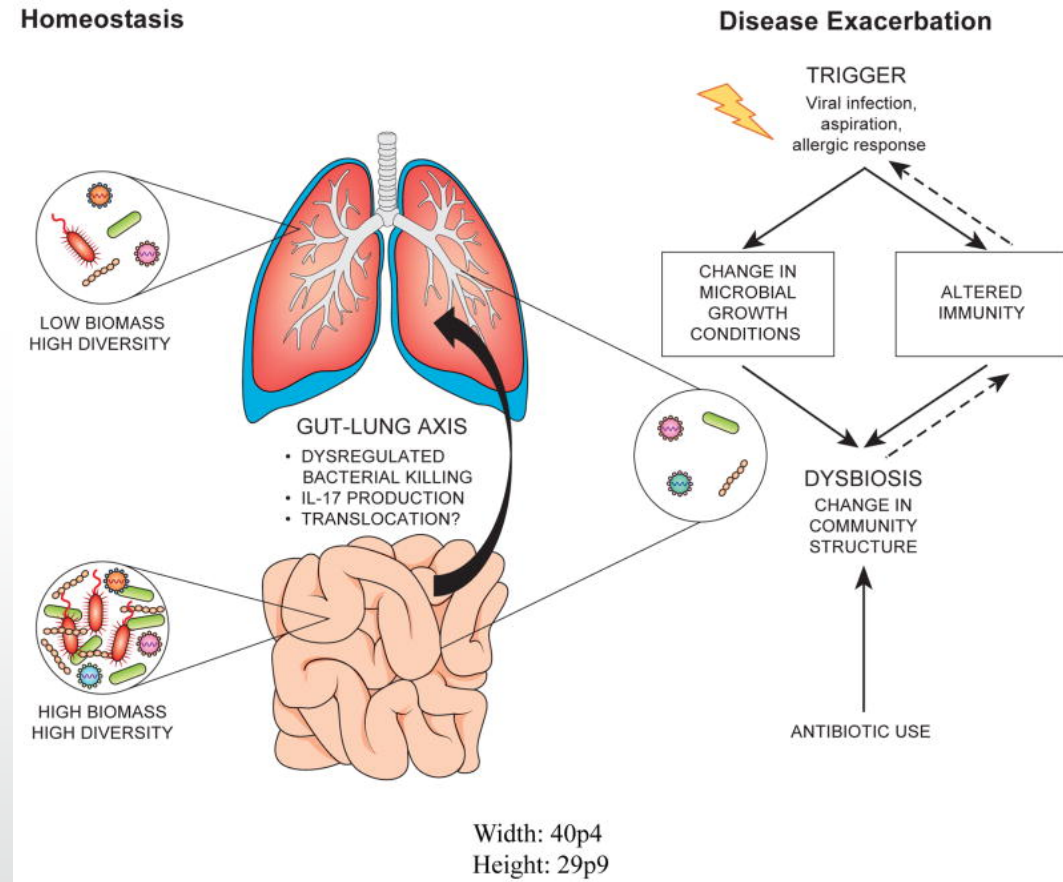
Airway macrophages

- Predominant inflammatory cell in the lung (95% BAL, 50% sputum)
- Phagocytic
- Reactive Oxygen and Nitrogen species
- MMP release
- Produce cytokines and lipid mediators
- Respond to local cytokine milieu



Healthy airway microbiome

- Use of culture independent methods such as 16s rRNA sequencing
- Relative abundance of 10-100 bacterial cells per 1000 human cells
- Dysbiosis in smokers and chronic lung disease

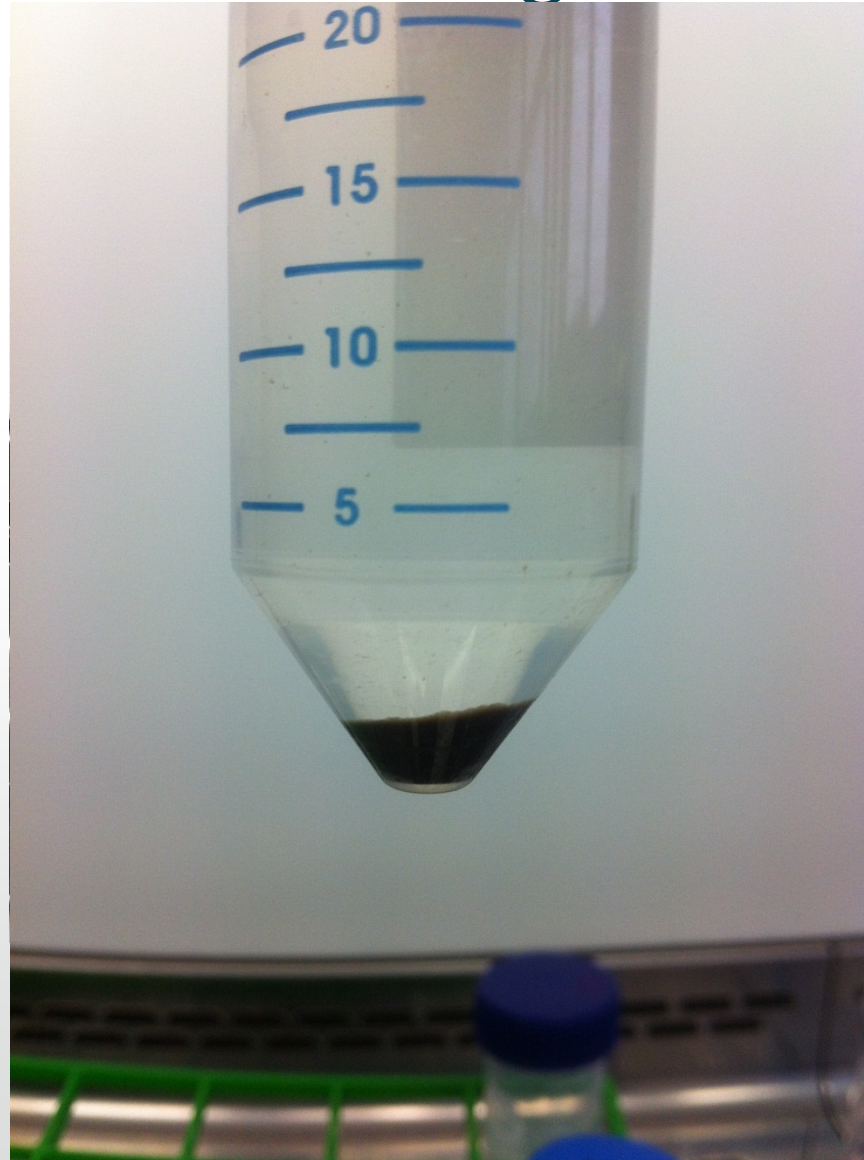


So what happens when cigarette smoke is inhaled?

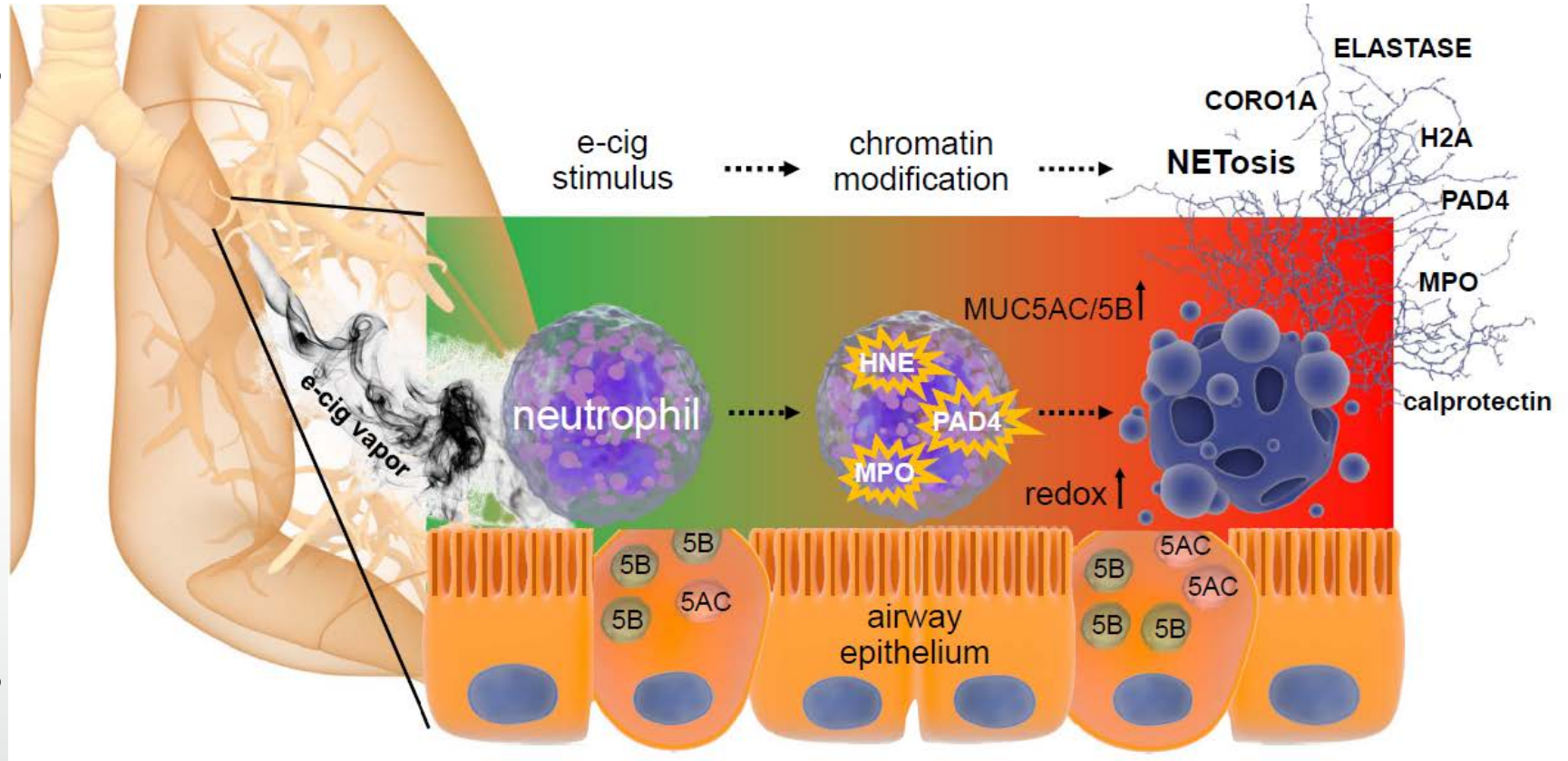


- >250 different compounds are inhaled. These include benzene, formaldehyde, arsenic and polonium 210
- Smoking also leads to inhalation noxious gases, e.g. CO and NO
- Large amounts of free radicals
- Particulates (<math><10\mu\text{m}</math> can penetrate the lungs, <math><2.5\mu\text{m}</math> infiltrate the alveolus, <math><100\text{nm}</math> can go through the respiratory barrier and accumulate in the internal organs)
- Tar – accretions of uncombusted hydrocarbons

Where do these toxins go?



Is Vaping any better than smoking?



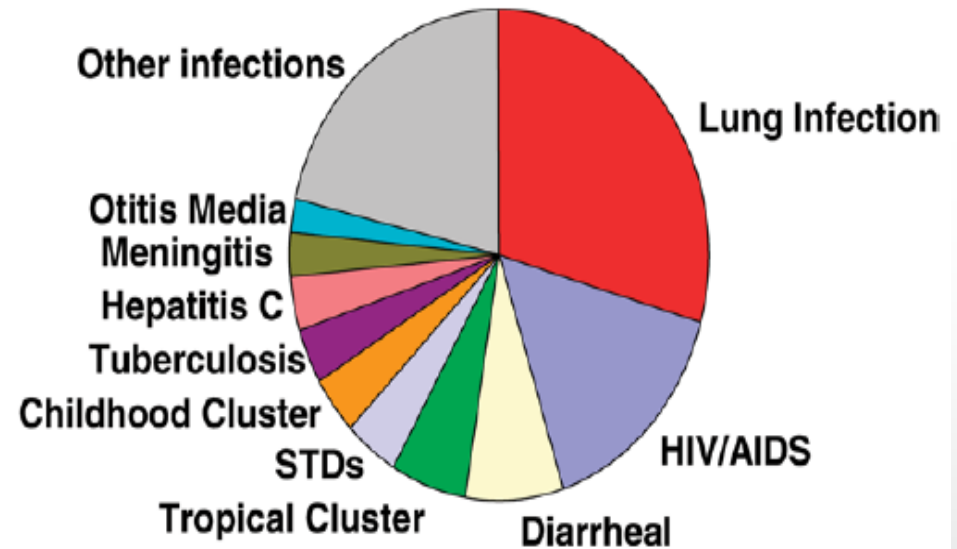
- Changes to innate defence proteins that are both similar to cigarette smoke and unique to vaping (Reidel et al 2017 Am J Resp Crit Care Med)

Effect of viral infections on chronic lung disease

Respiratory infections

- Respiratory infections account for approx 30% of deaths in developed world (WHO)
- Emerging pandemics can have substantial impact on mortality and economics
- Exacerbations of underlying respiratory diseases contributes to mortality and morbidity

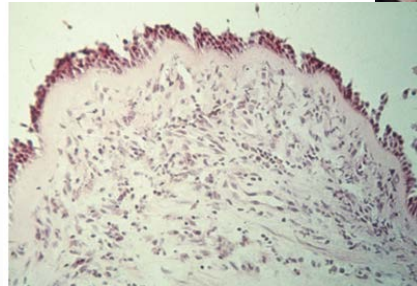
Wealthiest regions of the world



Asthma & COPD

- Chronic respiratory diseases characterised by airway inflammation and remodelling events

- Asthma – atopy/allergens, genetics

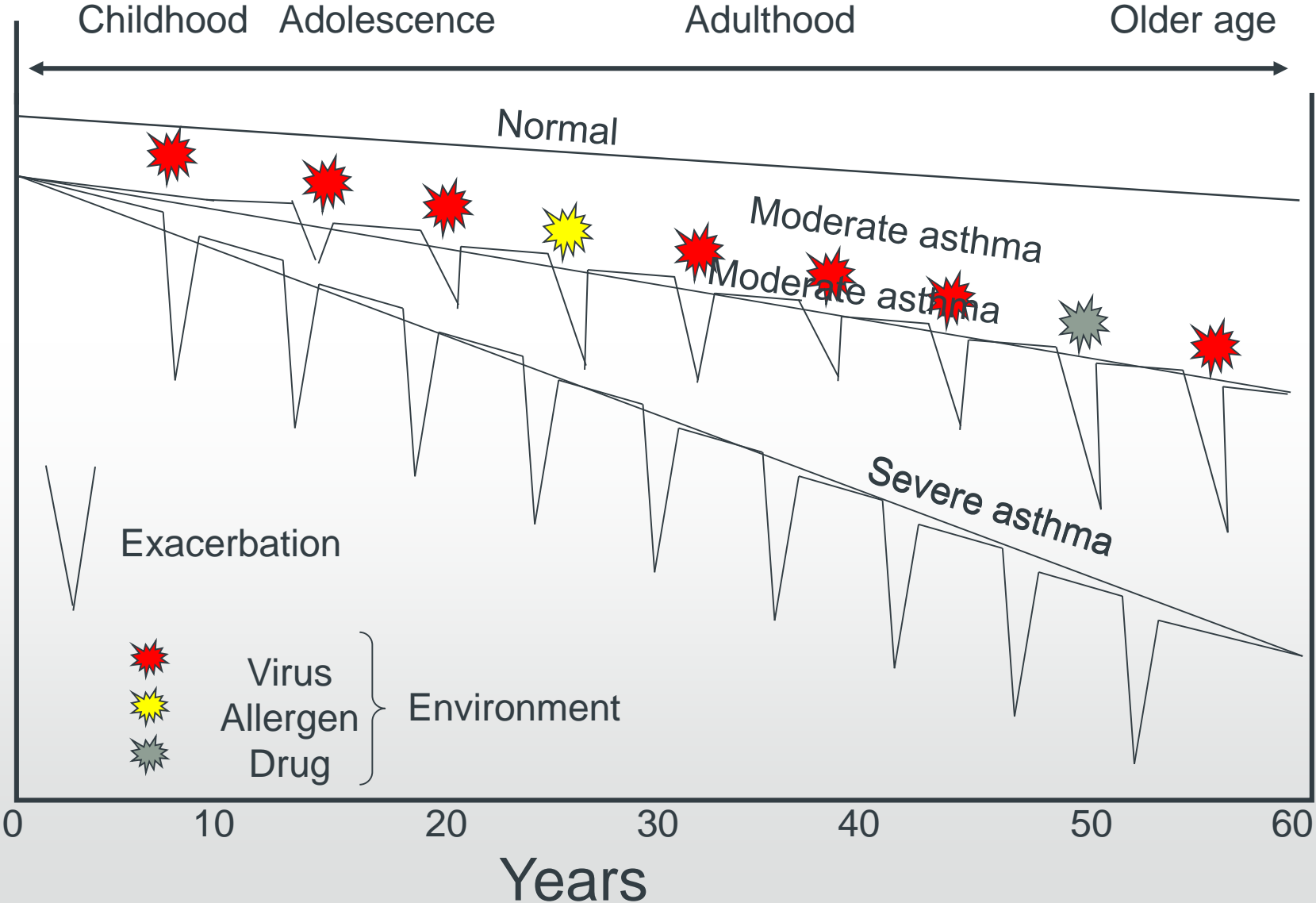


- COPD – smoking, particulate inhalation, genetics



- Viral infections can lead to exacerbations of these diseases

Exacerbations contribute to lung function decline

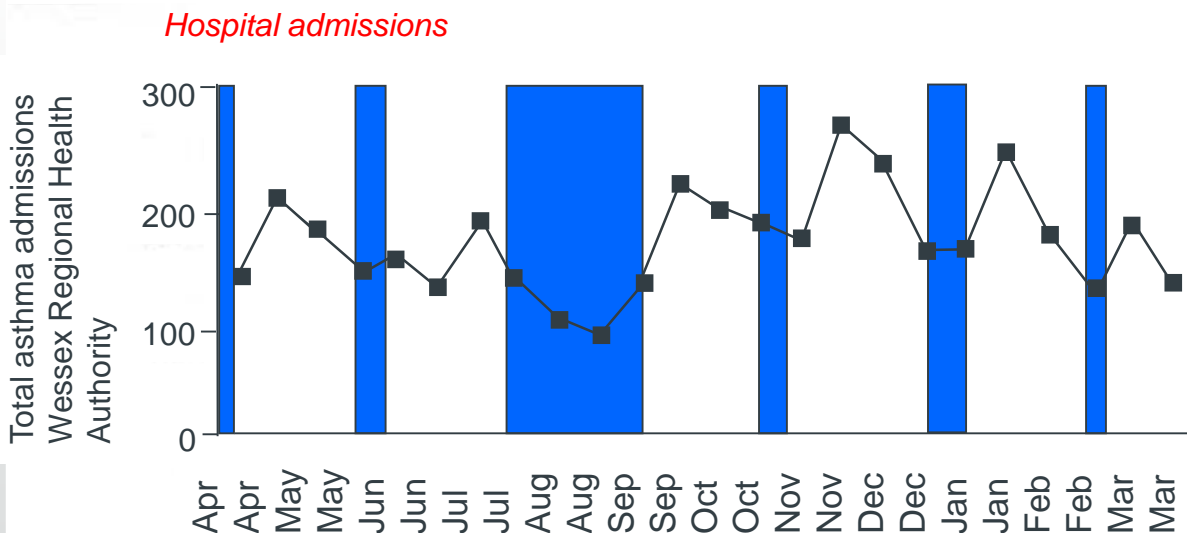
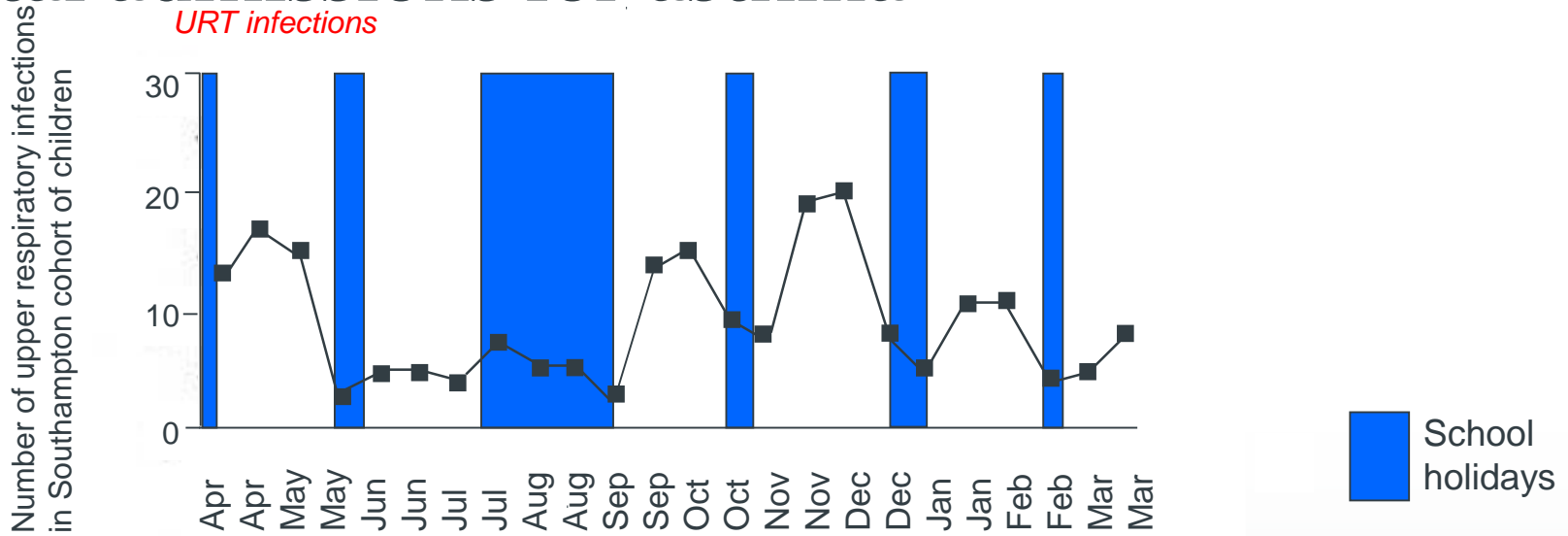


Respiratory viral infections

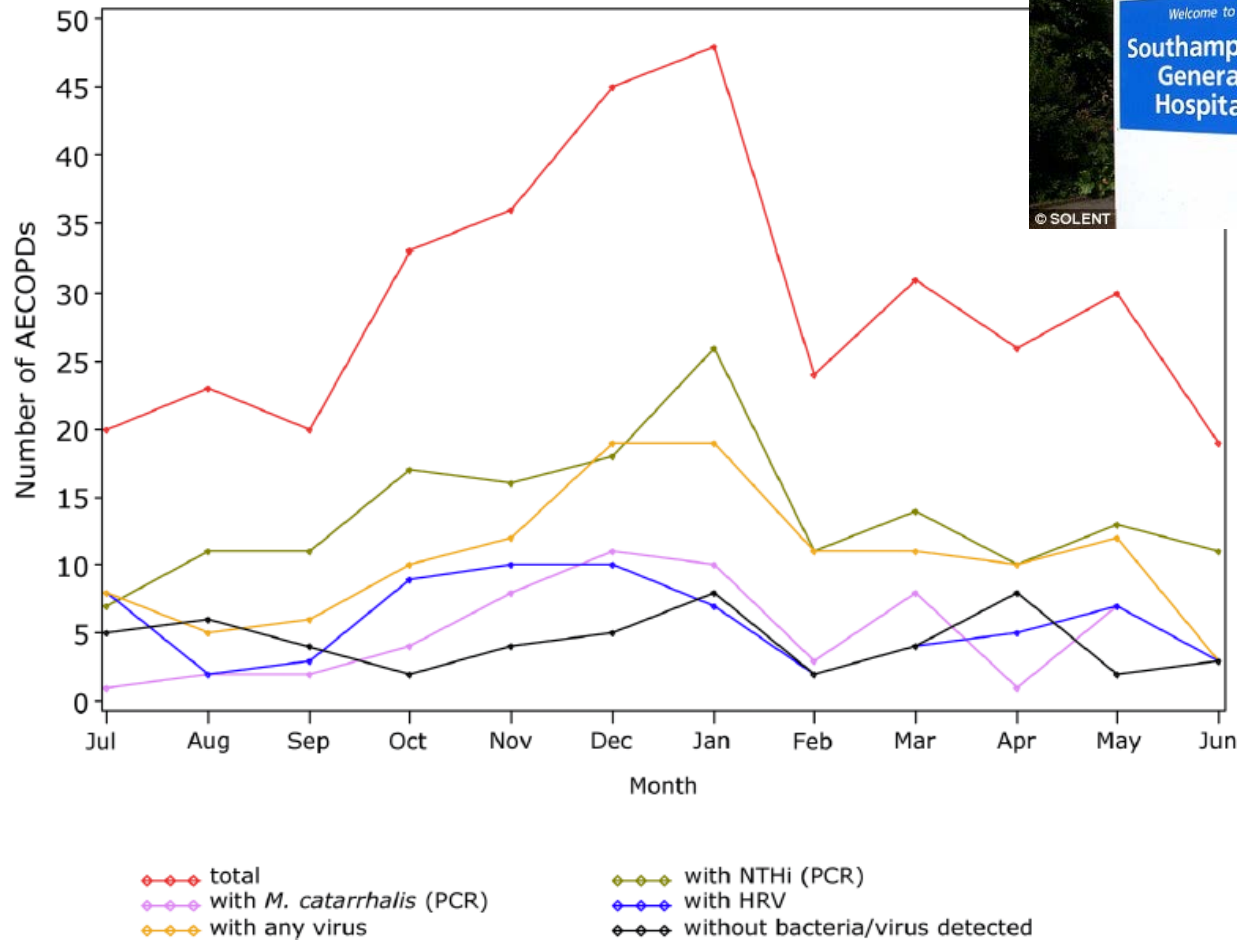
- Rhinovirus (HRV)
- Influenza
- Respiratory syncytial virus (RSV)
- Parainfluenza
- Adenovirus
- Coronavirus



Relationship between URTIs and hospital admissions for asthma



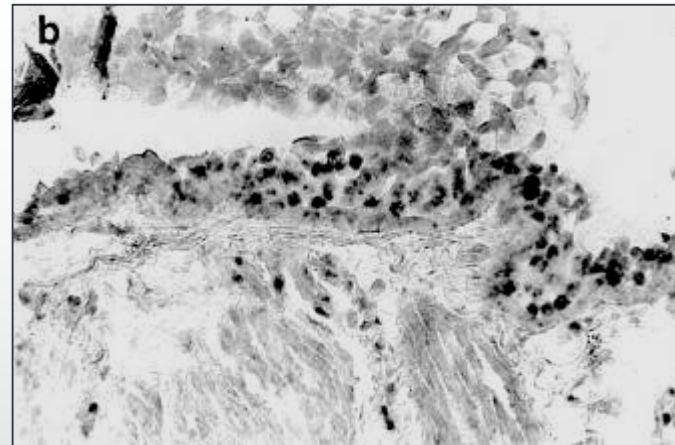
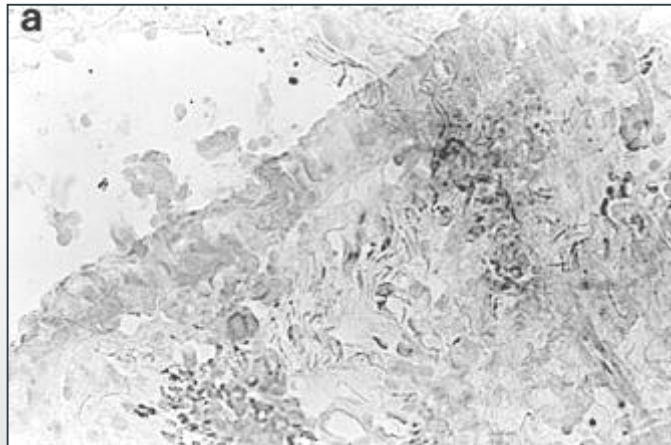
Seasonality of COPD exacerbations



Experimental Infection

Localization of HRV in the bronchi

- Rhinovirus infects lower airways



Role of Type 1 IFNs in virus infected cells

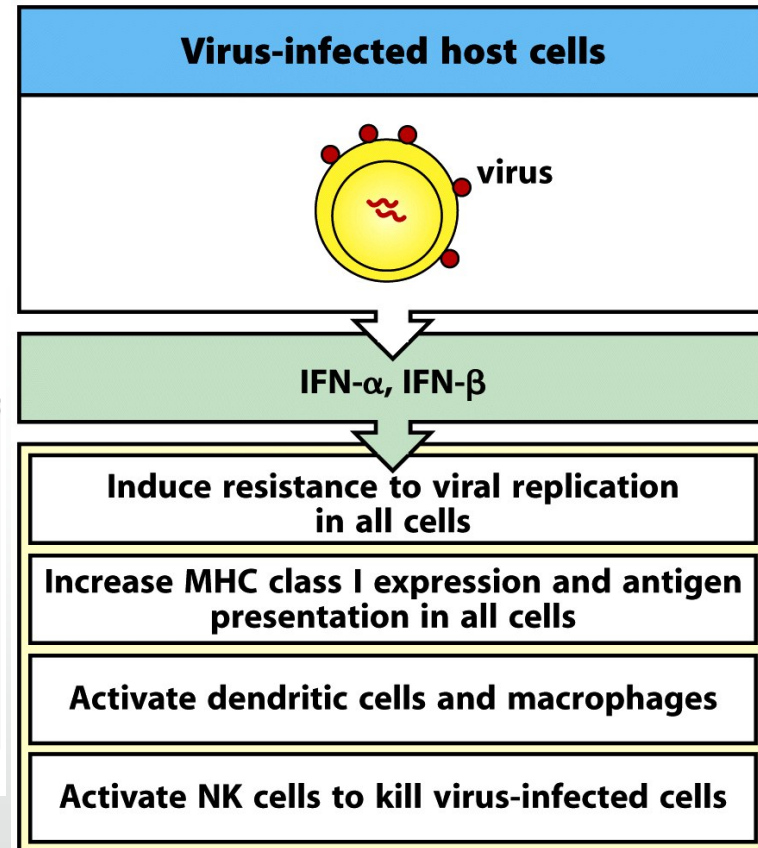
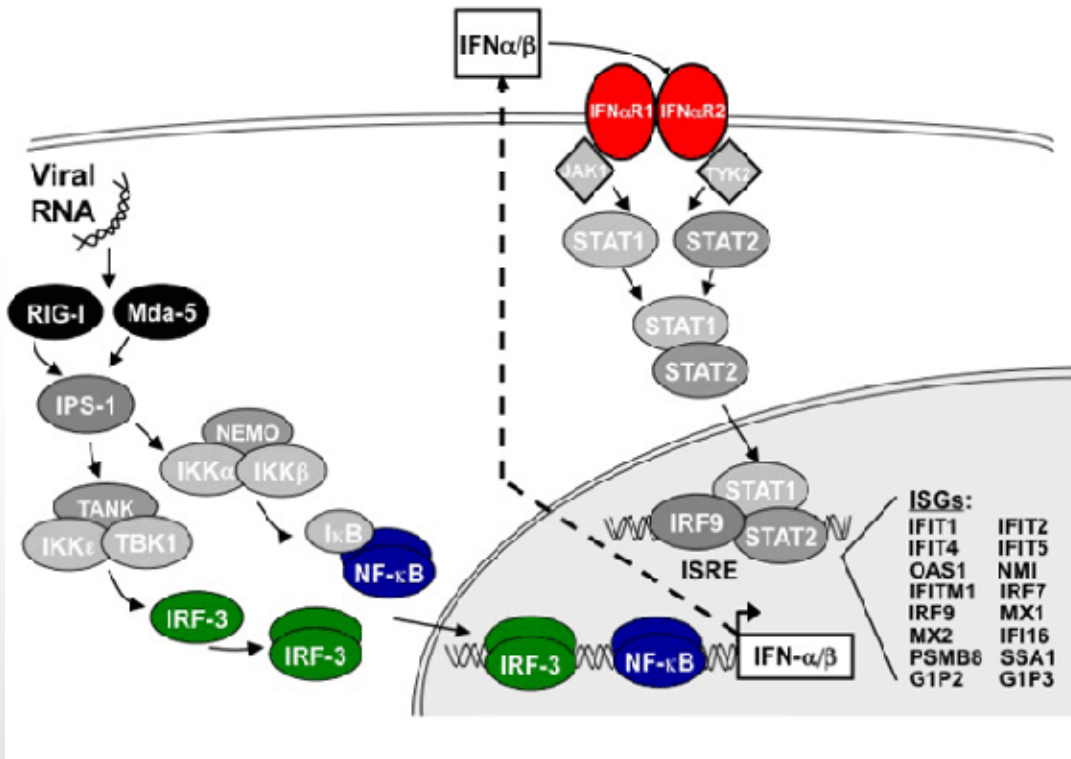
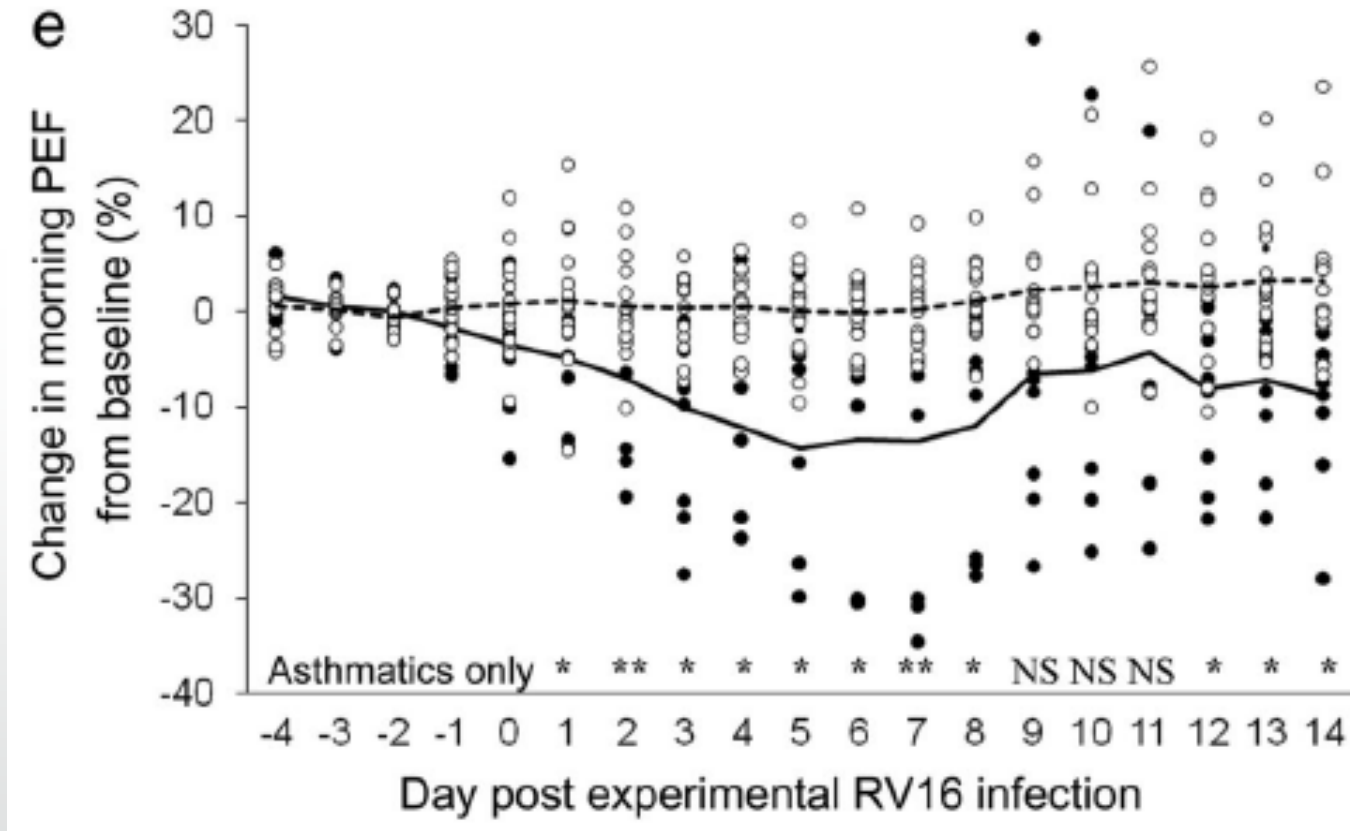


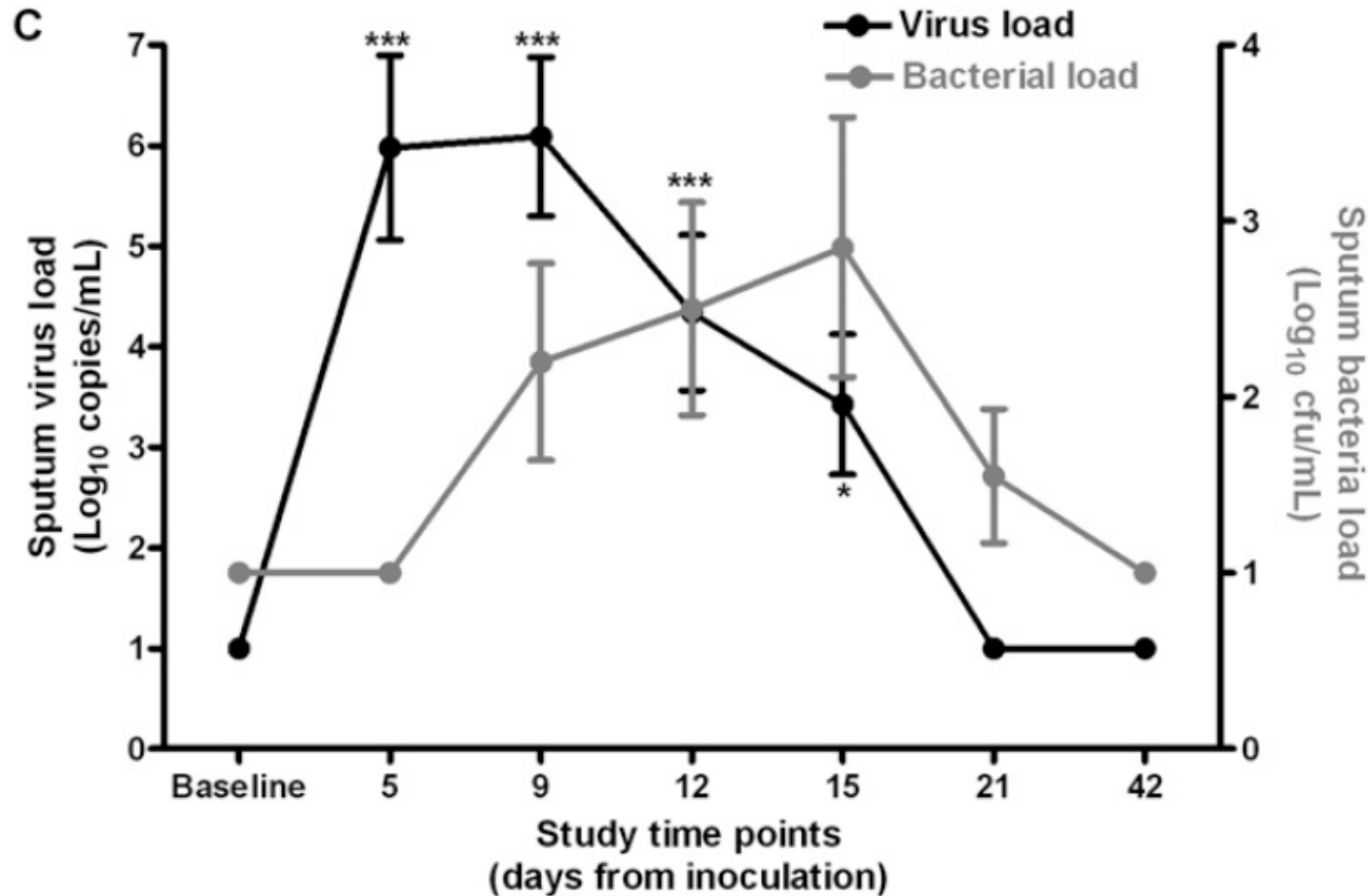
Figure 2-54 Immunobiology, 7ed. (© Garland Science 2008)

IFNs induced by activating TLR3, TLR7, RIG1 or Mda5

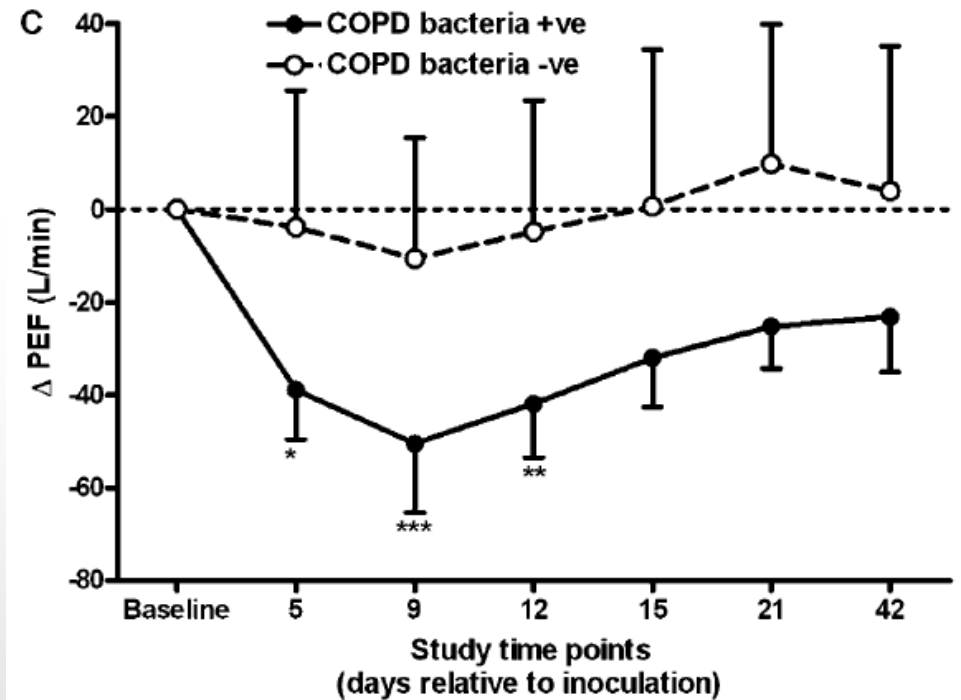
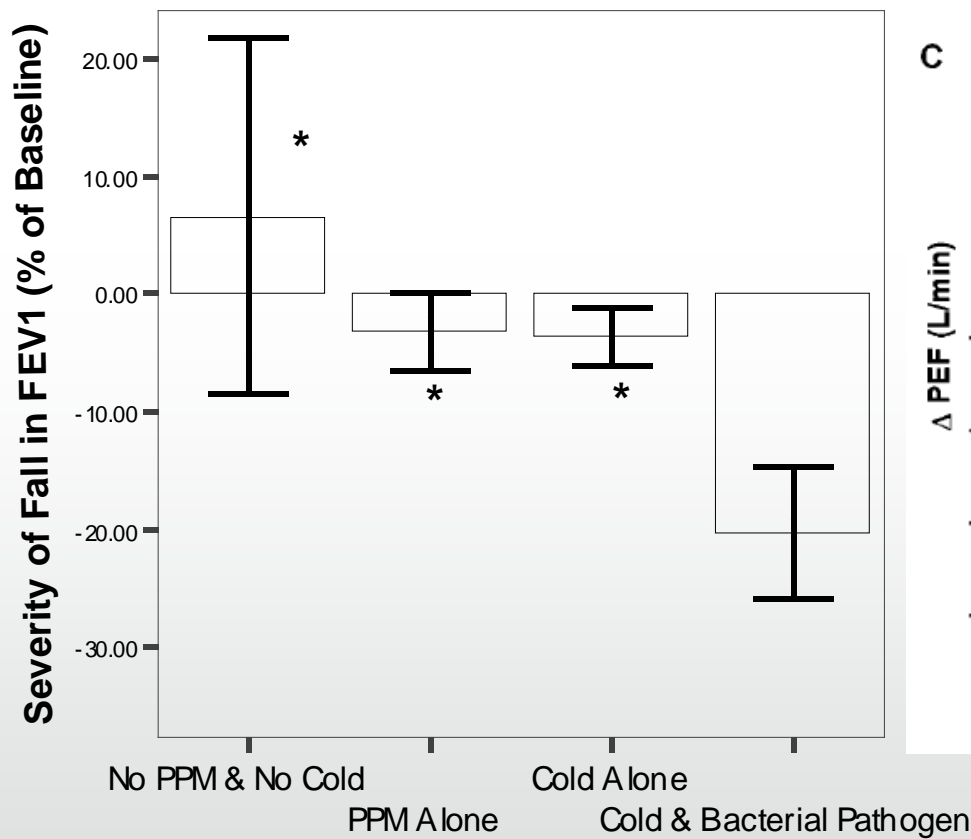
Experimental HRV infection causes LRT symptoms in asthma



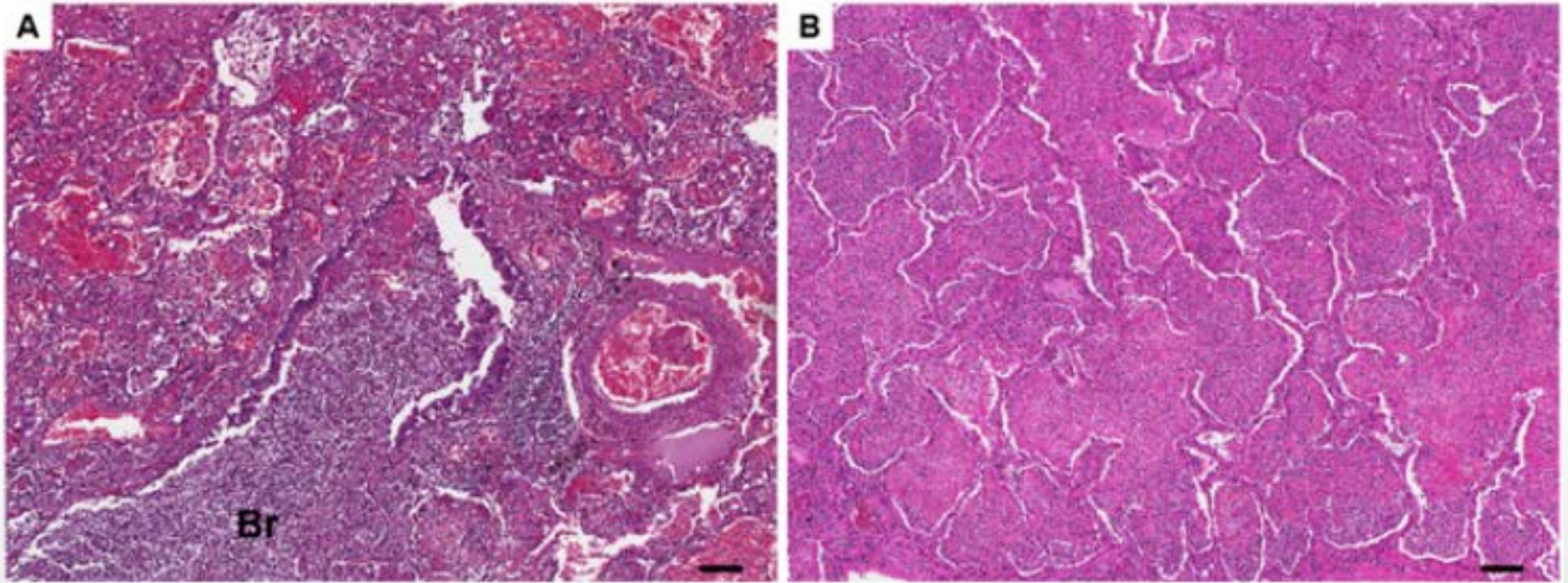
Bacterial and Viral Interactions



Bacterial and Viral Interactions

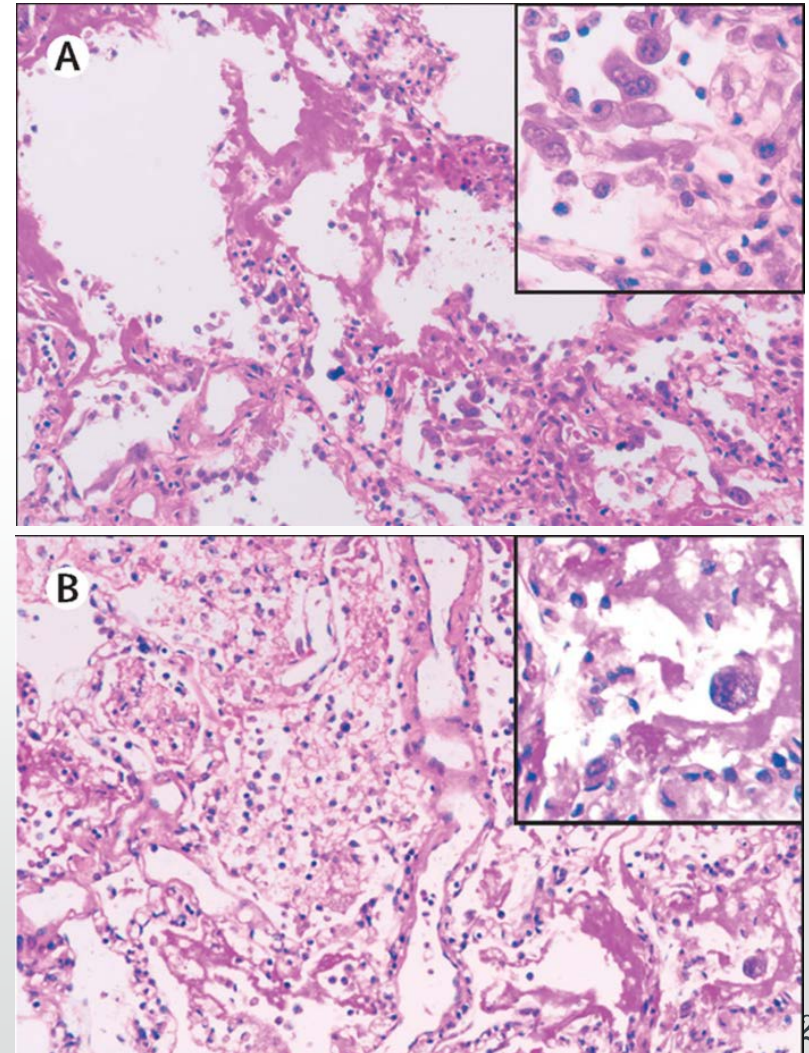


1918 pandemic influenza infection in human lung

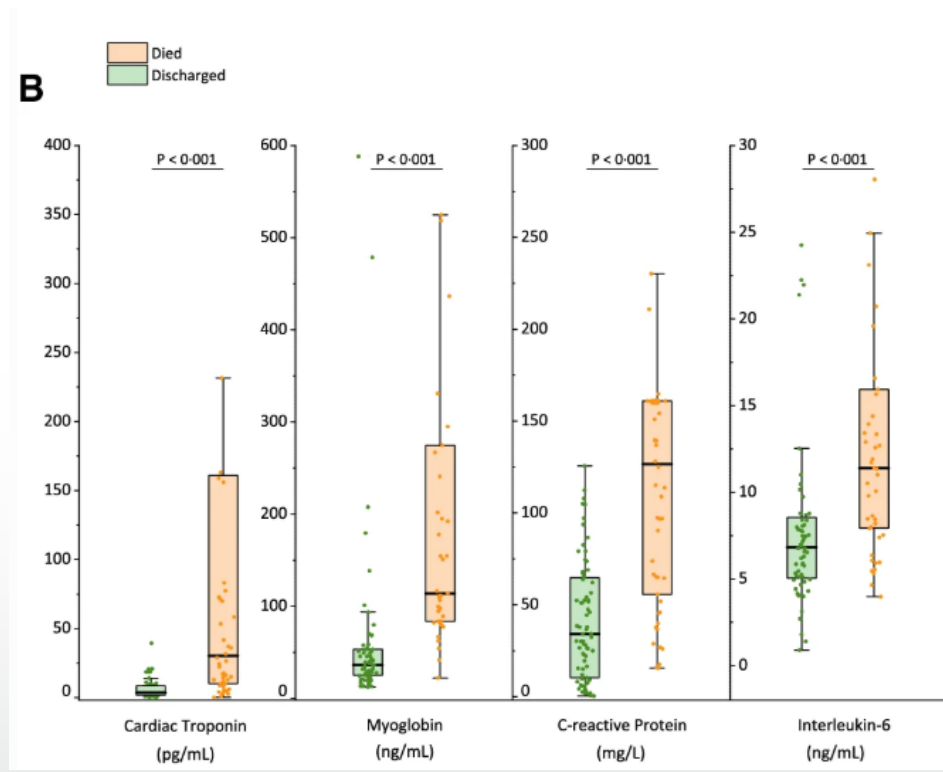
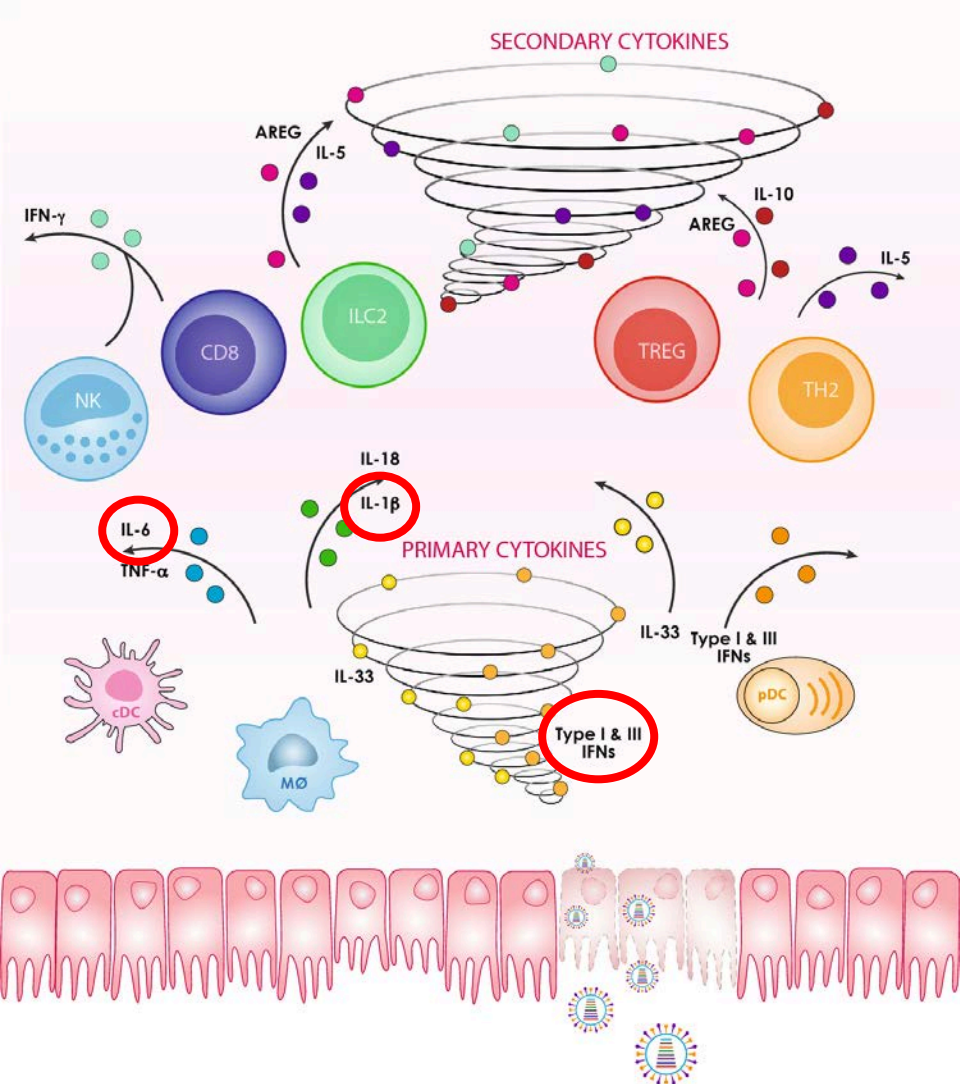


Respiratory infection with SARS-CoV-2

- Mild infection can progress to pneumonia and acute respiratory distress syndrome (ARDS)
- Diffuse alveolar damage, hyaline membrane formation consistent with haemophagocytic lymphohistiocytosis (HLH)
- Interstitial mononuclear inflammatory infiltrates of macrophages and lymphocytes



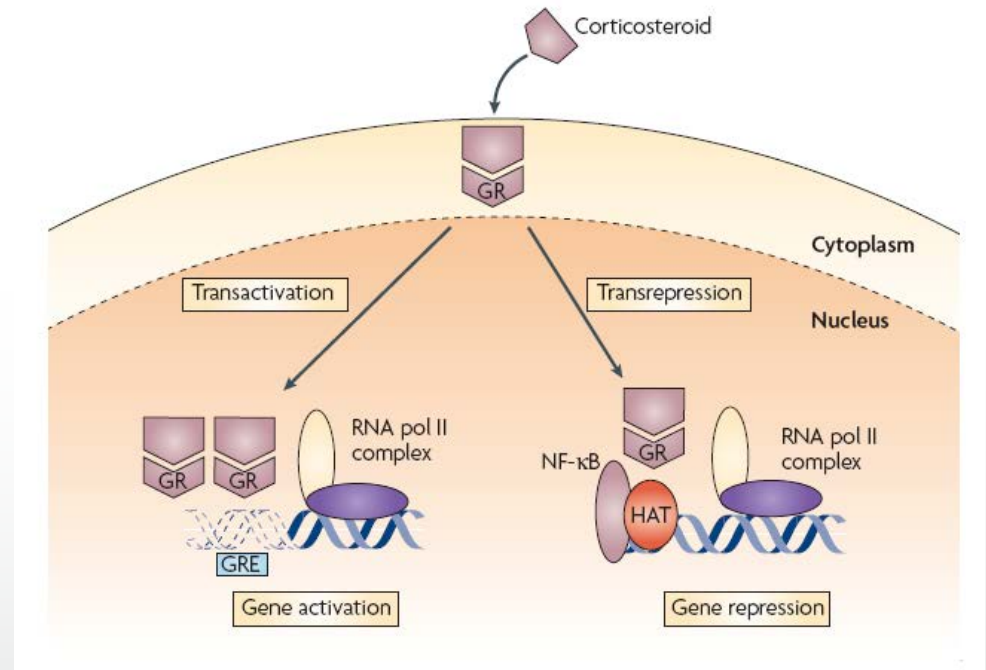
Role of cytokine storm?



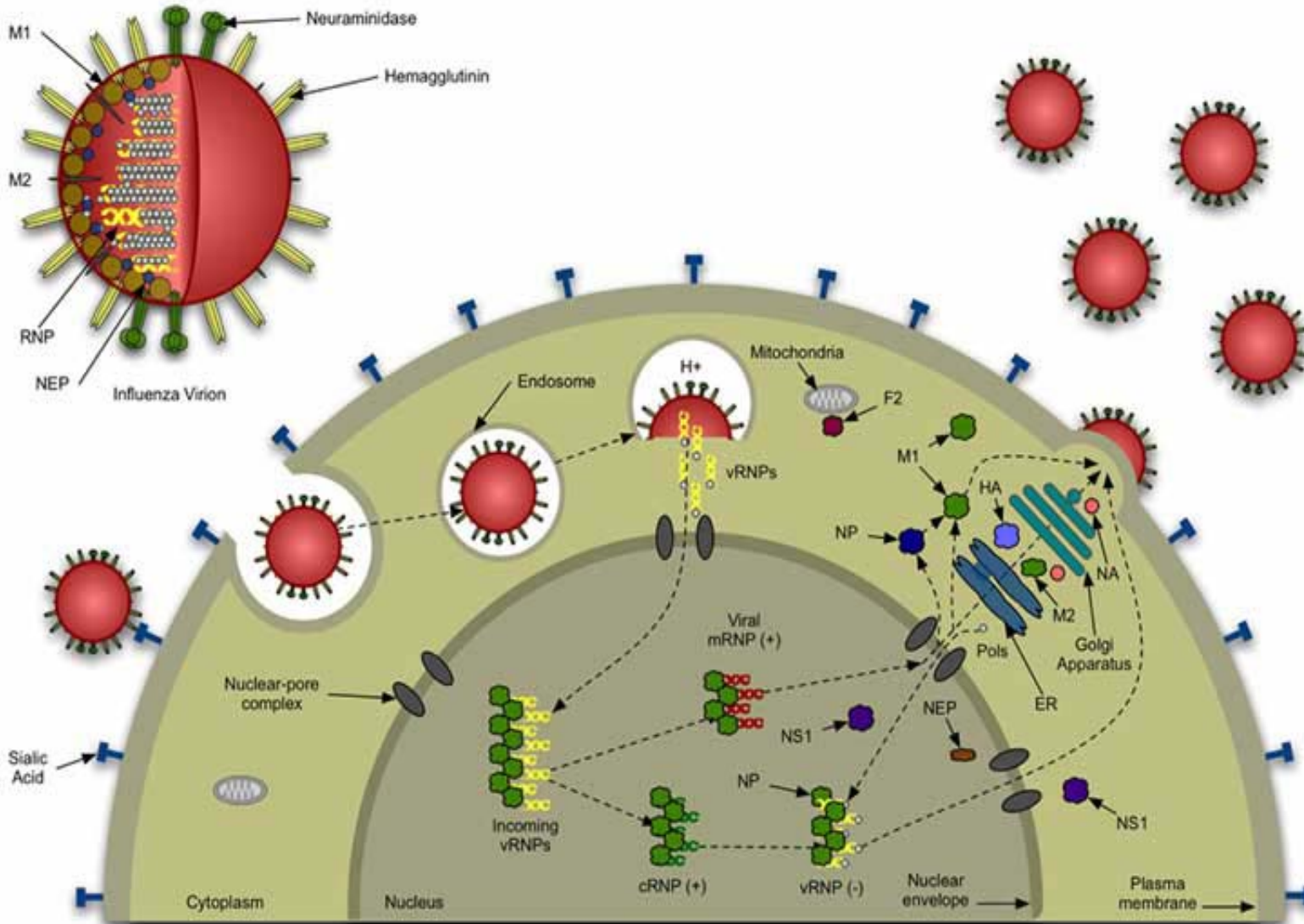
Where do we go from
here?

Steroids and anti-inflammatory drugs

- Inhaled steroids reduce exacerbation frequency but do not prevent exacerbations completely
- Highlights the inflammatory nature of exacerbations
- Dexamethasone increases survival of the ventilated COVID-19 patients



Anti-virals



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Health

Coronavirus: Protein treatment trial 'a breakthrough'

By Justin Rowlatt
BBC News

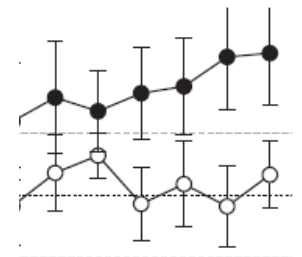
20 July

Coronavirus pandemic

- Licensed
- Phase II asthma t
- Provided severe as
- Decre
- Fewe
- More funct
- Larger s negative
- Clinical t

Clinically relevant difference

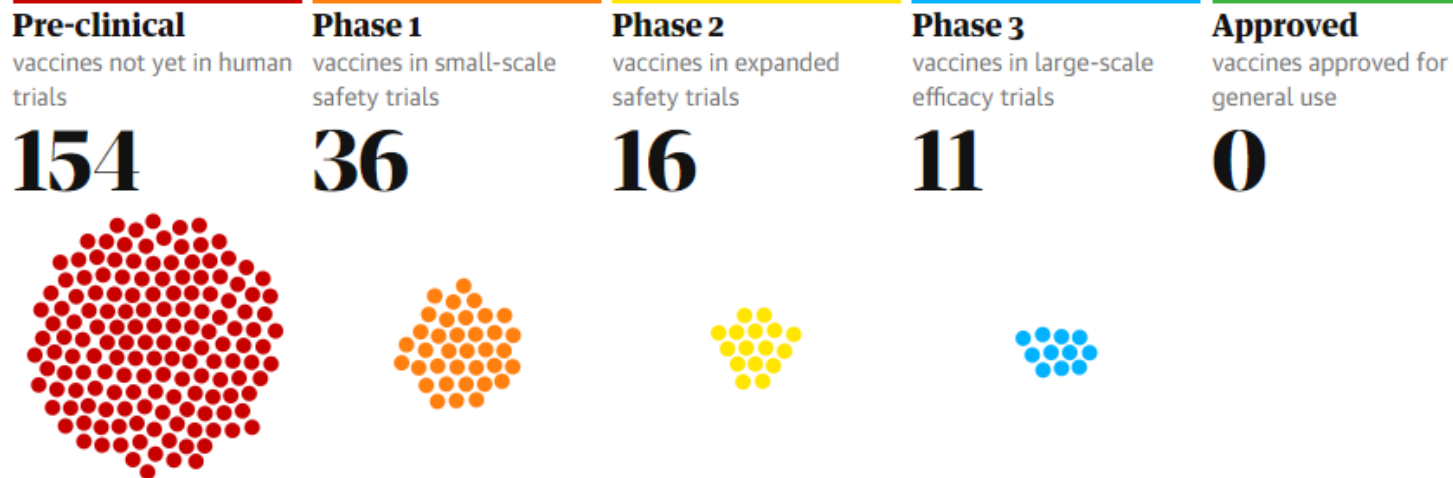
No change



9 10 11 12 13 14
day

Vaccination

- Influenza vaccination effective
- RSV – Phase 3 trials underway
- HRV >200 serotypes makes designing a vaccine difficult
- COVID-19



Source: WHO. Last updated 21 Oct

Summary

