Children's Health and Environment Program

Interactions between environmental exposures and Covid-19: why don't children get as sick?

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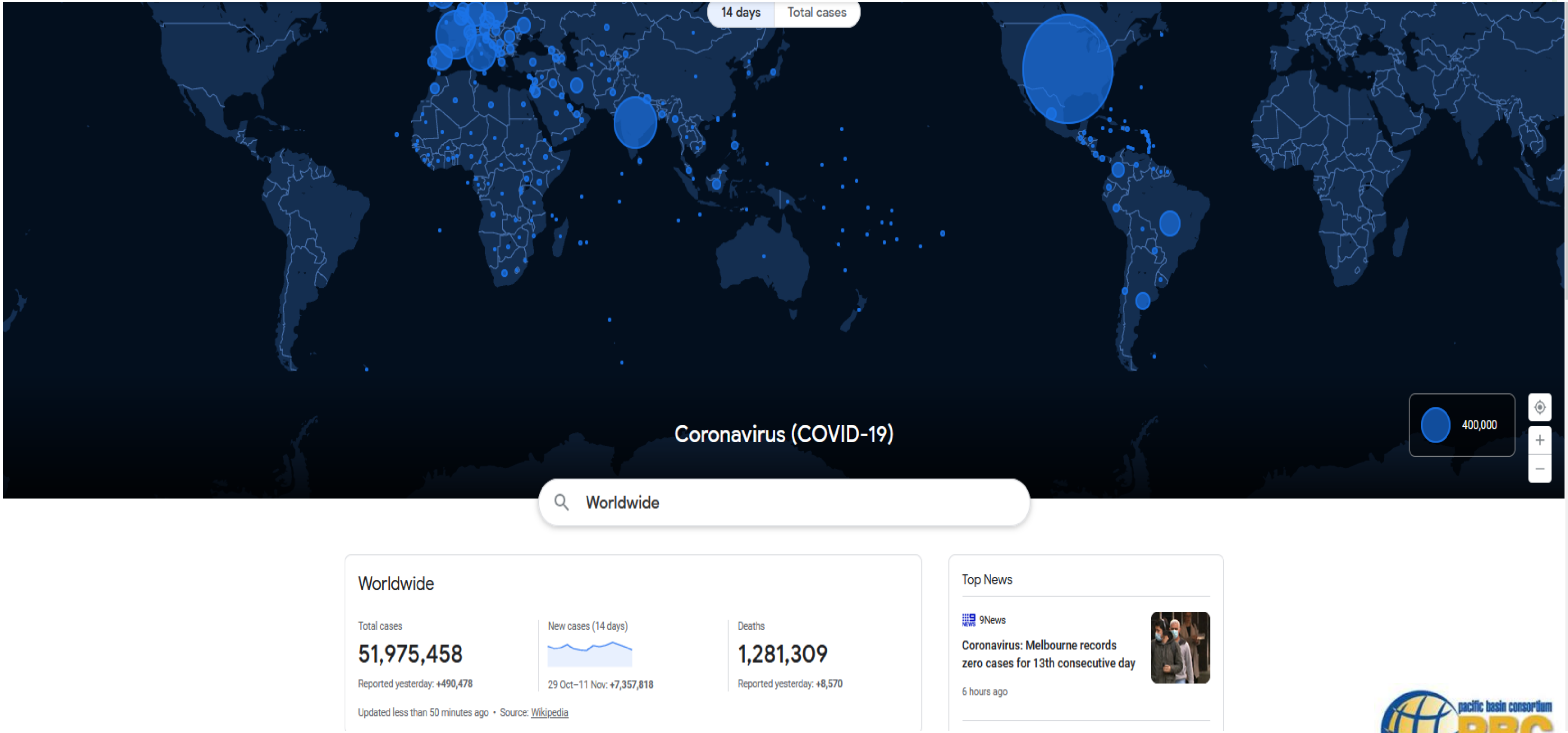
Covid-19

Why don't children get as sick?

What are the research questions / opportunities?

Covid-19

- SARS-Cov-2
  - Virus emerged in Wuhan; reported to WHO [21/12/19]; public health emergency [30/01/20]; pandemic declared [11/03/20]
  - Binds to ACE2 receptor, expressed in lungs, heart, kidney, intestine
- Covid-19
  - The diseased caused by SARS-Cov-2
  - Symptoms appear 2-14 days after exposure
    - Cough, shortness of breath, fever, chills, muscle pain, headache, sore throat
    - Loss of taste and smell
    - Diarrhoea
    - Severe disease associated with systemic “cytokine storm”, respiratory failure, death (2.5% case fatality globally)



Google News 12/11/2020

COVID-19 IN CHILDREN

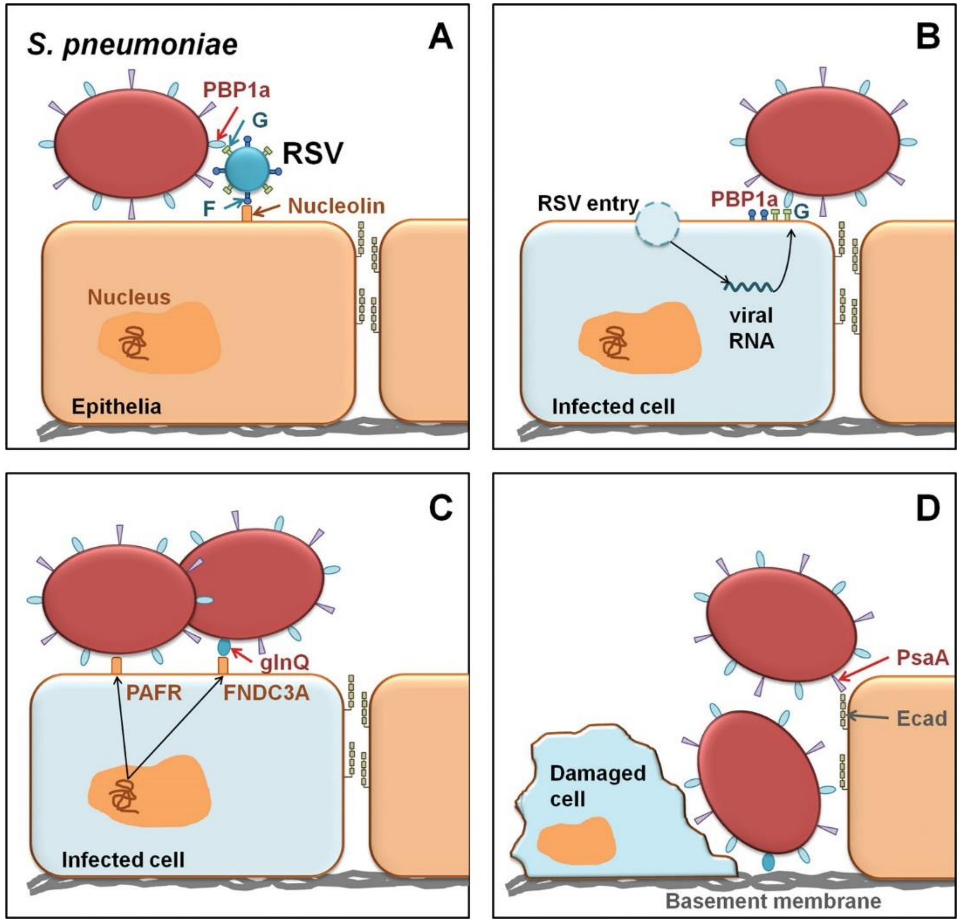
- Fewer children infected [USA data]:
  - Median age 11 years
  - 32% 15-17 y, 27% 10-14 y, 15% 5-9 y, 11% 1-4 y, 15% < 1y
  - Most mild illnesses with few deaths in young children
  - Toxic shock, systemic vasculitis (Kawasaki-like) in some
- Children may have higher viral load but milder illness [Yonker J Peds 2020]
- Role in community transmission uncertain

Epidemiological exposures and Covid-19

- Environmental exposures associated with increased Covid-19 include:
  - Ambient air pollution
    - 1μg/m^3 ↑ $PM_{2.5}$ → 8% ↑ death [Wu 2020]
  - Pesticides, chemical disinfectants, formaldehyde
  - Organic chemicals, heavy metals, EDC
  - ? Related to immune suppression, irritation, disturbing airway epithelium
- Children are more susceptible to environmental exposures
- Why do they get less Covid-19?

Potential mechanisms of viral:bacterial interactions in acute disease

A. Direct binding: "tug boat"
B. Viral glycoproteins act as bacterial "receptor"
C. Virus ↑ surface expression of bacterial binding proteins
D. Viral epithelial damage exposing basement membrane



Could mechanisms A & D operate with air pollution?

Brealey 2015 Fems microbiology letters

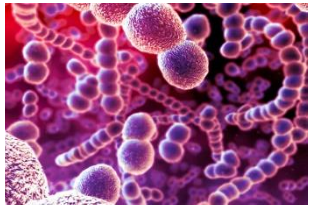
Air Pollution: combustion related and biological

Air pollution (PM 2.5), ozone

Car exhaust fumes

Cigarette smoke/ biomass

Pollens



Bacterial/ viral infection

ROS↑

Inflammation

Mitochondrial damage

DNA damage

Apoptosis

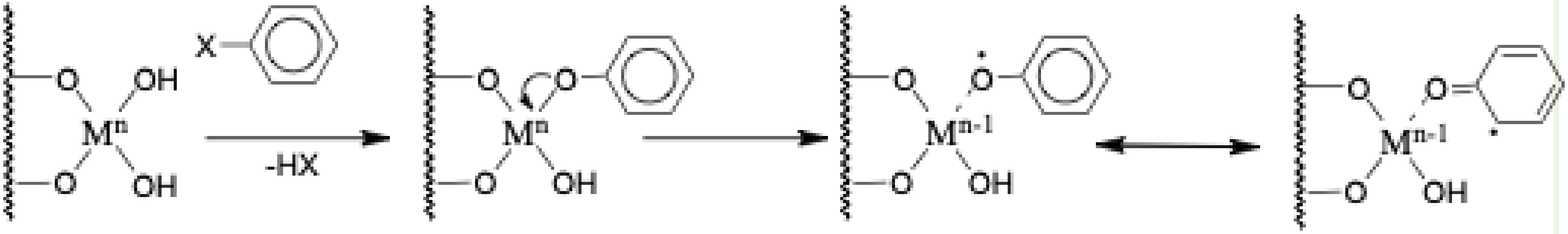
COPD

IPF

Asthma

COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; ROS: Reactive oxygen species

Environmentally persistent free radicals (EPFRs)

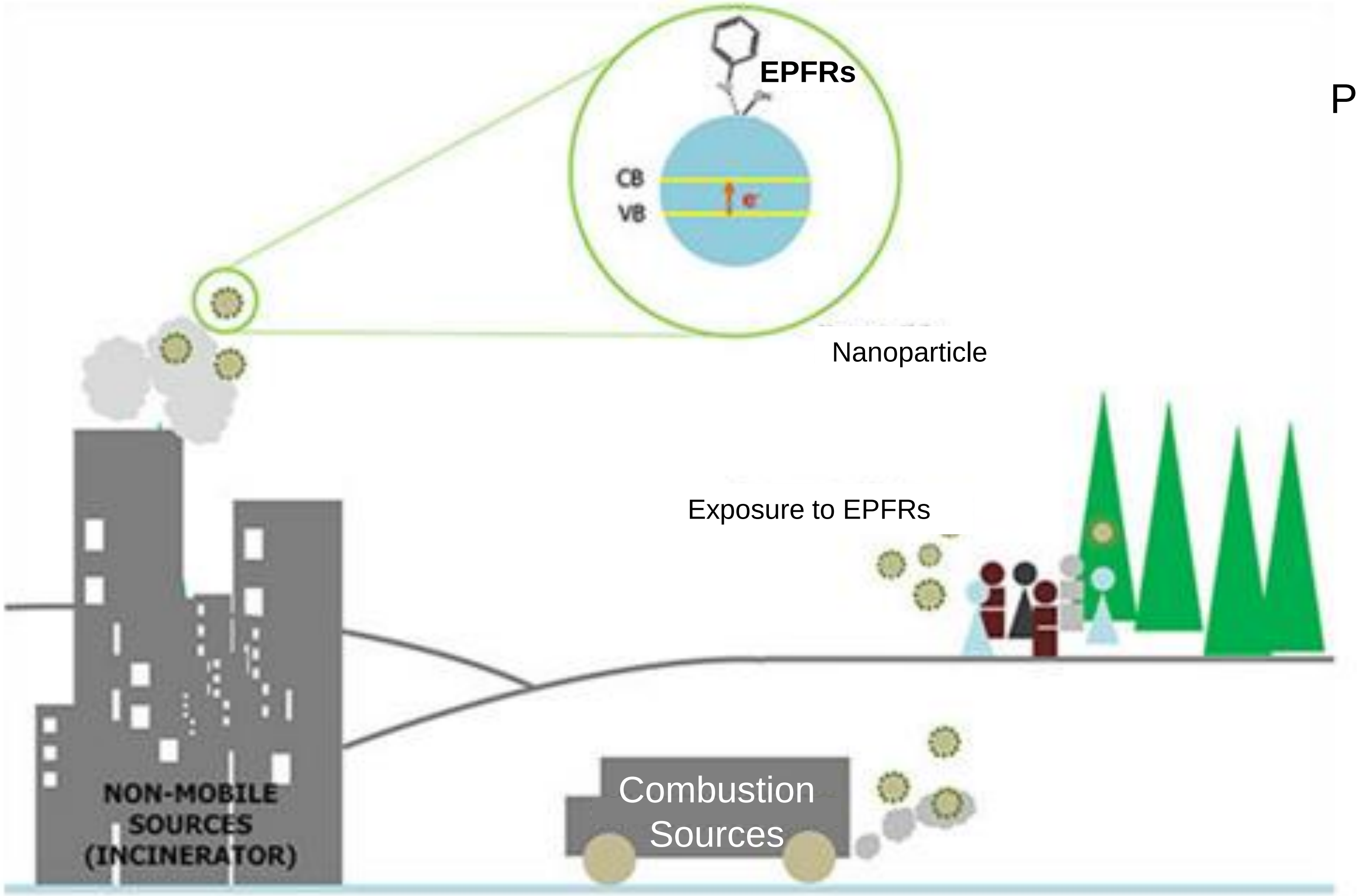


Physisorption followed by Chemisorption

Electron transfer

Stable EPFR

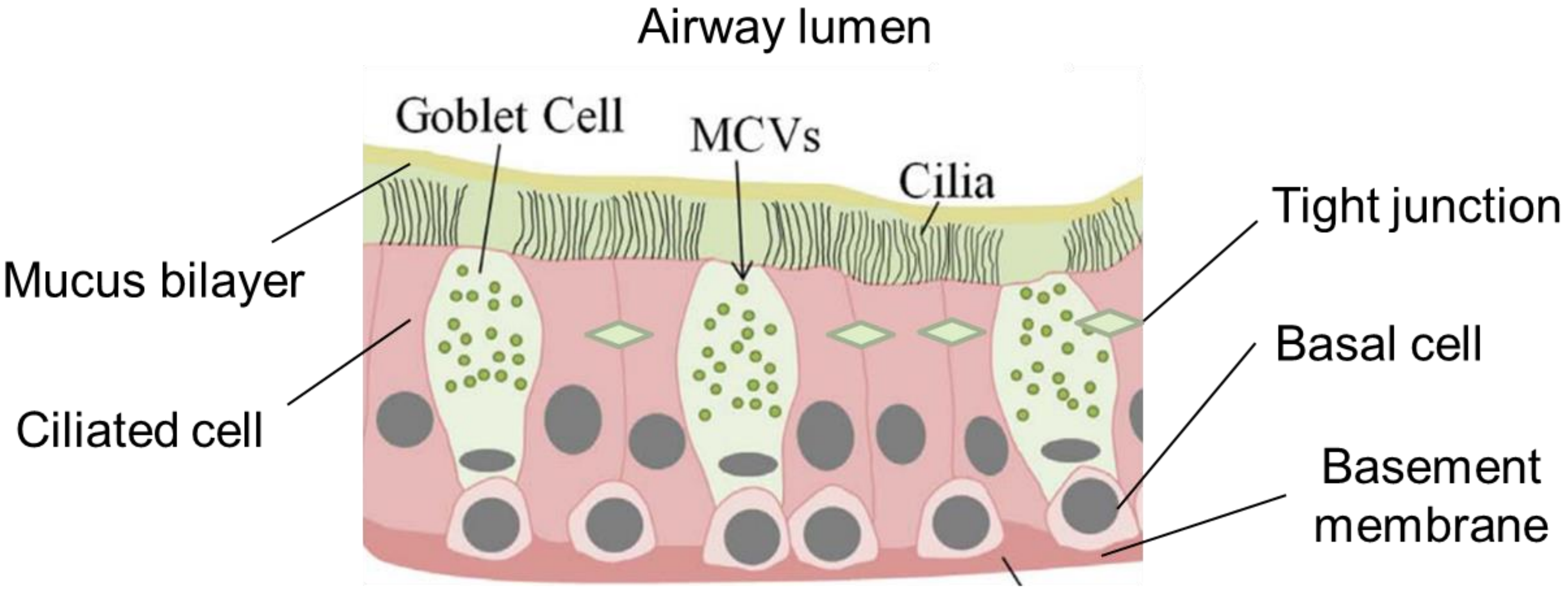
Environmentally persistent free radicals (EPFRs)

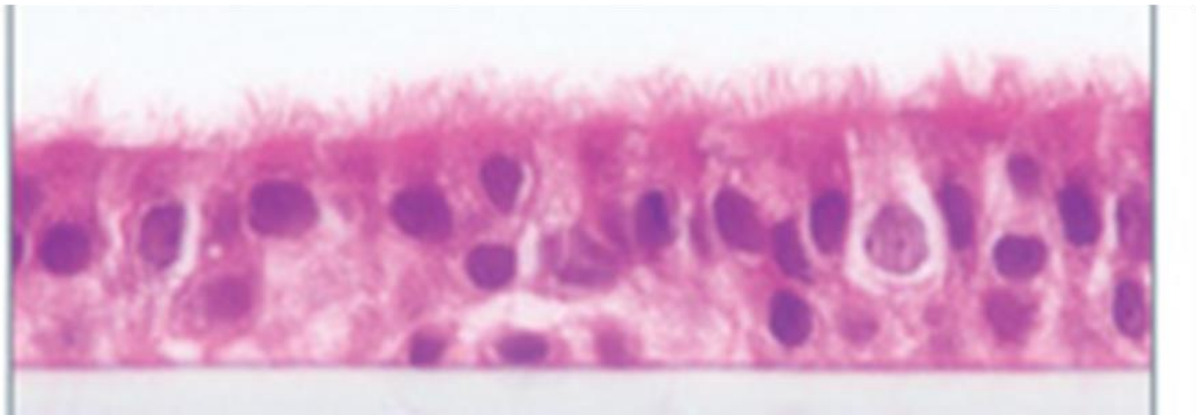


PM: particulate matter

(Vejerano, Rao et al. 2018)

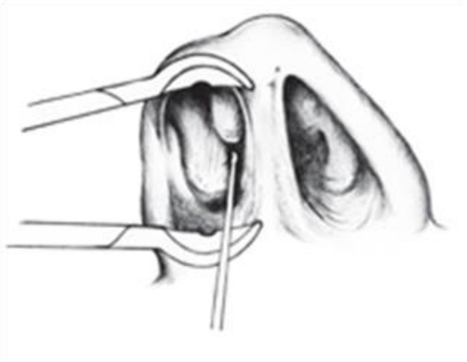
Airway Epithelium is the site of first contact



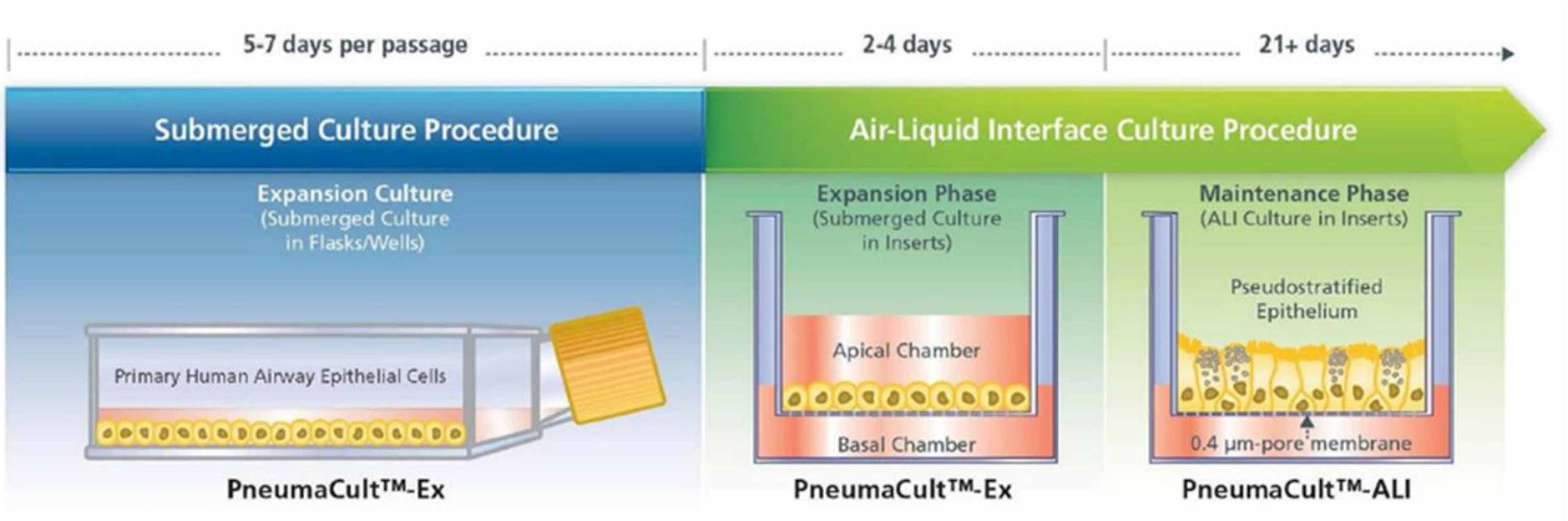


(Reid, Veerati *et al*. 2018)

Primary human nasal epithelial cells (HNECs) cultured at Air-Liquid Interface (ALI)

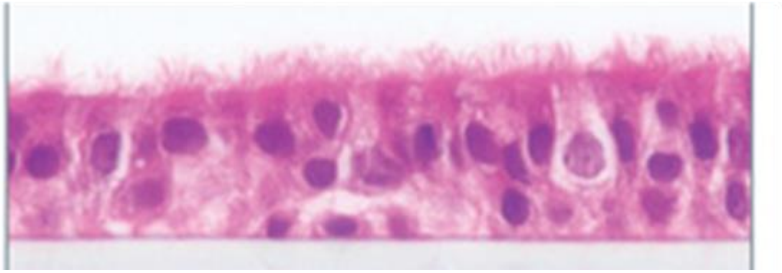


Nasal mucosal curette



(Arlington Scientific, Stem Cell Technology)

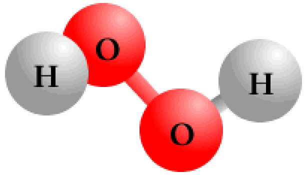
Oxidant exposure



Exposure

Outcome

H_2O_2



1h

Antioxidants

0h

4h

24h

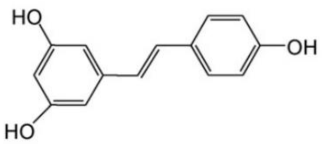
EPFRs

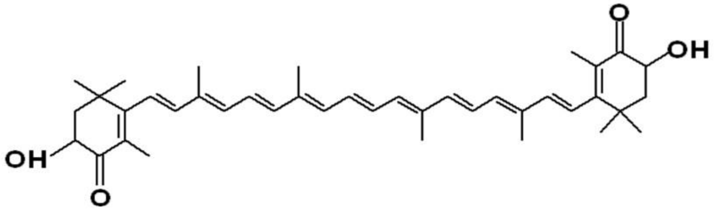
24h

4h

- Epithelial integrity: TEER
- Epithelial integrity: permeability
- Cell death: LDH
- Generation of mtROS: MitoSOX
- Gene expression
- Protein expression

ANTIOXIDANTS

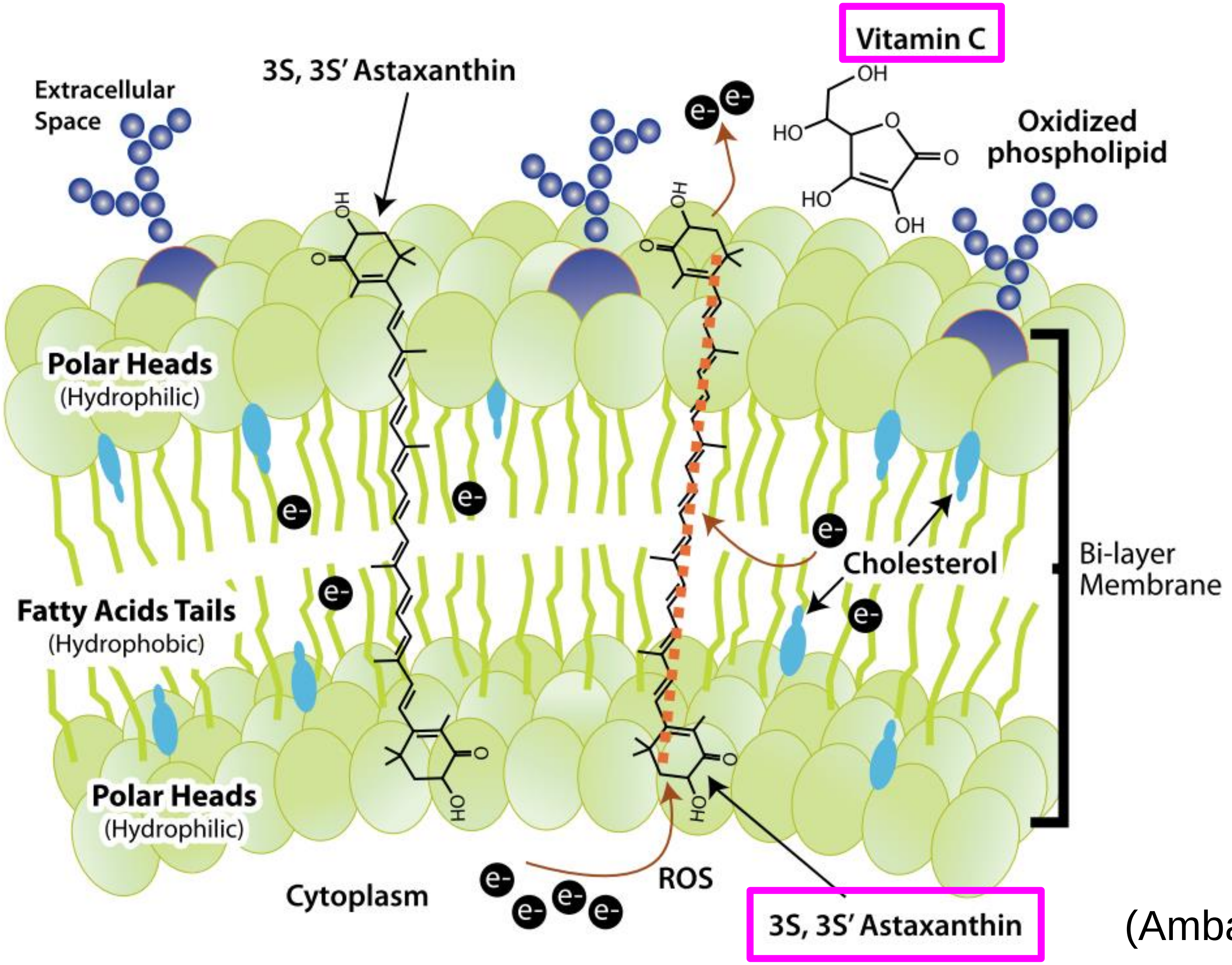


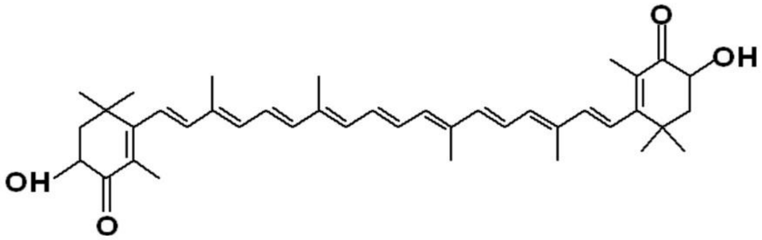


Resveratrol

Astaxanthin

Astaxanthin (3,3′-dihydroxy-b, b′-carotene-4,4′-dione)

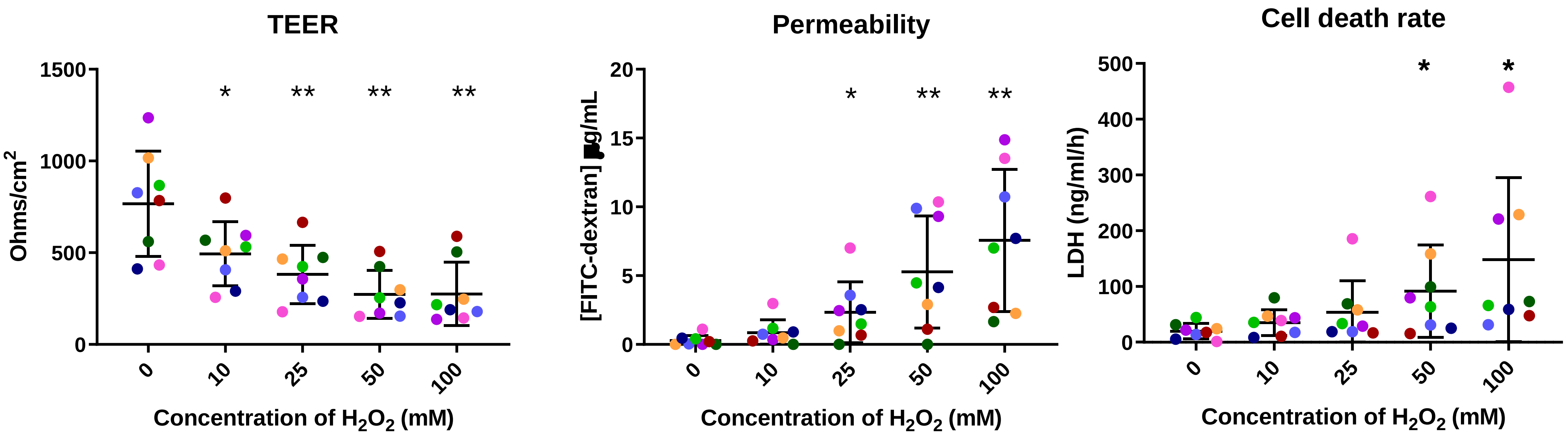




(Kidd 2011)

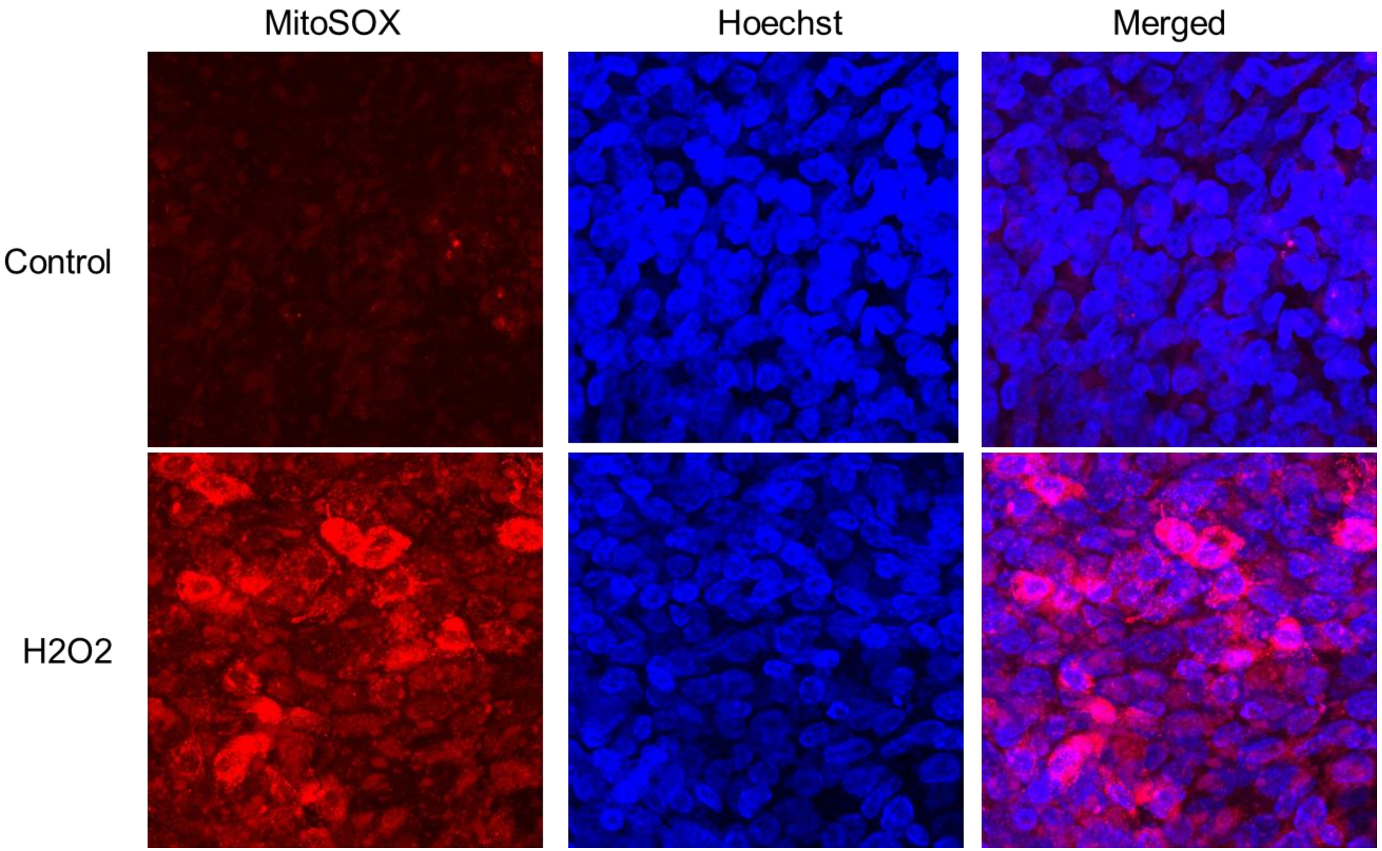
(Ambati, Phang et al. 2014)

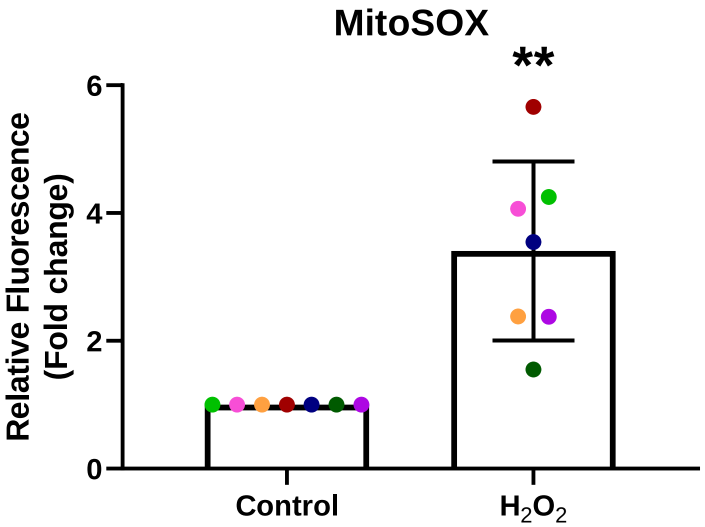
The effect of oxidative stress on cell integrity



Mean ± SD (n=8; *p<0.05; ** p<0.01)

H_2O_2 exposure induced mitochondrial reactive oxygen species generation

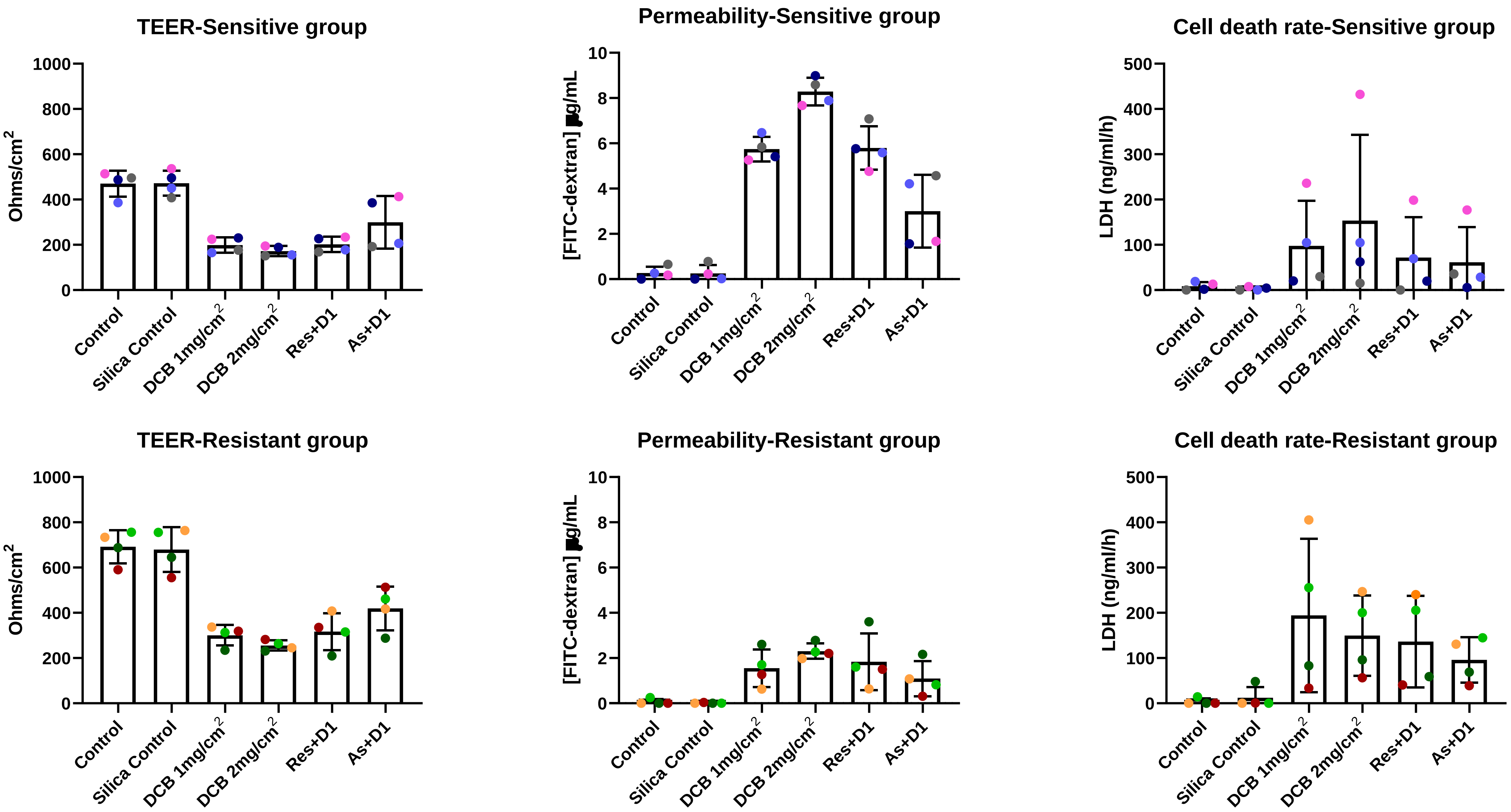




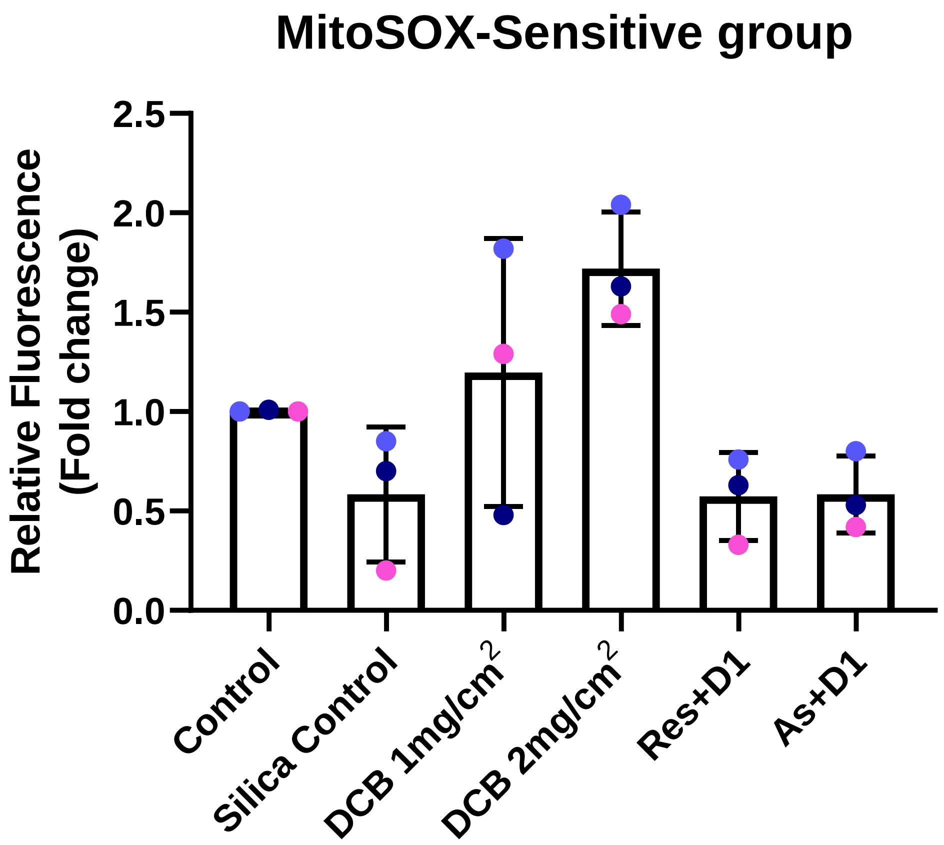
Mean ± SD (n=7; ***p*<0.01)

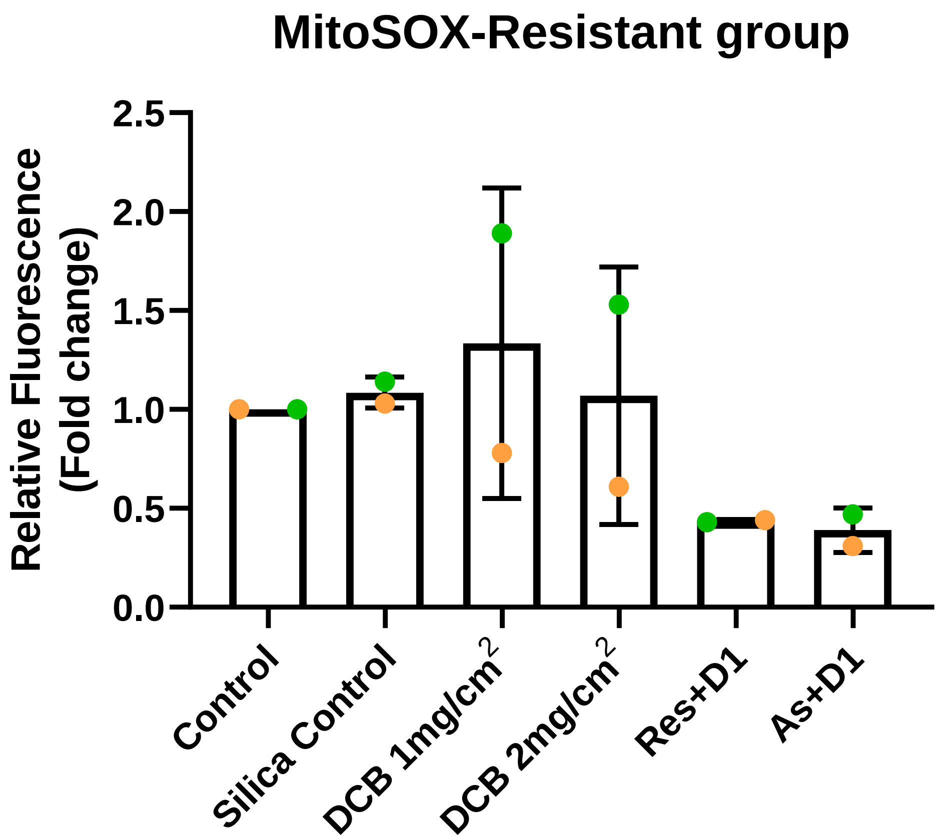
Red: mtROS; Blue: nuclei

EPFR IMPACT ON EPITHELIAL INTEGRITY

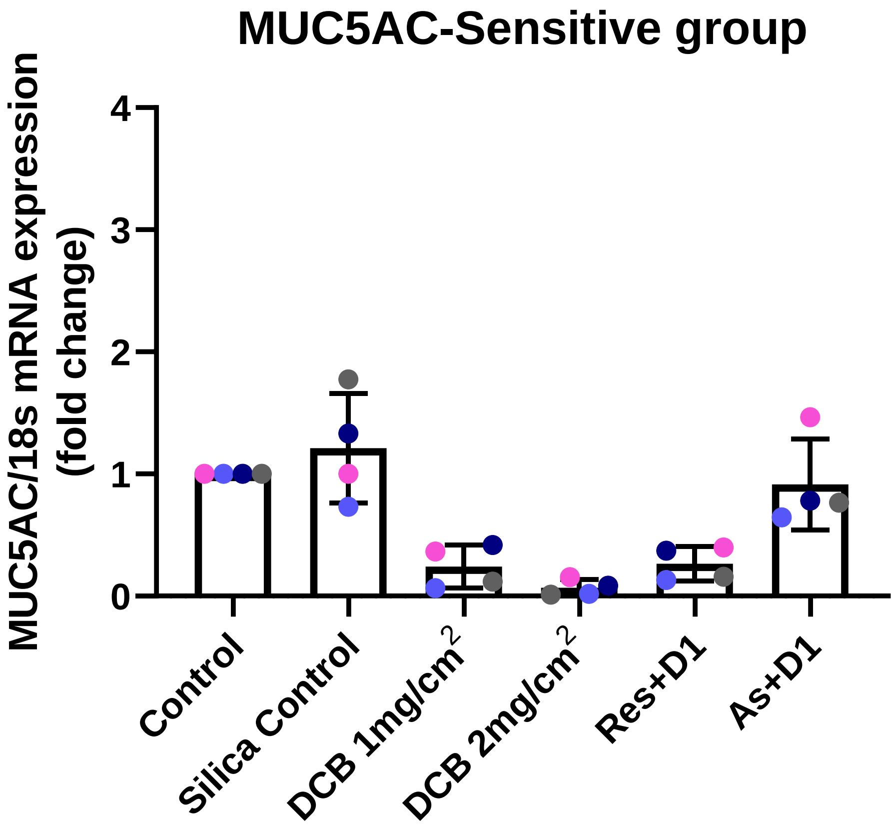


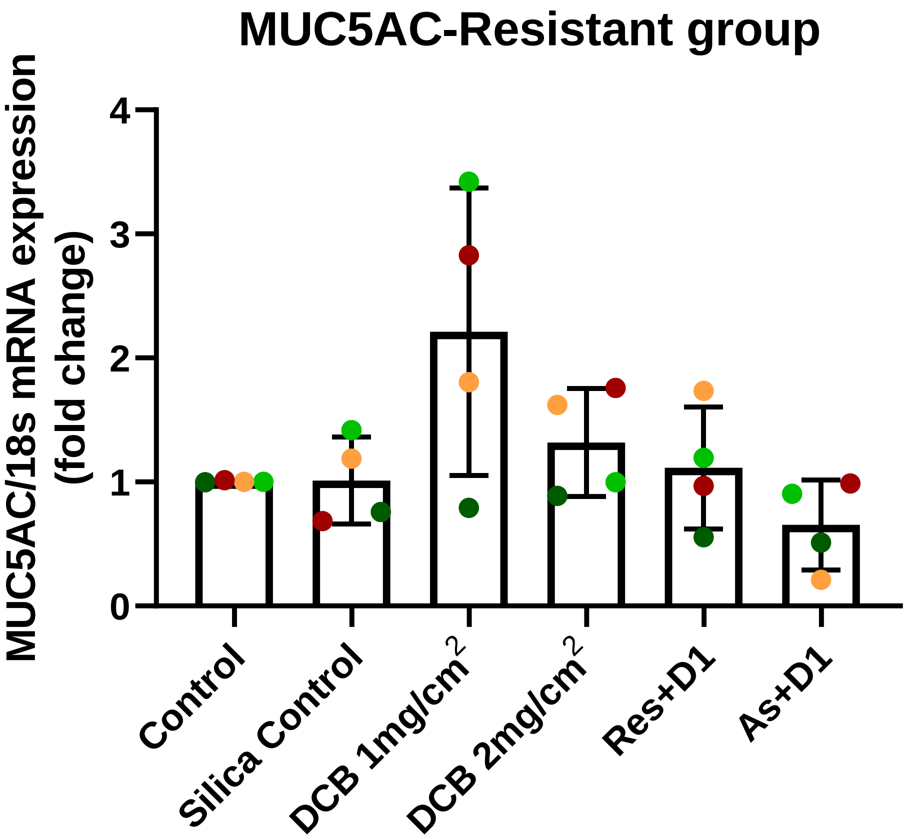
EPFRs exposure induced mtROS generation





Gene expression-MUC5AC





AIR POLLUTION AND COVID-19

- OS in nasal epithelium
  - Decreased epithelial integrity
  - Sensitive individuals can't mount a protective mucous response
  - Pre-treatment with anti-oxidants, especially astazanthin, mitigates the effects
- Air pollution and Covid-19
  - Could PM act as a viral carrier?
  - EPFR-induced OS would increase risk of Covid-19, especially in sensitive individuals.

Covid and children

- SARS-Cov-2 infection during fetal development
  - Vertical transmission appears uncommon unlike other viruses
  - Infants born to infected mothers do not appear to be affected
- Why?
  - Does the Th-1 biased IU environment provide protection, if so how?
- Research needs
  - Large scale epidemiological studies to determine the true rate of vertical transmission and effects on offspring of infected mothers
  - Mechanistic studies
    - animal models
    - Viral studies in placenta, amniotic fluid

Covid and children

- Age-based susceptibility / genetic susceptibility
  - Telomere length in neutrophils shorten with age
    - Short telomeres associated with increase systemic inflammation and more sever Covid-19
    - Shorter telomere indicates increased risk of Covid-19 death regardless of age
  - ACE2 receptor numbers
    - Some studies suggest children have more ACE2 in the lungs, can this be protective?
  - Anti-viral immunity
    - AEC from children produce more INF-λ than adults following SARS-Cov-2 infection.

COVID AND CHILDREN

- Previous Corona virus infection
  - Corona virus infections are common in children
    - Brisbane birth cohort, weekly nasal swabs for respiratory virus (4 endemic corona viruses) and bacteria
    - 11.5% infected in first 6 months, 33.4% by 12 months, 52.9% by 18 months, 72.2% by 2 y
    - Most 1st infections associated with resp symptoms, 20% asymptomatic
- Do infections with "harmless" corona viruses protect against Covid-19?
- Cross-reactive antibodies?

Interactions between environmental exposures and Covid-19: why don't children get as sick?

- Lots of unanswered questions and research opportunities
  - Large scale epidemiological studies
  - Mechanistic studies
    - Cell culture systems reflecting *in vivo* physiology
    - Animal models