AN UPDATE ON PATHOBIOLOGY AND AN APPROACH TO QUESTIONS THAT YOUR MOM MIGHT ASK YOU

Ali Broadhurst – Professional Swabber and Entrance 5 Goalkeeper

Tygerberg Hospital COVID Team April 2020

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Early View

Editorial

Pathogenesis of COVID-19 from a cell biologic perspective

Robert J. Mason

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Basing Respiratory Management of Coronavirus on Physiological Principles

Martin J. Tobin MD,

Division of Pulmonary and Critical Care Medicine,

Hines Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine,

Hines, Illinois 60141

(E-mail address: mtobin2@lumc.edu; Telephone: 708-202-2705)

3 STAGES OF INFECTION

1. Asymptomatic (1-2 days after infection)
SARS-CoV-2 binds to ACE2 in the nasal cavity, starts replicating
Patients are infectious, virus detectable on RT-PCR
?in future viral load can predict infectivity and course

2. Upper airways and conducting system (symptomatic)
Virus reaches upper airway – enhanced innate immune response
Inflammatory cytokines released
?can cytokine response predict outcome/progression
80% of infections end here

3. Hypoxia and progression to ARDS “Day 10”

Virus reaches gas exchange units (mainly subpleural)

Preferentially infects type II pneumocytes, they undergo apoptosis

Epithelial growth factors are released → normally type II pneumocytes differentiate into type I and type II pneumocytes, however aberrant secondary pathways for epithelial regeneration result in severe fibrosis and scarring

Elderly patients ⬇ mucocillary clearance therefore the virus can propagate faster to the gas exchange unit

MEASURING RESPIRATORY COMPROMISE

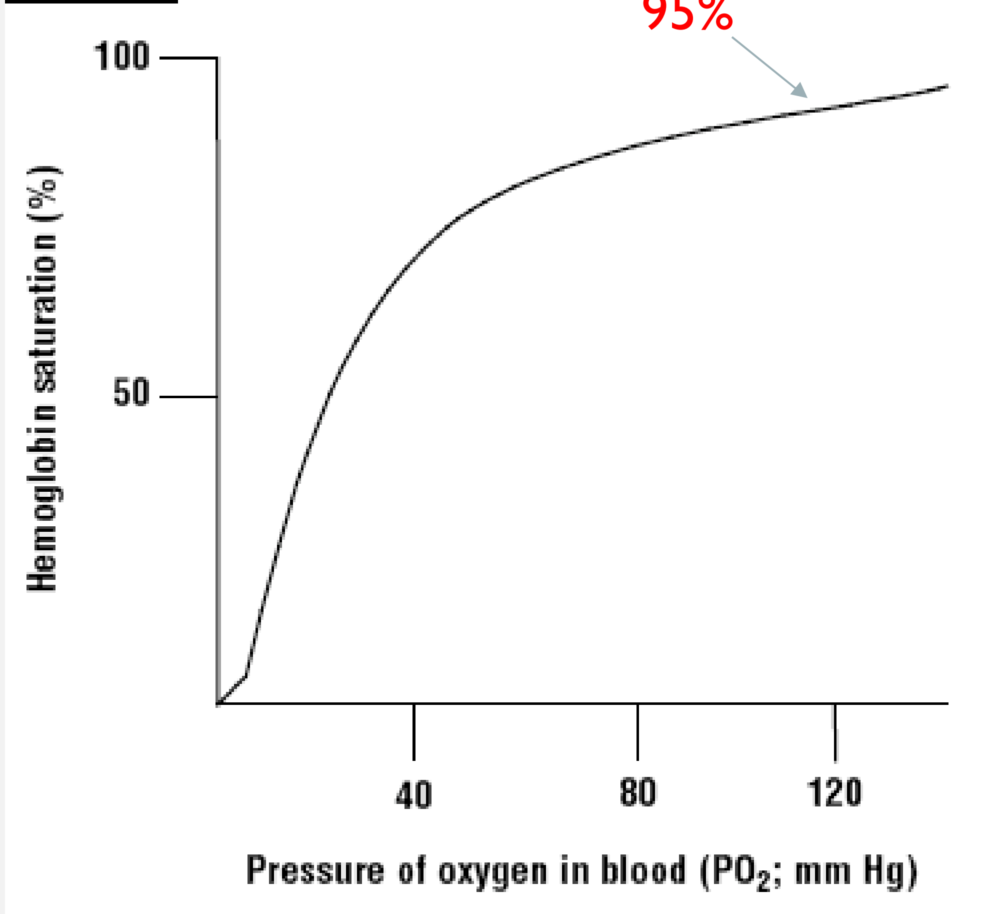
Sp02 and Sa02 can vary by as much as 4%

At sats of 95%, Pa02 can be 8 or 26 (flat line in curve)

This has implications when a patient has a high Fi02

Fi02 is also inaccurate in many cases – NP02 at 2l per minute can be anywhere from 24 – 35%

FIGURE 1



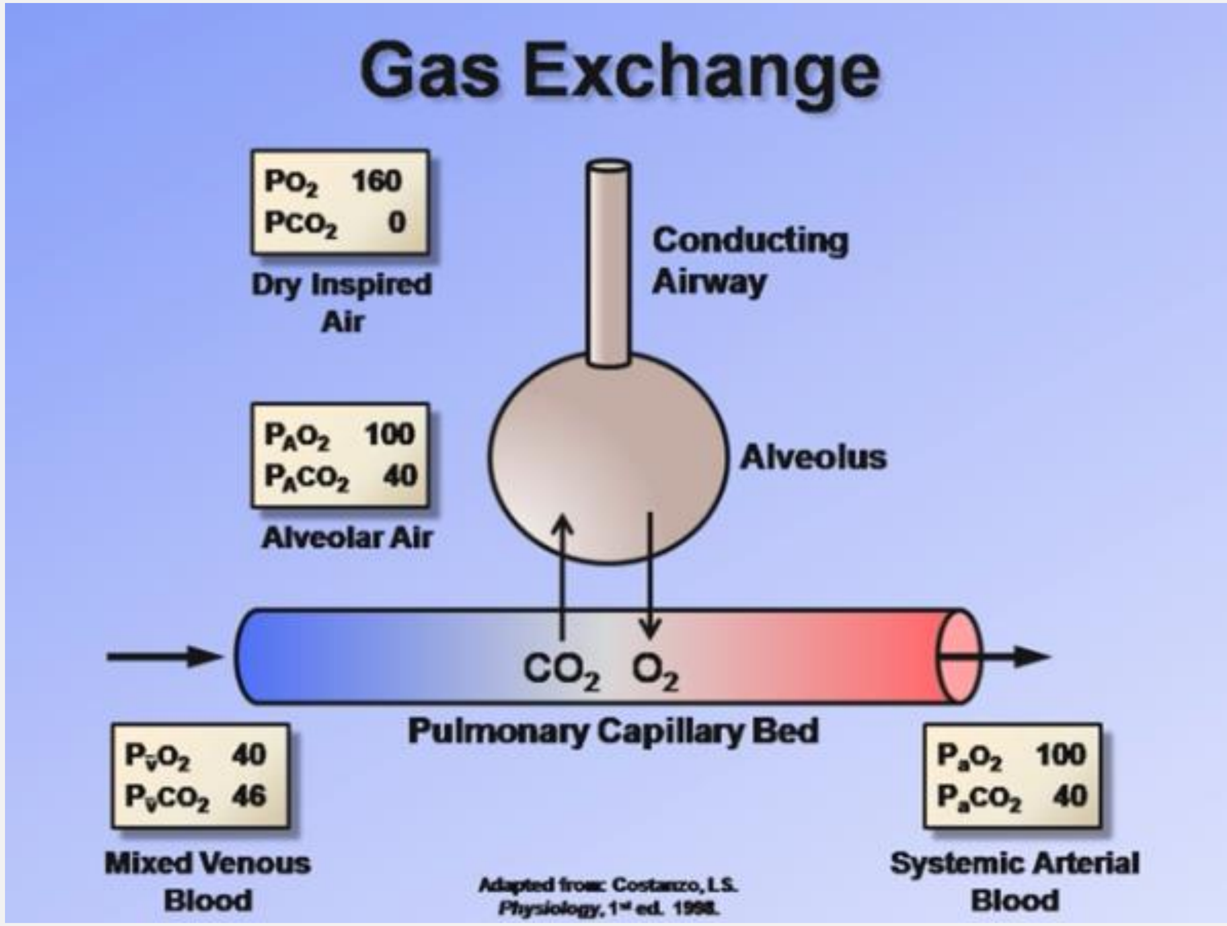
P/F RATIOS AND A-A GRADIENTS

P/F ratio - ratio of the Fi02 to the Pa02 – quick and easy way to work out extent of hypoxia, tells you less about the underlying cause

200 – 300 = ALI

<200 = ARDS (fairly random cut off)

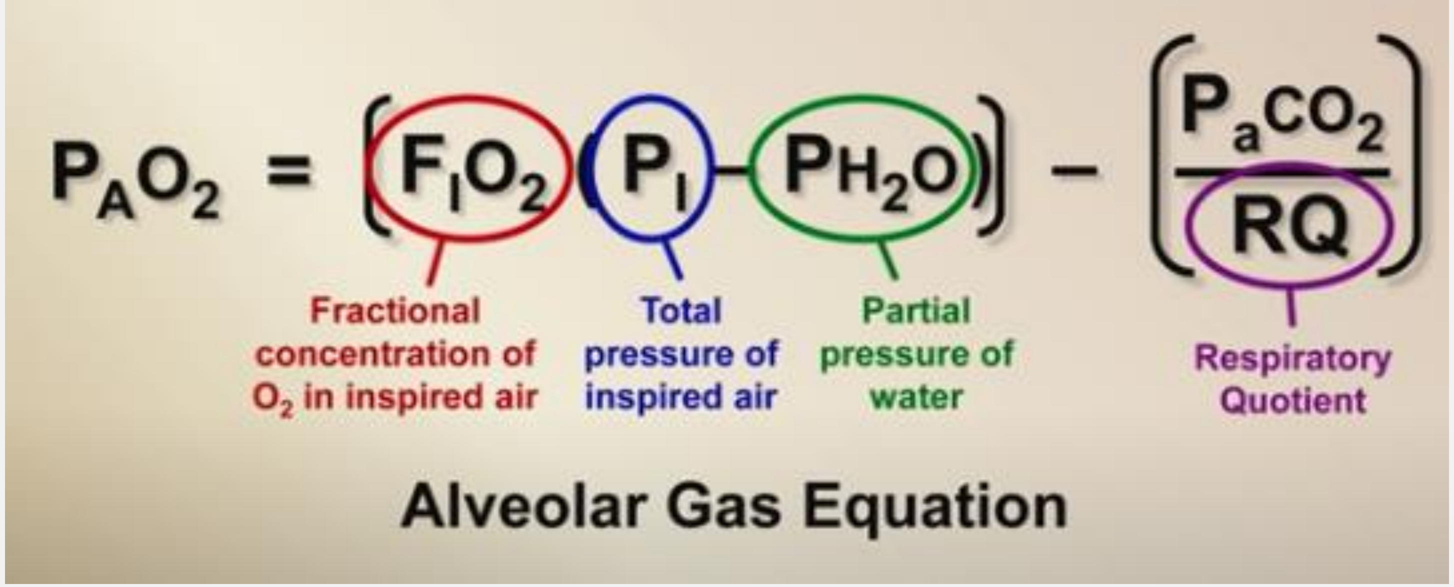
A-a gradient – difference between the partial pressure of oxygen in the alveoli (PA02) vs the blood (Pa02)



A-A GRADIENT

A-a gradient = PA02 – Pa02
Normal value = (age ÷ 4) + 4

A-a gradient abnormal: V/Q mismatch, shunting, diffusion problems
If A-a gradient is normal: hypoventilation or low pressure (altitude)



$$P_AO_2 = \left[0.21\,(760 - 47)\right] - \left(\frac{P_aCO_2}{RQ}\right)$$

Fractional concentration of O_2 in inspired air

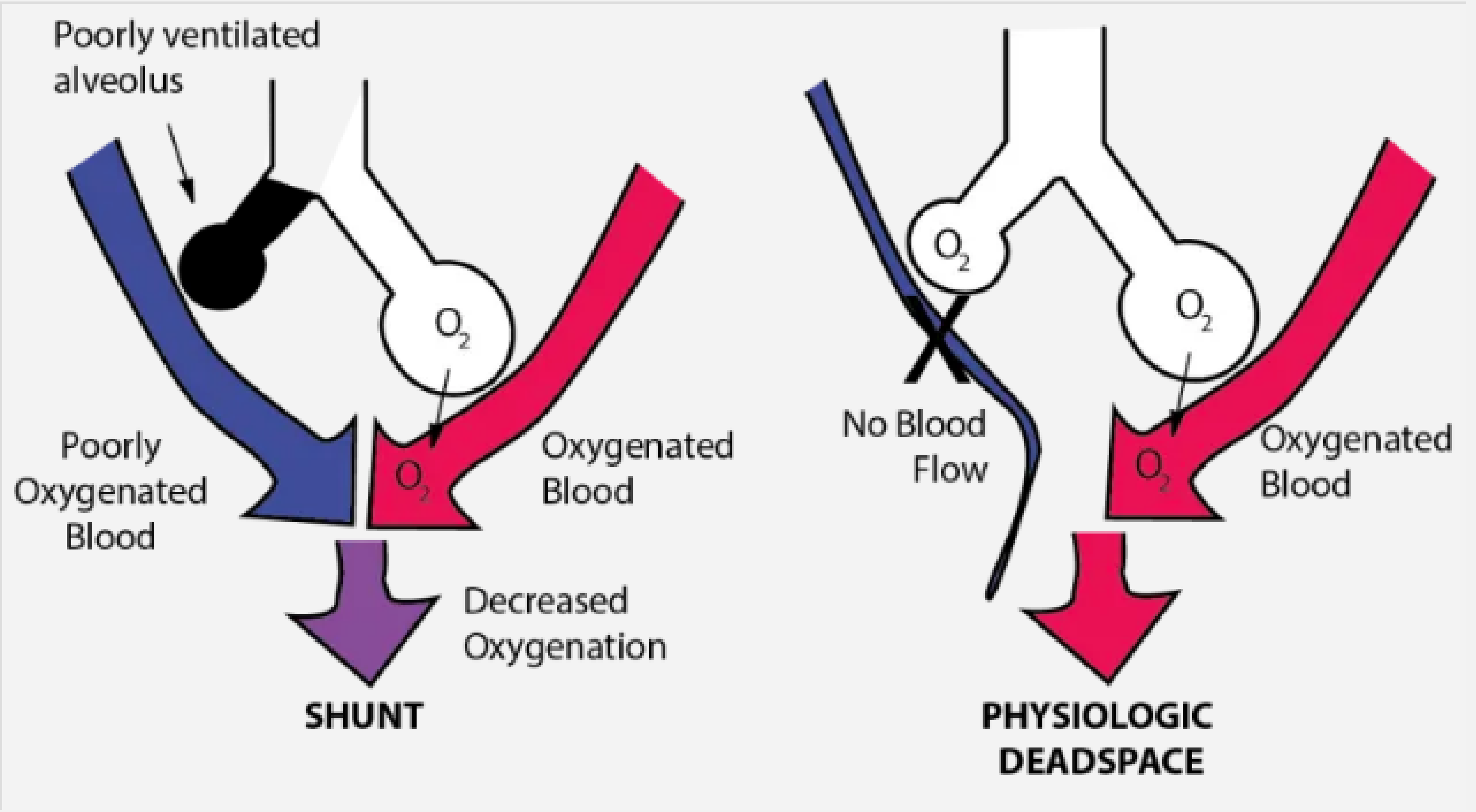
Total pressure of inspired air

Partial pressure of water

Respiratory Quotient

Alveolar Gas Equation

(on room air at sea level)


Poorly ventilated alveolus
O_2
Poorly Oxygenated Blood
O_2
Oxygenated Blood
Decreased Oxygenation
SHUNT
O_2
O_2
No Blood Flow
O_2
Oxygenated Blood
PHYSIOLOGIC DEADSPACE

SYNOPSIS OF THE AUTHOR'S MESSAGE

A-a gradient more accurate predictor of underlying cause than P/F ratio: excludes hypoventilation as a cause (unlikely COVID) and better quantifies hypoxia

COVID results in shunting or a V/Q mismatch.

If Pa02 increases with supplemental 02 = V/Q mismatch – patients can avoid intubation by increasing the Fi02

If Pa02 does not increase with increased Fi02, these patients have severe shunting and are likely to require intubation

Severe hypoxia does not necessarily correlate with CXR findings

ASSESSING ORGAN DAMAGE

End-organ function difficult to assess – results from anaerobic metabolism

When Pa02 drops, oxygen extraction from tissues increases

End-organ damage only presents when oxygen delivery is <25%

Mechanical ventilation buys you time at a significant risk

Weaning patients from mechanical ventilation must be a priority in these patients to avoid further complications

INTUBATING PATIENTS WITH COVID

Clinical decision taking into account hypoxia, dyspnoea, respiratory rate and other factors

Dyspnoea not typically sensed until Pa02 is <8kPa (or lower)

Respiratory rate of 25 – 35 is an appropriate response to lung inflammation and is not an indication by itself for intubation – more important is work of breathing (pleural pressure swings and tidal volume)

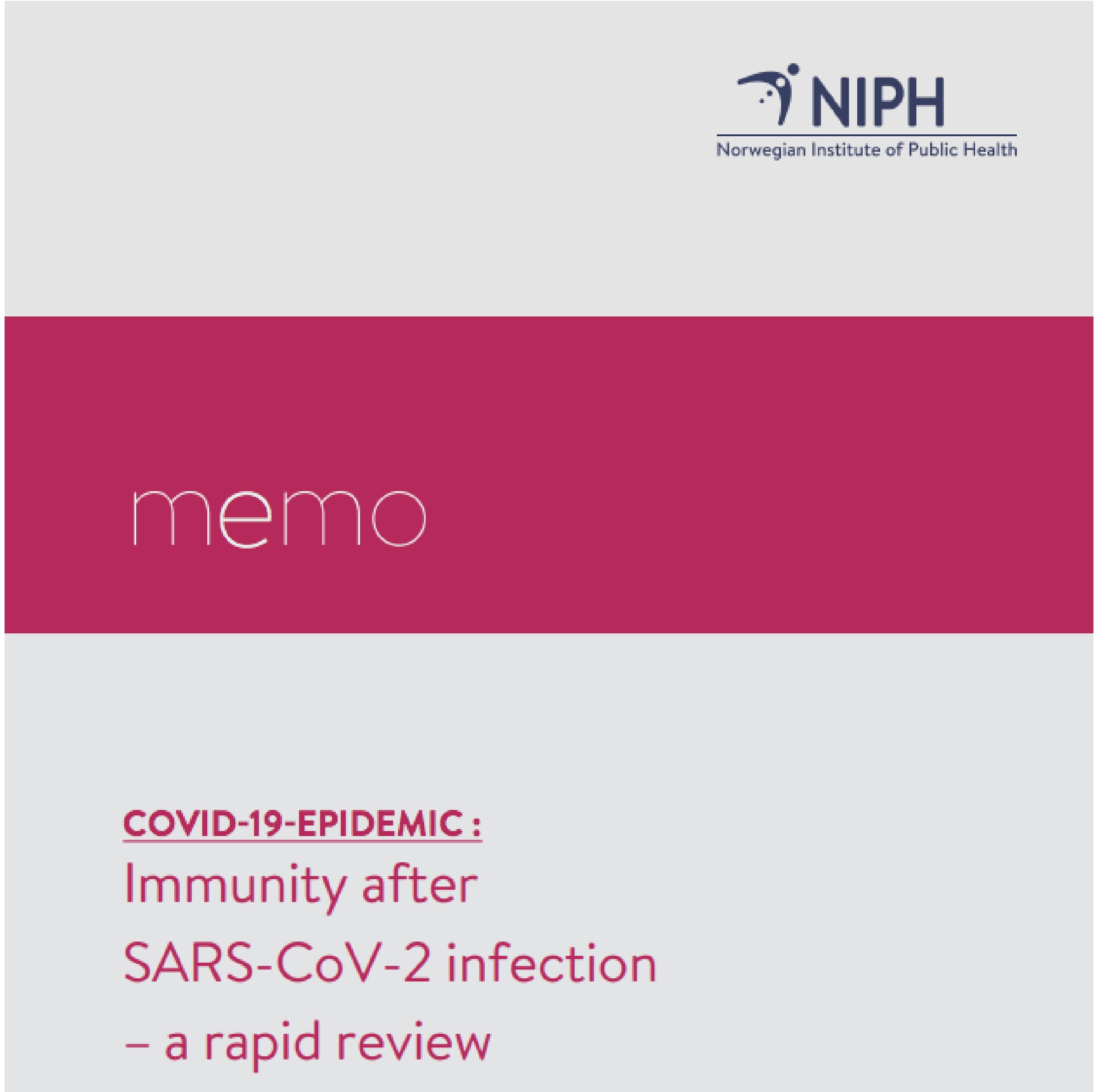
Assessed clinically by palpating phasic contractions of the sternocleidomastoid muscle during inspiration

CAN YOU GET COVID MORE THAN ONCE?

One paper from China – 2 cases

- 39 year old lady: 6/7 Hx of typical symptoms; CT – bilateral GG infiltrates with RT-PCR positive; treated symptomatically and had 2 x negative RT PCR nasal swabs prior to DC
- 50 year old male smoker – 2/7 Hx of a LRTI; CT chest showed bilateral GG infiltrates with RT PCR positive for SARS-Cov-2 on admission and D8, 2x negative swabs prior to DC

- Surveillance swabs: RT-PCR positive at day 6 post discharge; however symptoms were improving and repeat CT chests showed ongoing improvements
- Both readmitted with 2 x negative swabs subsequently
- Authors postulate that this may be due to a problem with false negatives relating to testing, or a heterogenous presentation of the same disease, stating that larger trials need to be conducted to assess whether you can infected or not and how long a RT PCR may stay positive for


NIPH
Norwegian Institute of Public Health

memo

COVID-19-EPIDEMIC :
Immunity after SARS-CoV-2 infection – a rapid review

Summary of Key Points

- Many articles not peer-reviewed emanating out of China
- Information from SARS-CoV and animal studies
- Variable rate of seroconversion and production of IgG and IgM antibodies detected; likely due to variable test sensitivities
- Rate of seroconversion does not appear to be affected by disease severity
- Two long-term studies on SARS-CoV (similar virus, also infects via ACE2 receptor) - IgG levels present 13 years post infection; second study showed sustained IgG levels at 2 years but decline after 3rd year
- Study of 6 mothers who gave birth to infants who tested negative for SARS-CoV-2 showed that all 6 infants had antibodies

bioRxiv preprint doi: https://doi.org/10.1101/2020.03.13.990226.

Reinfection could no

ed rhesus macaques

Linlin Bao[†,1], Wei Deng[†

i Liu[†,2], Jing Xue[†,1], Qi Lv[†,1], Jiangning Liu[1], Pin

u[1], Fengdi Li[1], Zhiguang Xiang[1], Haisheng Yu[1], Sh

Wang[1], Shunyi Wang[1], Zhiqi Song[1], Wenjie Zhao[1], Yunlin Han[1], Linna Zhao[1], Xing Liu[1], Qiang Wei[1], Chuan Qin[*,1]

VERDICT:

No convincing evidence for early re-infection, but further evidence and better tests needed to assess seroconversion

Seriously limited long-term data on long-term immunity

Re-infection is theoretically possible but would likely result in a milder illness

COULD BCG OR OTHER IMMUNISATIONS BE PROTECTIVE?

IS THE BCG THEORY IMPLAUSIBLE?

No!

- BCG has an immunomodulatory effect; anti-viral activity – increased epigenetic promotion of pro-inflammatory cytokines; anti-viral IL-1B upregulated

- RCT in Indonesia –BCG monthly for 3 months significantly lowered the rate of respiratory tract infections in people >65 years

- Paper Guinea-Bissau in 2000 – significantly lower all-cause mortality in children vaccinated with BCG

- Used in immunotherapy for early stage bladder cancer – given intravesically; mechanism is still unknown after being in use for 40 years; probably works through modulation of adaptive immunity

Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study

Aaron Miller, Mac Josh Reandelar, Kimberly Fasciglione, Violeta Roumenova, Yan Li, and Gonzalo H. Otazu*

Department of Biomedical Sciences, NYIT College of Osteopathic Medicine, New York Institute of Technology, Old Westbury, New York, USA

*Correspondence to: gotazual@nyit.edu

Abstract

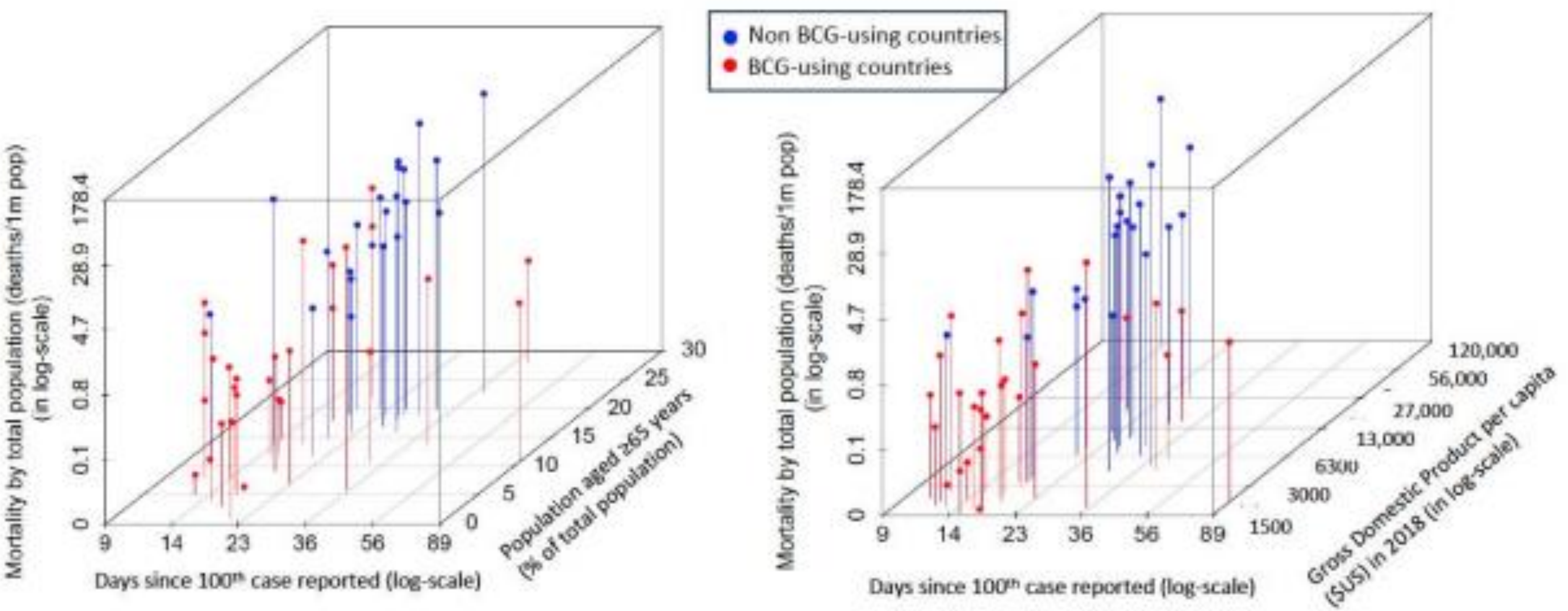
COVID-19 has spread to most countries in the world. Puzzlingly, the impact of the disease is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure. Here we propose that national differences in COVID-19 impact could be partially explained by the different national policies respect to Bacillus Calmette-Guérin (BCG) childhood vaccination. BCG vaccination has been reported to offer broad protection to respiratory infections. We compared large number of countries BCG vaccination policies with the morbidity and mortality for COVID-19. We found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population. We also found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19.

FINDINGS

- Italy vs Japan argument – Japan: no strict isolation policy, low rates of transmission and deaths (both developed, high average age)
- Countries with universal BCG vaccination policies have significantly lower COVID-19 death rates (easier to measure than cases, less likely to under-report)

- Significant and linear correlation between number of years that BCG vaccine was available vs death rate - Spain – BCG universal for 16 years with a death rate of 29.5/million people, Denmark 40 years with 2.3 death/million people
- Middle and high income countries without universal BCG vaccination have 4 times the amount of cases per million people when compared to those with universal BCG vaccination ($p=0.0064$).

Figure 2: Association between COVID-19-attributable mortality and BCG use in national immunization schedules, propotion of population aged ≥65years, time trajectory on the epidemiological curve and country-specific GDP per capita. Each dot is representative of a country. Red dots=BCG-using countries; Blue dots=Non BCG-using countries.



MULTIPLE POTENTIAL CONFOUNDERS

Presence of comorbidities – however in many Asian countries, rates of T2DM have overtaken those of Europe (6% vs 11%)

Older population in Europe and higher income countries (however Japan has one of the highest average ages in the world)

Reporting errors

Genetic factors (CCL2, mannose binding lectin, ACE2) all currently under investigation

Temperature and humidity may have a (modest) effect

Large lag between proven symptomatic infection and death (2-8 weeks)

VERDICT

Initially at least, there is strong epidemiological weight of data behind BCG

BCG has a biologically plausible mechanism for reducing both the severity and the spread of SARS-CoV-2

There are excessive confounding factors at present which need to be investigated in clinical trials before we can even begin to hope about BCG being protective in any way

If proven effective, the timing of the vaccine in order to be effective needs to be interrogated

There is zero chance that BCG vaccination is going to be a magic bullet for COVID

ASYMPTOMATIC CARRIERS

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Universal Screening for SARS-CoV-2 in Women Admitted for Delivery

TO THE EDITOR: In recent weeks, Covid-19 has rapidly spread throughout New York City. The obstetrical population presents a unique challenge during this pandemic, since these patients have multiple interactions with the health care system and eventually most are admitted to the hospital for delivery. We first diagnosed a case of Covid-19 in an obstetrical patient on March 13, 2020, and we previously reported our early experience with Covid-19 in pregnant women, including two initially asymptomatic women in whom symptoms developed and who tested positive for SARS-CoV-2,

for SARS-CoV-2 on admission became symptomatic postpartum; repeat SARS-CoV-2 testing 3 days after the initial test was positive.

Our use of universal SARS-CoV-2 testing in all pregnant patients presenting for delivery revealed that at this point in the pandemic in New York City, most of the patients who were positive for SARS-CoV-2 at delivery were asymptomatic, and more than one of eight asymptomatic patients who were admitted to the labor and delivery unit were positive for SARS-CoV-2. Although this prevalence has limited generalizability to

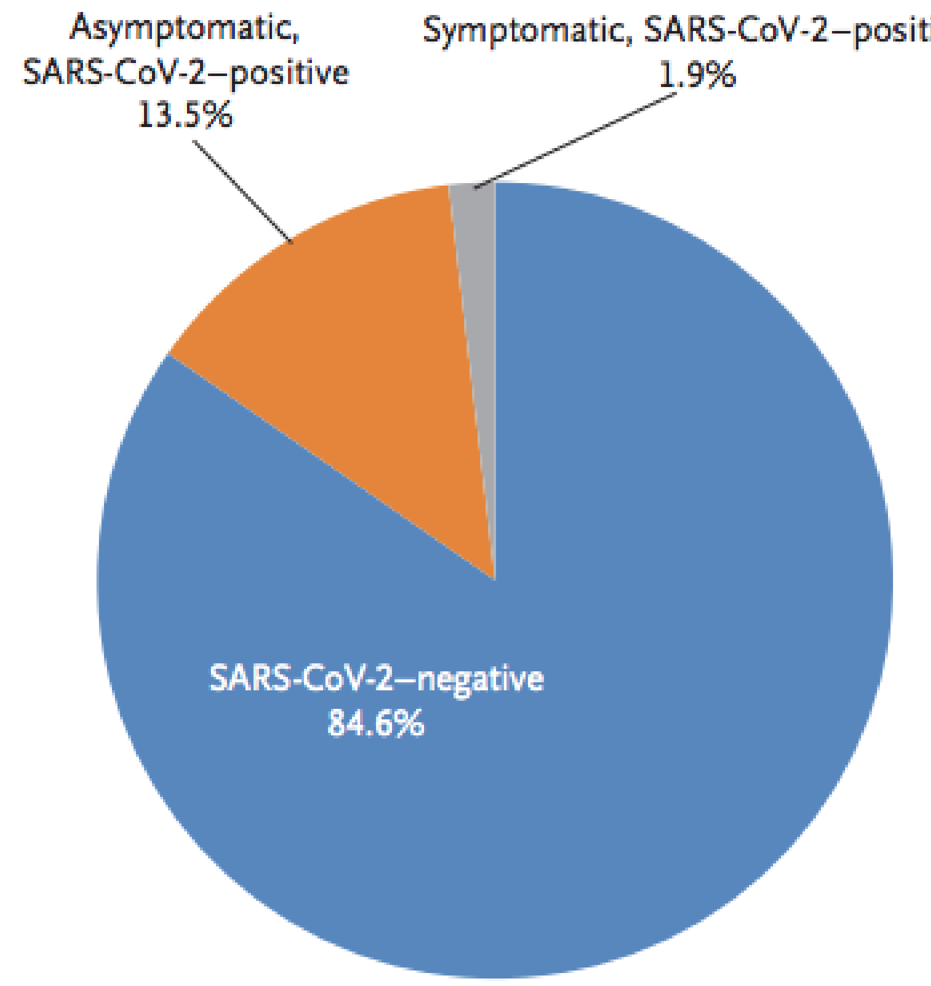


Figure 1. Symptom Status and SARS-CoV-2 Test Results among 215 Obstetrical Patients Presenting for Delivery.

"No longer were there individual destinies; only a collective destiny, made of plague and emotions shared by all"

"Once the faintest stirring of hope became possible, the dominion of plague had ended"

Albert Camus, The Plague

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