Welcome!
This webinar will begin at 7PM MST

1 Chat
2 Q&A
3 Leave Meeting

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Note: If you leave the webinar and sign back in, be advised that the Q&A and Chat features may not refresh to show previous information that was shared.

COVID CORNER
Ongoing COVID-19 updates brought to you by The Office of CME&PD and The Physician Learning Program
Moderators

Kelly Burak
Any direct financial payments, gifts, in-kind compensation or honoraria
- Employee, University of Calgary

David Topps
Any direct financial payments, gifts, in-kind compensation or honoraria
- Director Rural Education for CME& PD and PLP offices

Territorial Acknowledgement

Source: https://www.ucalgary.ca/Indigenous
Housekeeping

- Multiple speakers will address various aspects of the topic
- There will be a Q&A after all the presentations
- Use the Q&A box to enter questions by text. No spoken questions.
- **Refer to this how-to-guide for info on Questions, Chat, etc.**
- We get lots of questions: scan the list and give a thumbs up if you are interested in a question already posed.
- Formal notices, copyright, declarations and disclaimers will be offered throughout the presentation and within the chat box

Disclosure of Financial Support

- The program was developed and planned to achieve scientific integrity, objectivity and balance
- This program has received educational grants from the
  - College of Physicians Surgeons of Alberta
  - Alberta Health Services
  - Calgary Health Trust
Scientific Advisory Group COVID-19 Recommendations

novel coronavirus (COVID-19)

AHS' Scientific Advisory Group is connecting with clinicians, operational leaders, researchers and other experts to review emerging evidence and guidance of national and international bodies to provide information for focused areas of healthcare in relation to COVID-19. These resources are created to provide research informed advice to AHS physicians, staff, patients and families. Reports are updated frequently based on emerging evidence or concerns.

COVID-19 Resources for AHS Staff & Health Professionals

COVID-19 Scientific Advisory Group

Rapid Evidence Report

Key Research Questions:
1. What is the impact of virtual visits (e.g. videoconferencing, telephone, texting, email) compared with or in addition to in-person visits on process outcomes, patient and provider satisfaction, quality of care, and access to provider?
2. Are there differences in the evidence base and recommendations for types of visits and provider?

June 12, 2020

www.albertahealthservices.ca

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Key Messages from the Evidence Summary

- Primary Care address multiple issues
  - Systematic reviews, meta-analysis of small RCTs (risk of bias)
  - Patients and MDs are satisfied with virtual care
  - Virtual care = ↓ visit time, ↓ travel costs, ↓ lab/DI test, ↓ urgent / F2F visits
- Specialty Care more narrow focus
  - Larger number of high-quality studies, including meta-analysis (risk of bias)
  - High levels of satisfaction across broad patient populations
  - Virtual care = in-person care with improved access and lower costs (rural setting)
- Uptake and satisfaction
  - Age, rurality and socio-economic status may influence (requires further study)
COVID CORNER Webinar:
Lessons Learned from the Last 3 Months

Presenters:
Deena Hinshaw MD FRCP CCFP
Lynora Saxinger MD FRCP C TropMed
Craig Jenne BSc PhD PDF
Learning Objectives

- Describe the impact of public health measures and our preparation for the 2nd wave
- Interpret the emerging evidence for anti-virals and disease modifying therapies
- Recognize the challenges and timelines for a vaccine

COVID-19 in Alberta: Wave one lessons learned

Deena Hinshaw MD FRCPC CCFP
Chief Medical Officer of Health, Alberta Health; Associate Clinical Professor, Department of Medicine, University of Alberta; Clinical Assistant Professor, Department of Community Health Sciences, Cumming School of Medicine, University of Calgary

Disclosure
- Any direct financial payments, gifts, in-kind compensation or honoraria: Employed by the Government of Alberta
Learning Objectives

At the end of this session, participants will be able to:

- Explain the differences between the Alberta COVID-19 model outputs, actual health system impact, and comparisons with other provinces;
- List key factors in predicting severe outcomes from COVID-19 based on Alberta data;
- Discuss merits and challenges of different approaches to testing for COVID-19; and
- Compare and contrast international and local lessons learned from Wave One.
Alberta COVID-19 epi curve up to June 19


Model prediction – total attack rate


This material is for individual use only and not to be used for further dissemination.
Model prediction hospitalization – April 8

![Model prediction hospitalization – April 8](https://www.alberta.ca/stats/covid-19-alberta-statistics.htm)

Model prediction hospitalization – April 28

![Model prediction hospitalization – April 28](https://www.alberta.ca/stats/covid-19-alberta-statistics.htm)
Model prediction compared with ON and QC

![Graph showing model prediction compared with ON and QC]

Source: Alberta Health Surveillance and Epidemiology

Peak severe outcome rate per capita

<table>
<thead>
<tr>
<th></th>
<th>Alberta (April 30)</th>
<th>B.C. (April 4)</th>
<th>Ontario (May 5)</th>
<th>Quebec (May 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak hospitalization rate per 10,000</td>
<td>0.24</td>
<td>0.26</td>
<td>0.71</td>
<td>2.2</td>
</tr>
<tr>
<td>Peak ICU rate per 10,000</td>
<td>0.05</td>
<td>0.14</td>
<td>0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Total death rate per 10,000</td>
<td>0.34</td>
<td>0.33</td>
<td>1.77</td>
<td>6.34</td>
</tr>
</tbody>
</table>

Source: Alberta Health Surveillance and Epidemiology
Severe outcomes by age (counts)


Severe outcomes by comorbidity (proportion)

Molecular testing

- Diagnosis of acute infection
- Detects presence of viral RNA
- Does not distinguish between viable and prolonged shedding
- Purposes for use:
  - Case management
  - Contact tracing
  - Outbreak ID and management
  - Population point in time prevalence monitoring

Serologic testing

- Determination of past infection
- Detects antibodies against SARS-CoV2
- Unclear relationship to immunity
- Purposes for use:
  - Population spread monitoring
  - Case management (rare)
  - Outbreak ID and management (rare)
  - Contact tracing (rare)

Temporal pattern in viral shedding

Asymptomatic testing April 27 – June 22

<table>
<thead>
<tr>
<th>Classification: Protected A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Total people tested</th>
<th>Total positive</th>
<th>Percent positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contacts of cases</td>
<td>2,168</td>
<td>189</td>
</tr>
<tr>
<td>Outbreak-associated</td>
<td>5,558</td>
<td>168</td>
</tr>
<tr>
<td>Voluntary asymptomatic</td>
<td>44,620</td>
<td>12</td>
</tr>
</tbody>
</table>

Source: Alberta Health Services Surveillance and Reporting

Molecular testing by age group and gender

[Graph showing molecular testing by age group and gender]

Source: Alberta Health Services Surveillance and Reporting


This material is for individual use only and not to be used for further dissemination.
Serology and immunity

- Are people who recover from COVID-19 immune to future infections?
- Do currently available serology tests serve as an accurate measure of immunity?

https://www.nature.com/articles/s41591-020-0965-6.pdf
Alberta learnings from wave one

- Highest risk setting for outbreaks and severe outcomes – continuing care residences
- High risk settings for transmission:
  - Occupational: food processing facilities, warehouses
  - Non-occupational: social events, indoors more risky than outdoors, religious gatherings if no protective measures, high intensity group exercise
- Children do not seem to be a major driver of infection (similar to what has been seen in other jurisdictions)
- Need to balance risk of infection with risk of broad lock-down measures in all settings

International comparisons

- New Zealand – strict lockdown for elimination
- Japan – approach: avoid closed spaces, crowded places and close contact
- Iceland – broad population testing, aggressive tracing and containment
Deaths per 10,000, Alberta and Sweden


International intervention review

- Looked at China, Italy, Iran, France, South Korea and the US
- Estimated that measures have prevented 62 million confirmed (530 million total) infections in these countries
- Heterogeneity of results, but overall, interventions found to be effective include:
  - Limiting or prohibiting gatherings
  - Home isolation for those who are ill
  - Business closures/work from home
  - Travel limitations

International evidence review

- Modeling study emphasizes the importance of contact tracing, isolation and quarantine
  - Most effective combination is isolation of those who are ill, quarantine of household contacts, and manual contact tracing of all close contacts

Kucharski et al. Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. Lancet Infect Dis. Published online June 16, 2020 https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930457-6

Public face masks – emerging evidence

- US ecologic study suggests mandatory mask policies had a statistically significant effect on reducing growth rates
- UK modelling study suggests a population benefit of universal face mask wearing, even if efficacy of droplet blocking is only 50%
- WHO recommendation for medical masks for those at risk and use of non-medical masks where there is widespread transmission and in indoor, crowded settings.

Wave two – what should we expect?

- Timing – dependent on population behavior
- Local intervention more likely to be used than province-wide measures
- Importance of collective action cannot be over-emphasized, including use of face masks in crowded indoor spaces, encouraging anyone who is ill to stay home and get tested, and ongoing distancing measures, cleaning and hand hygiene.

Three things:

1. No silver bullet – we are each other’s protectors
2. Balance will be key to success
3. What the future holds is up to us
Therapeutics Update

Lynora Saxinger MD FRCPC CTropMed
Co-Chair, Scientific Advisory Group, Alberta Health Services; Associate Professor, Division of Infectious Diseases, Departments of Medicine and Medical Microbiology and Immunology, University of Calgary

Disclosures
- Any direct financial payments, gifts, in-kind compensation or honoraria: LEO Pharma
- Grants or Clinical Trials: CSL Behring

Learning Objectives

A High Level View of COVID THERAPEUTICS

1) Is hydroxychloroquine safe? Should trials continue? What about prophylaxis for HCW?
2) Which anti-viral agents hold the most promise...is remdesivir going to help?
3) What other strategies are beneficial for managing COVID-19 patients? e.g. prone ventilation
This was planned a few weeks ago, which is a whole epoch in the COVID geologic timescale

*I thought I'd be saying “it's looking bad for hydroxychloroquine, and awaiting news of remdesivir...”*

Instead:
- HQ is done
- Remdesivir is promising
- surprise, dexamethasone is a contender.


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Subsequently....

- May 22 – local HOPE study suspended (no harm signal, may pool data)
- Oxford RECOVERY trial halted HQ arm June 5 (criticized re: higher dosing)
- WHO halted HCQ trials June 17
- NIH trial halted June 20, Novartis trial halted June 22
- FDA revoked emergency use authorization J25
  - USA said to have 63 million doses that can’t be used outside of a trial

Remdesivir

- Broad acting antiviral with in vitro activity against coronaviruses
- Currently the most promising antiviral – available only in trials and expanded access protocol (not in Alberta)
  - Previously studied in Ebola, and planned for MERS-CoV trial
  - Gilead started planning increased production with early reports from Wuhan (had 5000 patient courses in Switzerland and California and 90,000 courses in Edmonton)
Remdesivir: evolving literature

- Time to clinical improvement as outcome measure
  - This could mean discharge-ready for discharge, off oxygen
- NIAID ACTT-1 study: placebo controlled, 11d versus 14 d recovery and mortality at day 14 7.1 versus 11.9 percent
- Trials suggest 5 vs 10 day therapy equivalent overall
  - 10 days may be better in severe disease
- Ongoing trials with baricitinib and tocilizumab
Dexamethasone

• Early reports from China, Italy and Spain suggested widespread use of dexamethasone with various combinations
  • Some literature supporting it’s use in ARDS, pneumonia, septic shock, accelerates ventilator weaning, ? Mortality benefit
• Oxford based RCT press release June 16 was picked up widely and suggested to be a “life saving” drug
  • Medicine by press release (cuts deaths in ventilated patients by 1/3 and death in admitted patients on oxygen by 1/5.)
  • But...trust, peer review (recent retractions of Surgisphere data)
  • Protocol available, additional data in preprint came out June 22

https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(19)30417-5.pdf
RECOVERY trial

- Pragmatic open label multi centre RCT 176 hospitals
- Overall mortality 454/2104 dexamethasone (21.6%) versus 1065/4321 (24.6%) (rate ratio 0.83)
  - 6 mg daily for 10 days (fairly small dose)
  - Ventilated: 29% versus 40.7% mortality (0.65)
  - On oxygen: 21.5% versus 25% mortality
  - Admitted no oxygen: 17.0 versus 13.2% mortality (1.22 (.93-1.61)
    - no benefit ? Harm
  - Hospitalization 1 day shorter
- Preliminary results still (28% outcome unknown), non blinded, pts perceived at higher risk from steroid not enrolled

Note only 1 day difference in length of stay

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Hospitalized Patients with COVID-19, **Day 28 Mortality**

**RECOVERY-Dex and ACTT-1-Remdesivir**

*based on available data as of 17 June 2020*

<table>
<thead>
<tr>
<th>Study and Group</th>
<th>N</th>
<th>Treatment</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone vs. Usual Care (1:2)</td>
<td></td>
<td>Dexamethasone</td>
<td>Usual care only</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1007</td>
<td>29.0%</td>
<td>40.7%</td>
<td>-11.7%</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>3883</td>
<td>21.5%</td>
<td>25.0%</td>
<td>-3.5%</td>
</tr>
<tr>
<td>No respiratory support/room air</td>
<td>1535</td>
<td>17.0%</td>
<td>13.4%</td>
<td><strong>3.6%</strong></td>
</tr>
<tr>
<td>Remdesivir vs. Placebo (1:1)</td>
<td></td>
<td>Remdesivir</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>127</td>
<td>~22.2%</td>
<td>~20.6%</td>
<td><strong>1.6%</strong></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>421</td>
<td>~3.5%</td>
<td>~11.9%</td>
<td><strong>-8.4%</strong></td>
</tr>
<tr>
<td>No respiratory support/room air</td>
<td>272</td>
<td>~1.5%</td>
<td>~6.0%</td>
<td><strong>-4.5%</strong></td>
</tr>
</tbody>
</table>

Source: www.recoverytrial.net, @DrNickEsson, Beigel et al. NEJM 2020
So….antivirals early, anti-inflammatory later?

- Remdesivir was useful for those on room air/with minimal support requirements and those on oxygen as well, no benefit in ventilated patients

- Dexamethasone may help the most in mechanical ventilation patients (where remdesivir had little effect), no benefit and possible harm earlier

Note, equivalent doses of other steroid were to be allowed in protocol, so...
Convalescent Plasma: CONCOR Trial (concor1.ca)

- Existing data: uncontrolled, nonrandomized, small numbers
- RCT: safe, ? Possible benefit in severe disease (Li et al)
- Might be best positioned early in disease

Welcome To CONCOR-1 Clinical Trial Website

This trial is a North American collaboration involving clinicians, researchers and scientists from different fields and institutions
Other immunomodulators

Not recommended outside of trials
Tocilizumab: relatively more data available
  • preprint retrospective studies suggesting possible benefit
    • [https://www.medrxiv.org/content/10.1101/2020.06.08.20125245v1](https://www.medrxiv.org/content/10.1101/2020.06.08.20125245v1)
    • [https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1](https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1)
  • Observational study where 90% of severe patients received tocilizumab, improved oxygenation and biomarkers
  • Signal of superinfection (54% vs 26%)

Prone positioning

• In moderate-severe ARDS, reduces mortality by 16% likely by reduced ventilator induced lung injury
• Hypoxemia may improve but unclear effect on clinical outcomes
• Potential risks – aspiration, hemodynamic instability, delayed intubation, cardiac arrest, pressure ulcers
• Not recommended routinely outside clinical trials:
  • Patient can rotate themselves, is non in respiratory distress, no airway issues
  • Requires appropriate care setting and care pathway

Takeaways: 3 months of COVID therapeutics

- COVID has resulted in unprecedented speed of
  - Adoption of therapies with unproven benefit
  - Proliferation of poor-quality trials ...now more good quality trials
  - Spread of conspiracy theories and myths
- We learned that
  - Evidence based medicine can be done quickly and collaboratively
  - “getting the info out there” may NOT help answer the questions
  - Preprint can sink or swim, and press releases may need caution

From Bench to Bedside: Vaccine development

Craig Jenne BSc PhD PDF (University of California & University of Calgary)
Canada Research Chair, Imaging Approaches Toward Studying Infection; Associate Professor, Department of Microbiology, Immunology & Infectious Disease and Department of Critical Care Medicine, University of Calgary

Disclosures
- See next slide
Office of Continuing Medical Education and Professional Development. COVID Corner June 24 - Lessons Learned from the Last 3 Months

Disclosure
A) Research Support:
• Title of Grant: Development of Vaccines to Prevent SARS-CoV-2 Infection of High-Risk Individuals
  Funder: CIHR Operating Grant: COVID-19 May 2020 Rapid Research Funding Opportunity (2020-05-12)
• Title of Grant: Imaging COVID-19 Lungs to Uncover Therapies
  Funder: CIHR Operating Grant: COVID-19 May 2020 Rapid Research Funding Opportunity (2020-05-12)
• Title of Grant: Therapeutic Approaches to SARS-CoV-2 and Other Pathogenic Coronaviruses
  Funder: CIHR Operating Grant: Canadian 2019 Novel Coronavirus (COVID-19) Rapid Research Funding Opportunity (2020-02-18)
• Title of Grant: Socio-Cultural Implications of COVID-19: Educating, Engaging & Empowering the Public
  Funder: CIHR Canadian 2019 Novel Coronavirus (2019-nCoV) Rapid Research Grant
• Title of Grant: Intravital Imaging of Cancer Immunotherapy
  Funder: Women in Insurance Cancer Crusade
• Title of Grant: Role of tissue factor in the initiation of inflammation in response to Influenza A virus infection.
  Funder: Lung Association of Alberta & NWT
• Title of Grant: Intravital microscopy of the immune response to influenza infection in chickens
  Funder: University of Calgary Margaret Gunn Endowment for Animal Research
• Title of Grant: Interaction between inflammation, immunity and coagulation in highly pathogenic influenza infection
  Funder: University of Calgary Office of the Associate Dean Research
• Title of Grant: Mapping the host inflammatory response to highly pathogenic influenza A infection
  Funder: University of Calgary URGC Seed Grant
• Title of Grant: Role of intravascular thrombin on platelet activation and lung inflammation during Influenza A virus infection
  Funder: Lung Association of Alberta & NWT
• Title of Grant: Mapping the host inflammatory response to highly pathogenic influenza A infection
  Funder: University of Calgary URGC Seed Grant

B) Infrastructure
1. Title of Grant: Intravital Imaging of Viral and Bacterial Infections
  Funder: Canadian Foundation for Innovation JELF

C) Research Contracts
1. Research Contract: MedImmune (research arm of AstraZeneca): Immune Complex Clearance by the Liver. (2015-2016) Intravital imaging of immune complex capture in the liver. Total funds received: $3,000
2. Research Service Agreement: Baxalta (Takada Pharmaceuticals): Gene Therapy Delivery and Host Response to Viral Infection (2016-2020) Intravital imaging of viral delivery and the ensuing host inflammatory response. Total Funds Received: $181,500
3. Research Contract: Gilead (Co-Investigator with Dr. Carla Coffin): Intravital Microscopy of Viral Hepatitis in Living Woodchucks (2020-2021). Using intravital imaging to study delivery, innate immune response and cellular recruitment to the liver following viral hepatitis. Total funds received: $90,000

Learning Objectives
• Understand where SARS-CoV-2 originated and the impact of zoonotic infections on human health
• Understand what is known (unknown) about SARS-CoV-2 immunity
• Introduction to the various vaccine platforms being explored for the prevention/treatment of COVID-19 including work currently underway at the University of Calgary
• Overview of vaccine progress and potential deployment
• What I have “learned” these past 3 months....
COVID-19: What is it?

COVID-19: Where did it come from?

• COVID-19 is a ZOONOTIC disease
  • an infectious disease caused by a pathogen (an infectious agent) that has “jumped” from an animal to a human

• Animal viruses acquire mutations that enable it to infect human cells and tissues

Horseshoe Bat?  Pangolin?  Human

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Zoonotic Disease

- 60% of existing human infectious diseases are zoonotic
- At least 75% of emerging infectious diseases of humans (including Ebola, HIV, and influenza) have an animal origin
- 5 new human diseases appear every year. Three are of animal origin
- 80% of agents with potential bioterrorist use are zoonotic pathogens

OneHealth: OIE - World Organisation for Animal Health www.OIE.INT

Zoonotic Disease

- 1981 HIV
- 2009 H1N1 (Swine) Flu Pandemic
- 2002 (Severe Acute Respiratory Syndrome) SARS
- 2013 (Middle Eastern Respiratory Syndrome) MERS
COVID-19 “Strains”

- SARS-CoV-2 emerged from an animal virus due to mutations
- Single strand RNA genome prone to random mutations
- Continues to mutate within the human host (<1/10 the rate of flu)
- Multiple variants have emerged but no new “strain”

COVID-19 Variants

- Debate if variants are “stronger”, “weaker”, “more transmissible”
- Variants allow for tracking and enhanced epidemiology
- No mapped mutations yet appear to impact the potential immunogenicity of vaccine targets - GOOD
- SARS-CoV-2 is likely endemic, as such, the only way to deal with now it is through the modulation of our immune response (vaccination)
COVID and Immunity

Types of Immunity

- **Humoral Immunity** (antibodies, serology) – specific blood proteins produced to recognize, bind and neutralize a pathogen – prevents infection altogether, neutralizes new viral particles limiting their spread

- **Cellular Immunity** (T cells) – specific immune cells that recognize and kill infected host cells – mitigates infection, shortens duration, lessens severity but only after a patient actually becomes infected
COVID and Immunity

• Immunity to coronavirus is often short lived when compared to other viruses
  • Antibodies against SARS: ~2y
  • T cell immunity longer (10+ years)

• SARS-CoV-2?
  • We are learning as we go.......
COVID and Immunity

• Many recovered patients demonstrate seroconversion
  • Anti-SARS-CoV-2 IgM and/or IgG

• Work in the UK suggests broad CD4+ and CD8+ T cell immunity\(^1\)
  • Recognition of a broad range of peptides and robust IFN-γ production

• Unknown if people can be re-infected
• Substantial variation in the quality and quantity of these measured immune responses

\(^1\) bioRxiv 2020.06.05.134551; doi: https://doi.org/10.1101/2020.06.05.134551  NOT PEER REVIEWED

COVID and Immunity

• Study of COVID patients (n=1470), health care workers (n=3832), general workers (n=19555) and non-COVID patients (n=1616) in Wuhan China

• Potential exposures before person-to-person transmission was suspected and prior to widespread use of PPE

• 89.8% COVID patients, 4.0% health care workers, 4.6% general workers, 1.0% of other patients were IgG+

• Modeling suggests 10-80x more health care workers would have been infected than what seroconversion suggests.

• Does mild/asymptomatic infection induce immunity?  

medRxiv preprint doi: https://doi.org/10.1101/2020.06.13.20130252  NOT PEER REVIEWED
COVID and Immunity

- Many recovered patients demonstrate seroconversion
  - Anti-SARS-CoV-2 IgM and/or IgG
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“There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.” WHO April 24, 2020
COVID and Lasting Immunity

- Longitudinal study of symptomatic & asymptomatic patients
- Similar seroconversion during acute infection 81.3 vs. 83.8% IgG+
- 8w later (early convalescence) 60% vs. 87.1
- **40% of asymptomatic patients became seronegative within 8w**
- These patients did develop an immune response but it was short lived


COVID and Convergent Immunity

- Analysis of antibody profiles from recovered patients
- Antibodies recognize many different epitopes (targets) on the SARS-CoV-2 virus – **not all actually neutralize the virus**
- Plasma collected 5-6w post onset of symptoms had low titers of neutralizing antibodies (**present but in low numbers**)
- Variety of neutralizing antibody clones but many recognize common targets (**RBD of Spike**) – may identify good vaccine targets

COVID and Vaccines (considerations)

• Waning humoral immunity
• Not all antibodies are protective
• More durable T-cell mediated immunity?
• Virus is mutating
• Antibody Dependent Enhancement (ADE)....

COVID and ADE

• Non-neutralizing antibodies can help viruses enter cells
• Bypass specific viral receptors, use immune receptors to enter
• Significant problem with Flavivirus (Dengue, Zika, etc)
• Reported in animal models and cell culture experiments studying SARS and MERS 1-4

2) Yip et al. Hong Kong Med J 2016
3) Wang et al. Biochemical and Biophysical Research Communications 2014
COVID and ADE

• Recently the biological impact of ADE for coronaviruses has been questioned \(^1\)

• Although substantial evidence in animal models, there is a lack of biological evidence in human patients \(^2-^3\)

• Must proceed with caution....

• Less of a concern with T cell vaccines

1) EJ. Yager Clinical Immunology 2020
2) Ulrich et al. Cytometry 2020
3) Eroshenko et al. Nature Biotechnology 2020
COVID Vaccine Platforms

- Currently no approved coronavirus vaccine in humans
- Design of coronavirus vaccines for veterinary medicine has been a long, frustrating endeavor
- For H1N1 in 2009 we had an approved vaccine in <6m; built off a pre-existing vaccine platform (simply change the antigen)
- No such starting point for SARS-CoV-2.....

COVID Vaccine Platforms

- >10 vaccines are currently in clinical trial (phase I and above) with >200 additional vaccines in preclinical development
- Many different approaches are being explored
  - Protein + adjuvant
  - Inactivated virus
  - mRNA
  - DNA plasmid
  - Engineered viral vectors
COVID Vaccine Platforms

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- Many different approaches are being explored
  - Protein + adjuvant
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  - mRNA
  - DNA plasmid
  - Engineered viral vectors
Protein and Inactivated Virus Vaccines

- Classical vaccine strategy (influenza, tetanus, Hep B)
- Easy to make, cheap, mass production
- Generates robust antibody-mediated immunity
- Often limited T cells response
- Tends to lack precision (neutralizing vs. non-neutralizing antibodies)
- Duration of immunity may be limited (a few years)

COVID Vaccine Platforms

- >10 vaccines are currently in clinical trial (phase I and above) with >200 additional vaccines in preclinical development
- Many different approaches are being explored
  - Protein + adjuvant
  - Inactivated virus
  - mRNA
  - DNA plasmid
  - Engineered viral vectors
mRNA and DNA Vaccines

- New approach to vaccination in humans
- No pathogen is involved – only the genetic sequence coding for a viral protein and the body’s own cells make the target protein
- Gene sequences can be optimized/modified to enhance expression, mutate key amino acids, etc.
- Cheap and easy to mass produce
- Generates both antibody and T cell immunity

LNP encapsulated mRNA

- mRNA sequence embedded in a lipid-nanoparticle
- Protection of mRNA during delivery and rapid uptake by host cells
- Delivered mRNA is translated to protein in the cytoplasm
- Lipid nano-particle can act as an adjuvant, stimulating the immune response
- Current targets: Spike, and the RBD peptide of Spike
LNP encapsulated mRNA

DNA Plasmid

- Gene sequence within a carrier DNA plasmid
- Must enter cell and move to nucleus
- Transcribed into mRNA → translated to protein
- DNA sequences can be stimulates for innate immunity (TLRs)
- Some risks (integration into host DNA, anti-DNA immunity)
- How do you deliver a plasmid?
DNA Plasmid

- Gene sequence within a carrier DNA plasmid
- Must **enter cell and move to nucleus**
- Transcribed into mRNA $\rightarrow$ translated to protein
- DNA sequences can be stimulates for innate immunity (TLRs)
- Some risks (integration into host DNA, anti-DNA immunity)
- How do you deliver a plasmid?
  - **ELECTROPORATION** of the patient

COVID Vaccine Platforms

- >10 vaccines are currently in clinical trial (**phase I and above**) with >200 additional vaccines in preclinical development
- Many different approaches are being explored
  - Protein + adjuvant
  - Inactivated virus
  - mRNA
  - DNA plasmid
  - Engineered viral vectors
Engineered Viral Vectors

- Modify a “harmless” virus to look like SARS-CoV-2 (pseudotyped) or use virus to deliver genes coding for target proteins to host cells
- Uses viruses already approved for gene therapy or cancer therapy
- Currently trials are using Adenovirus vectors with others (Vesicular Stomatitis Virus (VSV), Vaccinia) in development

Pseudotyped Virus
**Pseudotyped Virus**

Deadly Virus (SARS-CoV-2) → “Harmless” Virus (VSV) → Engineered Viral Vaccine (VSV-SARS)

**Engineered Viral Vectors – Advantages**

- Engineer specific immune targets (gene sequences)
- Replicating virus engages the immune system, robust response
- Elicits both antibody and T cell immunity
- Can deliver whole proteins, parts of proteins or multiple targets to generate a “designer” immune response
Engineered Viral Vectors – Local Efforts I

• The University of Calgary is a driving force behind the development of virus-based vaccines for COVID-19

• Building off of an established platform for the development of oncolytic viruses, Dr. Mahoney has initiated the development of pseudotyped VSV expressing Spike protein

https://ucalgary.ca/news/cancer-covid-med-school-researchers-may-hold-key-vaccine-creation

Engineered Viral Vectors – Local Efforts I

• Initially funded by anonymous private donors, this early research push provided pilot data for an application to the CIHR COVID-19 Funding Call in May.

• Partnered with Dr. John Bell (CHEO), this project has received federal funding to advance vaccine development in animal models, positioning the technology for human trials in the coming year.

  • CIHR Project: Development of Vaccines to Prevent SARS-CoV-2 Infection of High-Risk Individuals – Lead: Dr. John Bell (CHEO), Drs. Doug Mahoney and Craig Jenne at the University of Calgary
Engineered Viral Vectors – Local Efforts II

- The University of Calgary is also involved in another project focused on developing virus-based COVID vaccines
- Funded by the CIHR with Dr. Tom Hobman as the lead, this project seeks to identify new antiviral compounds while simultaneously developing a virus-based vaccine that delivers genes coding for specific T cell-optimized, SARS-CoV-2 target proteins to host cells.

  - CIHR Project: Therapeutic Approaches to SARS-CoV-2 and Other Pathogenic Coronaviruses – Lead: Dr. Tom Hobman (UofA); Drs. Markus Czub, Guido van Marle and Craig Jenne at the University of Calgary

COVID Vaccine – an International Effort

- An urgent need for a vaccine mobilized the international community.
- Between Feb 15th and Jun 18th, the WHO listed 29 registered clinical vaccine trials (Phase I or above) addressing more than 10 different vaccine formulations, 3 of which are Phase II or Phase III trials
- Early results show immune response in volunteers (seroconversion)
- Awaiting efficacy data on infection prevention
- Results anticipated Sep/Oct 2020 for the first of these vaccines
COVID Vaccine – an International Effort

- Pending results (Fall 2020) – vaccines will be submitted to the FDA for approval (Health Canada to follow later)
- Guarded optimism for vaccine approval in 2020.
- Once approved – the vaccine will have to be mass produced (time)
  - Some companies have indicated that if results from Phase III trials are positive, vaccine production will begin in advance of approval to minimize the time delay
- Vaccine distribution in Canada spring/early summer 2021

COVID Vaccine – Priorities

- Unknown how international players will “share” access to vaccine
- Unlikely enough vaccine will be available to vaccinate all Canadians for a number of months following Health Canada approval
- May need to prioritize who has access to initial doses
  - At risk populations (co-morbidities)
  - Elderly
  - Health Care Professionals
COVID-19 vaccine a matter of 'when not if,' but must be produced safely: Fauci

The Associated Press · Posted: Jun 23, 2020 1:16 PM ET on CBC.ca

What I have “learned” these past 3 months....

• Canada (Alberta) handled COVID much better than many of our peers.

• The interpretation of the term “rapid development” is wildly different for the public vs. the scientific community.

• Social distancing is a highly effective tool for limiting viral spread – it sucks, but it is highly effective.

• The public genuinely wants to learn and understand (though sometimes struggles with what “isolate” means).

• Despite some success with COVID (screening, contact tracing, restrictions) that “flattened the curve” we need to be better prepared to deal with future emerging disease - history tells us there will be more....
Thank you!
Stay safe and carry on ...
(while physical distancing)

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@JenneLab

Q&A

Deena Hinshaw  Lynora Saxinger  Craig Jenne  Braden Manns
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The COVID-19 Pandemic: A Test of System-Level Physician Wellness

By the end of this session participants will be able to:
1. Describe how the existing system-level approach to physician wellness supported physicians during the pandemic
2. Recognize gaps in the system-level physician wellness supports during the pandemic
3. Identify strategies for addressing gaps in physician wellness support, anticipating future crises
Evaluation Survey

- Your feedback is essential; please complete the online evaluation survey
  https://survey.ucalgary.ca/jfe/form/SV_6stci4aWfVGJ1Jz

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