Hot Topics in Infectious Diseases

(For Infection Control Practitioners)

SASKPIC Conference 2023
Satchan Takaya BSc MD FRCPC
Clinical Associate Professor, Division of Infectious Diseases
University of Saskatchewan
Senior Clinical Advisor, IPC, SHA
We acknowledge that the land on which we gather today, Treaty 4 territory, is the traditional territory of the Cree, Saulteaux, Dakota, Nakota, and Lakota peoples, and the homeland of the Métis Nation. We pay our respect to the First Nations and Métis ancestors of this land, and reaffirm our relationship with one another.

I also acknowledge that we come from many parts of the province today, and that the land and people of treaties 2, 5, 6, 8, and 10 are woven within this province.
Disclosures:

- Honorarium - ViiV Regional advisory board
- Honorarium - Moderna regional advisory board
- There are no identifiable conflicts of interest with today’s presentation
Objectives:

Suggested “Hot Topics” of 2023

- **VIRAL HEMMORHAGIC FEVERS**: To discuss the clinical presentation of some viral hemorrhagic fevers (Ebola virus disease, Marburg virus disease, CCVF)
- **ANTIMICROBIAL RESISTANCE**: What’s new with ARO’s
- **RESPIRATORY VIRUSES**: what to expect this fall
Coronavirus confirmed as pandemic by World Health Organization

Dr. Tedros Adhanom Ghebreyesus, WHO Director-General

Coronavirus outbreak has been labelled a pandemic by the World Health Organization (WHO).
What’s hot with Viral Hemorrhagic Fevers?
Why does it matter?

Conceptual progression of a viral haemorrhagic fever from animal reservoir to global pandemic:

Keys stages in the progression to a potential widespread epidemic are summarised. Stage 1, index-case potential, refers to spillover viral transmission from animal reservoir to index cases. Stage 2, outbreak potential, represents an index case infecting individuals within the local community or in a care-giving setting quantified via a composite indicator assessing outbreak receptivity. Stage 3, epidemic potential, reflects the widespread transmission of the virus both at regional and international scales.
The effects of global warming

- Increase in reservoir animals (eg. Bat species)
- Increase geographic spread of vector arthropods
- Lengthen duration of transmission season
- Increase natural disasters, risk of disease
- Increase antimicrobial resistance


• Many factors at play: land-use changes, the abundance of reservoir hosts, migration patterns, control measures, natural climate variability

• BUT…”it is clear that vectorborne disease systems (pathogens, vectors, and reservoir hosts) are highly responsive to the varied environments they inhabit and that observed changes in the rates of vectorborne diseases at given locations are often associated with concomitant changes in the local climate.”

• Aedes mosquitoes of Dengue fever, expanding from tropical and sub-tropical climates to Latin America, Caribbean, South Asia, and sub-Saharan Africa (now available in Florida, Texas, Arizona and Hawaii)

• Expansion of Ixodes ticks into Canada and Norway, with a corresponding increase in cases of Lyme disease
Viral Hemorrhagic Fevers

- 4 families of viruses

<table>
<thead>
<tr>
<th>Family of viruses</th>
<th>Vectors</th>
<th>Name of viral hemorrhagic fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunyaviridae</td>
<td>Mosquito</td>
<td>Rift valley fever</td>
</tr>
<tr>
<td></td>
<td>Tick</td>
<td>Crimean-congo hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td>Rodent</td>
<td>Hantavirus fever</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Mosquito</td>
<td>Dengue fever, yellow fever</td>
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<tr>
<td></td>
<td>Tick</td>
<td>Omsk fever, Kyasanur forest disease</td>
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<tr>
<td>Arenaviridae</td>
<td>Rodent</td>
<td>Lujos virus fever, lassa fever, argentine fever, Bolivian fever, venezuelan fever</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Bat</td>
<td>Ebola hemorrhagic fever, marburg hemorrhagic fever</td>
</tr>
</tbody>
</table>

- **WHO Risk Group 4** (high individual and community risk) -
  A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

- Global distribution, global community
- Person-to-person transmission occur for some
- Blood and body fluid transmission (nosocomial) also occurs
Ebola Virus Disease

• Discovered in 1976, along Ebola River in former Zaire (now Democratic Republic of the Congo)
• Low seroprevalence (1.4%) suggests asymptomatic infection doesn’t really occur
• Mortality ranges 50-90% depending on the type of ebola virus
• 4 types infect humans: *Ebola (Zaire ebolavirus), Sudan ebolavirus, Taï Forest ebolavirus, Bundibugyo ebolavirus*
• Natural reservoir: fruit bats; can be transmitted by non-human primates & other infected animals
• Sub-Saharan Africa
• Latest outbreak Sept 20, 2022 ~ Jan 11, 2023 (Sudan ebolavirus) in Mubende district, West Uganda with 142 confirmed cases with 55 deaths (34% fatality)
• Democratic Republic of the Congo, April~July and Aug~Sept 2022, total 6 cases, 100% fatality (Zaire ebolavirus)
Ebola Virus Disease

Ebola Virus Ecology and Transmission

Infection with an ebolavirus causes Ebola disease, a zoonotic disease that involves animals and people.

Animal-to-Animal Transmission

Evidence suggests that bats are the reservoir hosts for ebolaviruses. Bats carrying an ebolavirus can spread the virus to other animals, like apes, monkeys, and duikers (antelopes), as well as to people.

Spillover Event

A “spillover event” occurs when an animal (bat, ape, monkey, duiker) or person becomes infected with an ebolavirus through contact with the reservoir host. This contact could occur through hunting or preparing the animal’s meat for eating.

Human-to-Human Transmission

Once an ebolavirus has infected the first person, spread of the virus from one person to another can occur through contact with the blood and body fluids of sick people or with the bodies of those who have died of Ebola disease.

Survivor

Survivors of Ebola disease face new challenges after recovery. Some survivors report effects such as tiredness and muscle aches. Although rare, the virus can persist in certain parts of the body (brain, eyes, placenta, and testicles) and spread through contact to other people.
- Incubation 2-21 days
- Moves from “dry” to “wet” symptoms

Note:
On day 7-9 gastrointestinal symptoms can occur; vomiting, diarrhoea and abdominal pain
Death from hypovolemic shock and multiorgan failure: 6-16 days
Ebola Prevention & Treatment

- **Ebola vaccine** rVSV-ZEBOV (called Ervebo®) became FDA approved Dec 2019
- single dose vaccine, only against Ebola virus (species Zaire ebolavirus)
- Since 2020 recommended in US as pre-exposure prophylaxis for adults ≥ 18 years at potential occupational risk of exposure to Zaire ebolavirus:
  - Responding to an outbreak caused by Ebola virus
  - Lab staff working at biosafety-level 4 facilities working with live Ebola virus
  - Healthcare personnel working at federally designated Ebola Treatment Centers

- **Ebola treatments** now available
- 2020: FDA approval of 2 Zaire ebolavirus monoclonal antibodies Inmazeb™ & Ebanga™
  - Inmazeb™: 28-day mortality dropped from 51% to 33.8%
  - Ebanga™: 28-day mortality dropped from 49.4% to 35.1%

- **Best prevention remains avoidance!**
Marburg Hemorrhagic Fever

- Named for Marburg, Germany, lab outbreak 1967 (31 cases) in Marburg/Frankfurt/Belgrade
- Disease of Central Africa/Subsaharan Africa
- Outbreak in Equatorial Guinea Feb 13~June 8 2023: 16 confirmed & 23 probable cases, 12/16 and 23/23 died
- Outbreak in Tanzania Mar 21~May 31, 2023: 9 cases with 5 deaths (1 probable, 8 confirmed)
- Reservoir probably fruit bats (mines, caves) or other animals
- Easily transmissible thru blood and body fluid exposure
- Survives days on contaminated surfaces
- 5-10 day incubation
Marburg Hemorrhagic Fever

FACTS ON MARBURG

We all play an important role in the fight against Marburg.

What is the Marburg Virus?
Marburg is a serious and very contagious disease caused by the Marburg virus.

How does the Marburg Virus Spread?
The virus spreads when a person is in contact with the body fluids of someone who is sick with or has died from Marburg.

What are the Signs and Symptoms to Look for?

What Should You Do if You Know Someone with Signs of Marburg?
Act Quickly.
Notify Public Health Authorities Immediately.

https://www.cdc.gov/vhf/marburg/resources/index.html#print
Crimean-Congo Hemorrhagic Fever

- Usually a disease of Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north
- 2016 - Spain
- 2022 - Turkey
- With climate change, new cases seen in Europe as *Hyalomma marginatum* ticks found in new areas
- ~30% mortality rate
- Host is wild and domestic animals (cattle, goat, sheep, ostrich)
- Transmission through tick bite or infected livestock
- Incubation 5~13 days, death in 2 weeks of illness
- Jan 1~May 22, 2022 outbreak in Iraq with 212 cases, 27 deaths; most had history of livestock contact (sheep, cattle)
What’s hot with Antimicrobial Resistance Organisms?
Access
- Amoxicillin
- Amoxicillin and clavulanic acid
- Ampicillin
- Benzathine benzylpenicillin
- Benzylpenicillin
- Cefaclor or cefadroxil
- Chloramphenicol
- Clindamycin
- Closapine
- Doxycycline
- Gentamicin or amikacin
- Metronidazole
- Nitrofurantoin
- Phenoxymethylpenicillin
- Procaine benzylpenicillin
- Spectinomycin
- Sulfamethoxazole and trimethoprim

Core access antibiotics

Watch
- Anti-pseudomonal penicillins with beta-lactamase inhibitor
  (eg. piperacillin and tazobactam)
- Carbapenem or penem (eg, ertapenem, imipenem and cilastatin,
  meropenem)
- Cephalosporins, third generation (with or without beta-lactamase inhibitor;
  eg, cefixime, cefotaxime, ceftazidime, ceftiraxone)
- Glycopeptides (eg, teicoplanin, vancomycin)
- Macrolides (eg, azithromycin, clarithromycin, erythromycin)
- Quinolones and Fluoroquinolones (eg, ciprofloxacin, levofloxacin,
  moxifloxacin, norfloxacin)

Reserve
- Aztreonam
- Cephalosporins, fourth generation (eg, ceftazidime)
- Cephalosporins, fifth generation (eg, ceftolozane)
- Daptomycin
- Fosfomycin (intravenous)
- Oxazolidinones (eg, linezolid)
- Polymyxins (eg, colistin, polymyxin B)
- Tigecycline

Antibiotics that should only be used as a last resort when all other
antibiotics have failed

- Mike Sharland, et al. Classifying antibiotics in the WHO
  Essential Medicines List for optimal use—be AWaRe,
  The Lancet Infectious Diseases, Volume 18, Issue 1, 2018,
  Pages 18-20.

- https://adoptaware.org
Alphabet Soup or ARO’s

- **MRSA**  Methicillin Resistant Staphylococcus aureus
- **VISA**  Vancomycin Intermediate Resistant Staphylococcus aureus
- **VRSA**  Vancomycin Resistant Staphylococcus aureus
- **VRE**  Vancomycin Resistant Enterococcus faecium
- **ESBL**  Extended Spectrum Beta-Lactamase
- **CPE**  Carbapenemase Producing Enterobacterales
- **MDRTB**  Multi-drug Resistant Tuberculosis

What does this mean for the patient?
Methicillin Resistant Staphylococcus aureus (MRSA)

- Resistance conferred to most other beta-lactams (cefazolin, ceftriaxone, piperacillin-tazobactam, meropenem, ertapenem)
- Often resistant to other classes: erythromycin, clindamycin, ciprofloxacin, fuscidic acid
- Blurred line between HA-MRSA & CA-MRSA … most is now CA-MRSA
- From 2017 to 2021, 35% increase in rates per 10,000 patient days were observed for MRSA BSIs (CNISP)
- More virulent? PROBABLY! Panton–Valentine leucocidin (PVL) producing strains accounted for 35–45%
- More than 1 in 6 (17.5%) with MRSA BSI died within 30 days of diagnosis (all-cause mortality).
- Since 2020, Daptomycin resistant MRSA identified
VISA & VRSA

- So far remains rare
- VISA = Vancomycin MICs $\geq 4$ mcg/mL
- Risk factors (CDC): recent dialysis, methicillin-resistant S. aureus (MRSA) bacteremia associated with central venous catheters or prosthetic graft material, and prolonged vancomycin exposure (6 to 18 weeks) in the three to six months preceding infection
- US and Europe surveillance: VISA = 0.3% of S. aureus isolates
- VRSA = Vancomycin MICs $\geq 32$ mcg/mL
- Comes from transfer of vanA gene from VRE to S. aureus, first appeared clinically in 2002.
- On review 2002-2006, 7 cases in the US (Clin Infect Dis. 2008;46(5):668) all had prior colonization or infection with MRSA and VRE
- So far only 52 cases worldwide
Methicillin Resistant Staphylococcus aureus (MRSA)

- What does this mean?
  - Increase morbidity
  - Longer hospital stays
  - Permanent disability
  - Fewer treatment options


Recent patient on ID service RUH

Current treatment of MRSA infection

- **VANCOMYCIN** - glycopeptide: acute kidney injury, immune thrombocytopenia (DITP), neutropenia, rash

- **DAPTOMYCIN** - lipopeptide: won’t work in lungs, myositis, rhabdomyolysis, eosinophilic pneumonitis, rash

- **LINEZOLID** - oxazolidinone: bacteriostatic, many drug interactions (monoamine oxidase inhibitor, serotonin syndrome risk with serotonergic agents), myelosuppression

- **5th GEN CEPHALOSPORINS** - Ceftaroline, Ceftobiprole

- **OTHER**: Trimethoprim-Sulfamethoxazole, Clindamycin, Teicoplanin, Tigecycline
Future treatments of MRSA infection

- **Dalbavancin (Oritavancin)**
  - long-acting lipoglycopeptide (once a week!)
  - Risk of cross resistance to Daptomycin and Vancomycin
  - Not yet approved for anything but SSTI

- **Combination therapy**
  - Dapto + Ceftobiprole (Ceftaroline) - our current go-to if combo is used
  - Vanco or Dapto + “other” (Cefazolin, Cloxacillin, Gentamicin) -“no” due to increase toxicities or ineffective

- **Novel therapies:** Bacteriophages (Phage therapy) and endolysins ???

Vancomycin Resistant Enterococcus faecium (VRE)

- CNISP showed:
  - 43% increase in rates per 10,000 patient days for VRE BSIs (2017 ~ 2021)
  - 32.7% all-cause mortality for VRE BSI’s (2016 ~ 2020)
  - 89.9% of VRE BSI’s were acquired in a healthcare facility (2017 ~ 2021)
  - 99.4% of VRE BSI isolates were identified as Enterococcus faecium
  - Low levels of resistance to tigecycline (<1%), linezolid (<2%) and daptomycin (<9%) (2016 ~ 2020)
  - The once “harmless commensal organism” now causing significant morbidity and mortality
Is VRE more pathogenic?

• Little research to date

• “Putative” virulence factors being studied, some linked to vanA so could enhance virulence of vancomycin-resistant enterococcal strains

• Others are more predominant in *E. faecium*, such as cell surface adhesins that promote bacterial aggregation onto intestinal epithelium, renal cells, and extracellular collagen matrix

• *E faecium* also have virulence factors that enhance biofilm production, promoting IE and GU colonization

• Adhesins play role in infective endocarditis
How do we treat VRE?

- Most E. faecium are resistant to beta-lactams (ampicillin, carbapenems, cephalosporins)
- Options are:
  - **DAPTOMYCIN** - Low levels of resistance, no lung penetration
  - **LINEZOLID** - Low levels of resistance, limited by myelosuppression and drug interactions
  - **TIGECYCLINE** - Toxic, must be iv, must check susceptibility
  - **TETRCYCLINE** - Only ~30% susceptible
  - **QUINUPRISTIN-DALFOPRISTIN** - Toxic, and no longer FDA approved
  - **CHLORAMPHENICOL** - Toxic
  - **FOSFOMYCIN** - $$$ last line!
Carbapenemase Producing Enterobacterales (CPE)

- Thankfully CPE infection rates have remained low at 0.06 infections per 10,000 patient days (2018 to 2021)
- Thirty days all-cause mortality was 19.7% (n=38/193)
- 28.9% (n=48/166) of CPE infected patients reported travel outside of Canada and of those, 91.5% (n=43/47) received medical care while abroad

The predominant carbapenemases identified in Canada in 2021 were (88.7%):
- Klebsiella pneumoniae carbapenemase (KPC)
- New Delhi metallo-ß-lactamase (NDM)
- Oxacillinase-48 (OXA-48)

Table 55: Number and proportion of main carbapenemase-producing pathogens identified*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>2017 n</th>
<th>2017 %</th>
<th>2018 n</th>
<th>2018 %</th>
<th>2019 n</th>
<th>2019 %</th>
<th>2020 n</th>
<th>2020 %</th>
<th>2021 n</th>
<th>2021 %</th>
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<td>Klebsiella pneumoniae</td>
<td>51</td>
<td>25.4</td>
<td>66</td>
<td>28.2</td>
<td>57</td>
<td>21.3</td>
<td>48</td>
<td>19.5</td>
<td>51</td>
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<td>Escherichia coli</td>
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<td>29.9</td>
<td>54</td>
<td>23.1</td>
<td>83</td>
<td>31.1</td>
<td>83</td>
<td>33.7</td>
<td>69</td>
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<td>Enterobacter cloaceae complex*</td>
<td>39</td>
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<td>44</td>
<td>18.8</td>
<td>60</td>
<td>22.5</td>
<td>54</td>
<td>22</td>
<td>64</td>
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<td>7.0</td>
<td>6</td>
<td>2.6</td>
<td>5</td>
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<td>Serratia marcescens</td>
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<td>Citrobacter freundii</td>
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<td>Klebsiella oxytoca</td>
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<td>4.5</td>
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<td>2</td>
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<td>6.9</td>
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<tr>
<td>Others</td>
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<td>3.5</td>
<td>28</td>
<td>12</td>
<td>7</td>
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<td>Total number of isolates tested</td>
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<td>N/A</td>
<td>246</td>
<td>N/A</td>
<td>288</td>
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</tbody>
</table>

Abbreviation: N/A, not applicable

* Includes data for all isolates submitted

* Enterobacter cloaceae complex includes Enterobacter cloaeae and other Enterobacter spp. but excluding E. aerogenices
So what does this all mean for the patient?

- Carbapenems: our LAST RESORT?
  - Ertapenem
  - Meropenem
  - Imipenem
- Resistance to Carbapenems leaves very little option for treatment
- most new therapies not really available in Canada

https://www.idsociety.org/practice-guideline/amr-guidance/
But there’s more!
So many multi-drug resistant gram negatives

- extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E)
- AmpC β-lactamase-producing Enterobacterales (AmpC-E)
- carbapenem-resistant Enterobacterales (CRE)
- Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa)
- carbapenem-resistant Acinetobacter baumannii species (CRAB)
- Stenotrophomonas maltophilia

https://incacare.live/new-antibiotics-against-multidrug-resistant-gram-negative-bacteria/
https://www.publish.csiro.au/ma/Fulltext/ma13014
Future therapies for MDR gram negative organisms

- Selection based on the bug and the beta-lactamase

Antimicrobials for MDR GNB & Availability in AHS

1. Susceptibility testing available for all of these agents, except fosfomycin IV for non-E. coli Enterobacteriales. Contact microbiology lab.
2. Intrinsic resistance of: Proteus species, Providencia species, Morganella morgani, Serratia marcescens
3. Intrinsic resistance of: Proteus species, Providencia species, Morganella morganii
4. Special Access Programme contact information:
   - Website: [https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html](https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html)
   - Phone: (613) 941-2108 (Must press 0 to reach an on-call officer)
   - Fax: (613) 941-3194
   - E-mail: SAPPDRUGS@HC.SC.GC.CA

CPE = carbapenemase-producing Enterobacteriales
Class A CPE – includes KPC, K3, NEM, SME, IMM carbapenemases
Class D CPE – includes OXA carbapenemases
CPP = carbapenem producer
CRAB = carbapenem-resistant Acinetobacter baumannii
CRE = carbapenem-resistant Enterobacteriales
CRPA = carbapenem-resistant Pseudomonas aeruginosa
F = formulary
FRG = formulary, restricted with guidelines
MBL: metallo-β-lactamase
NF = non-formulary
SAP = Special Access Programme request
SM = Stenotrophomonas maltophilia
STEDT = Short Term Exceptional Drug Therapy request

Acknowledgments: Christine Ondro PharmD; Tanis Dingle MD; Susan Fryers BScPharm, ACPR

Reviewed by AHS Antimicrobial Stewardship Subcommittee, March 26, 2021
Approved by AHS Antimicrobial Stewardship Subcommittee, May 28, 2021
Last updated: July 28, 2023
Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa*

Anti-pseudomonal antibiotics are limited:
- antipseudomonal penicillins (piperacillin–tazobactam)
- cephalosporins (ceftazidime, cefepime)
- fluoroquinolones (ciprofloxacin, levofloxacin)
- aminoglycosides (tobramycin, gentamicin)
- carbapenems (meropenem, imipenem)
- Monobactam (aztreonam)

**MDR-PA:** R to one antibiotics in 3 classes

**XDR-PA:** R to one antibiotic in all but 1 or 2 classes

**DTR-PA:** R to everything but aminoglycosides
Running out of options…

• Antibiotic production is far behind rates of antibiotic resistance

• monotherapy with novel β-lactam/β-lactamase inhibitors:
  • ceftolozane–tazobactam
  • ceftazidime–avibactam
  • mepenem–cilastatin–relebactam

• combination therapy with conventional agents

• Cefiderocol, a novel siderophore cephalosporin

• Bacteriophage therapy? Lytic phages (topical, iv) infect a host bacterium, replicate, lyse the cell, may even reverse resistance mechanism. Need further PK/PD studies to address phage titers, susceptibility, phage resistance, and neutralizing antibodies
What’s hot with RESPIRATORY VIRUSES THIS FALL?

- RSV
- Coronavirus
- Human Metapneumovirus
- Influenza virus
- Adenovirus
Is “Tridemic” even a thing?

- Twindemic, Tridemic, “Flurona” are all words made up during the pandemic
- Has it happened?

Figure 1: Epidemic curve, respiratory illness by organism and test positivity, August 29, 2021 – August 12, 2023

Data sources: Panorama IOM extracted on August 14, 2023 (COVID-19 cases)
Respiratory Virus Detections Surveillance System (influenza and other respiratory) (RRPL extracted August 14, 2023)
As of September 4, 2022, COVID-19 cases include new and reinfections.

https://www.saskatchewan.ca/government/government-structure/ministries/health/other-reports/community-respiratory-illness-surveillance-program
What’s RSV?

- enveloped, negative sense, single-stranded RNA virus, Pneumovirus genus in the Paramyxoviridae family
- incubation period ranges from 2-8 days.
- symptoms within 4-6 days of getting infected.
- usually mild, cold-like symptoms: runny nose (rhinorrhea), coughing, sneezing, fever, wheezing, and/or decrease in appetite
- in babies, symptoms include irritability, decreased activity, and breathing difficulties.
- In kids under 1, is the most common cause of bronchiolitis and pneumonia (severe RSV infection)
- progress to lower respiratory tract disease in ~50% cases, esp in infants, older adults (+65), and immunocompromised
- 2-4X increased risk for childhood asthma
Why did RSV make headlines?

Since the beginning of the pandemic, many countries have observed a near total disappearance of RSV and influenza cases. With lifting of restrictions, increase cases and increase in age affected (from average 12 months, to 18.4 months). Interseasonal resurgence also occurred.

In Canada, between Aug. 29, 2020, and May 8, 2021: only 239/339 627 tests positive for RSV = 0.07%
Compare to Aug. 25, 2019, and May 2, 2020: 18860/412 861 tests positive for RSV = 4.57%
Compare to Aug 29, 2021 to April 30 2022: 28930/468636 tests positive for RSV = 6.17%

Number of positive respiratory virus tests
Figure 2: Number of positive respiratory virus tests reported by participating laboratories in Canada by surveillance week


Pascal M. Lavoie, Frederic Reicherz, Alfonso Solimano and Joanne M. Langley. CMAJ July 26, 2021 193 (29) E1140-E1141
Why did this happen with RSV?

LESS POPULATION IMMUNITY
• Pandemic restrictions reduced contact with circulating respiratory viruses
• Usually healthy adults have lifelong seasonal exposure to the virus that maintains memory B- and T-cell immunity (often asymptomatic)

LESS MATERNAL IMMUNITY
• pregnant individuals were less likely to be exposed to RSV
• Immunologically naive infants depend on passively transferred maternal antibodies to protect them at birth
• pregnant individuals less likely to boost their RSV antibodies to levels usually seen in the winter
• This raises a possibility that infants are less well protected than usual and could become sicker if they are infected this summer

OTHER FACTORS
• Cold medication shortage (increased demand off-season)
• Increase acute care capacity (surgical resumption), led to over capacity with RSV surge
RSV VACCINES!

Preparations authorized for use in Canada:

“Arexvy, an RSV vaccine, has been authorized for use in Canada for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older. NACI is reviewing the use of Arexvy. Recommendations and a chapter update will follow.”
- is on the SK immunization manual

Monoclonal antibodies:

SYNAGIS (palivizumab) (PVZ), humanized IgG1 monoclonal antibody directed to the RSV fusion protein (AstraZeneca Canada Inc.), licensed for prevention of RSV LRTI in high-risk children

BEYFORTUS\textsuperscript{TM} (nirsevimab) passive immunity, human monoclonal antibody. (AstraZeneca Canada Inc.). Pending NACI review. Long acting, only need one dose
Palivizumab

- Monthly administration (x4) during RSV season reduces hosp. risk for RSV by 55% in premature infants with or without chronic lung disease and by 45% in infants with hemodynamically significant congenital heart disease

- Specific recommendations: (CPS, AAP and NACI)
  - Born @ <30 wk GA and <6 months of life at start of season
  - HD significant cardiac disease and <12 months of life
  - BPD / CLD and <12 months of life, or <24 months if recent O2 needs

- Broader indications:
  - Infants in remote communities who would require air transport for hospitalization, born before 36 + 0 weeks’ GA and <6 months of age at the start of RSV season
  - Consideration may be given to administering palivizumab during RSV season to term Inuit infants until they reach six months of age

What about COVID-19?

National and regional trends

Figure 1. Count of total cases of COVID-19, province/territory as of September 2, 2023. (Last data update September 12, 2023, 9 am ET)

Hover over or tap regions to see cases, deaths in Canada over time. Click the play button to animate the map. Map data is available in .csv and .json formats and a data dictionary is available .csv format.

The count of total cases of COVID-19 in Canada was 4,716,005 as of September 2, 2023.

National and regional trends

Figure 1. Count of cases (latest week) of COVID-19, province/territory for the week of August 27 to September 2, 2023. (Last data update September 12, 2023, 9 am ET)

Hover over or tap regions to see cases, deaths in Canada over time. Click the play button to animate the map. Map data is available in .csv and .json formats and a data dictionary is available .csv format.

The count of cases of COVID-19 for the week of August 27 to September 2, 2023 in Canada was 4,476.
What about COVID-19?

National and regional trends

Figure 1. Count 🕒 of deaths (“latest 2 weeks”) 🕒 related to COVID-19, province/territory 🕒 for the weeks of August 20 to September 2, 2023 (Last update September 12, 2023, 9 am ET).

Hover over or tap regions to see cases, deaths in Canada over time. Click the play button to animate the map. Map data is available in .csv and .json formats and a data dictionary is available .csv format.

Canada 🇨🇦 93

Count of deaths related to COVID-19 for the weeks of August 20 to September 2, 2023 in Canada was 93.

National and regional trends

Figure 1. Count 🕒 of total deaths 🕒 of COVID-19, province/territory 🕒 as of September 2, 2023 (Last update September 12, 2023, 9 am ET).

Hover over or tap regions to see cases, deaths in Canada over time. Click the play button to animate the map. Map data is available in .csv and .json formats and a data dictionary is available .csv format.

Canada 🇨🇦 53,541

The count of total deaths of COVID-19 in Canada was 53,541 as of September 2, 2023.
What’s the hot variant now?

XBB.1.16 is no longer the most prevalent lineage group, as it has been passed by XBB.1.9.2, primarily driven by its EG.5 sub-lineages, over the last three weeks.
The many mutations of Omicron

Sources: Centers for Disease Control and Prevention, Nextstrain (CBC)
The current COVID-19 situation ...

The percentage of weekly positive tests up to September 2, 2023 in Canada was 15.1%.

NO MORE “WAVES”! Steady state of test positivity from 10.42 ~ 16.58%
What’s in store for COVID-19 vaccines?

On May 18, 2023, the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) released recommendations for updates to COVID-19 vaccine antigen composition:

• recommended a monovalent XBB.1 descendent lineage, such as XBB.1.5 or alternatively XBB.1.16.

• The International Coalition of Medicines Regulatory Authorities (ICMRA), European Centre for Disease Prevention (ECDC), the European Medicines Agency (EMA), and the US Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (FDA VRBPAC) also released decisions supporting XBB as a candidate for the COVID-19 vaccine composition update.

• Upcoming vaccine will be tailored to the SARS-CoV-2 XBB.1.5 sublineage

• Pre-clinical data: neutralizing antibody responses against Omicron sublineages, XBB.1.5, BA.2.86 (Pirola), & EG.5.1 (Eris)

• seasonality of SARS-CoV-2 has not been established, but target is for fall release to help reduce the impact of COVID-19 on the health system while other respiratory viruses are circulating
NACI National Advisory Committee on Immunization

Beginning in the fall of 2023 for those previously vaccinated against COVID-19, NACI recommends a dose of the XBB.1.5-containing formulation of COVID-19 vaccine for individuals in the authorized age group if it has been at least 6 months* from the previous COVID-19 vaccine dose or known SARS-CoV-2 infection (whichever is later).

Immunization is particularly important for those at increased risk of COVID-19 infection or severe disease, for example:

- Adults 65 years of age or older;
- Residents of long-term care homes and other congregate living settings;
- Individuals with underlying medical conditions that place them at higher risk of severe COVID-19;
- Individuals who are pregnant;
- Individuals in or from First Nations, Métis and Inuit communities**;
- Members of racialized and other equity-deserving communities;
- People who provide essential community services.

*(Strong NACI Recommendation)
Access to COVID Antivirals for Community Prescribers

**CLINICAL ASSESSMENT OF SYMPTOMS**
- Refer red flag symptoms, severe COVID symptoms to Emergency
- Refer Oncology and Transplant Patients to Specialist Team or Early COVID Therapeutics Team

**COVID-19 TEST**
(RAT, PCR) to confirm diagnosis
- RAT + self-testing; available in community
- PCR priority populations: SHA and MD/HP clinic only

**CONSIDER ANTIVIRAL THERAPY**
Review eligibility criteria: risk factors for severe disease, vaccination status, previous infections/treatments, age, duration of symptoms

- Eligible for Paxlovid™ (high risk of serious illness)
- Not eligible for Paxlovid™ but potentially eligible for remdesivir (high-risk, Paxlovid™ contraindicated)
- Not eligible for Paxlovid™, not eligible for remdesivir (low risk of serious illness, antiviral not necessary)

**Supportive Care**
- For more prescribing information: Link: Participating dispensaries

**Mild COVID-19 (Paxlovid™)**
REMINDER: Prescribing is ONLY allowed during a declared COVID-19 pandemic

**ARE ANY OF THE FOLLOWING PRESENT?**
- Difficulty breathing or worsening of respiratory symptoms
- Greater than 10 breaths per minute
- Shortness of breath at rest or requiring supplemental oxygen
- Respiratory distress (difficulty speaking in 1-2 sentences, severe wheezing)
- Hypoxia: oxygen saturation <93% or fever >38.3°C for >72 hours
- Severe dehydration, decreased urination or significant reduction in food or fluid intake
- Tachycardia (heart rate greater than 100 beats per minute)
- Persistent pain or pressure in the chest
- Lethargy, confusion, deterioration in level of consciousness

**ARE SYMPTOMS TYPICAL OF MILD COVID-19?**
- Age >18 years
- Previous COVID-19 infection in which it has been less than 90 days since symptoms have resolved
- Previously received 2 courses of COVID-19 antiviral (i.e. Paxlovid™, remdesivir)
- Pregnant or breastfeeding or unknowing if contraceptively abstaining
- No positive confirmed PCR test or RAT, or symptomatic
- Unvaccinated or unvaccinated age >18 to <55 years without a high risk factor or immunocompromised
- Fully vaccinated (unless immunocompromised or age >70 with either ≥1 high risk factors (diabetes, chronic renal or liver disease, or ≥2 high risk factors))
- Renal impairment: ≥30mL/min or on dialysis
- Active liver disease

**ARE ANY OF THE FOLLOWING PRESENT?**
- ≥5 days since symptom onset (not a remdesivir eligible up to ≥ 8 days)
- Asthmatic, uncontrolled, or uncontrolled HTN
- Active treatment for cancer
- Hematopoietic stem cell transplant
- Solid organ transplant
- Maotivates to severe primary immunodeficiency
- Absolute contraindications for remdesivir (not to be used in cases of severe immuno-compromise)

**Non-pharmacologic treatment** (DTC symptomatic treatment as indicated)
- Paxlovid™ in Adults ≥18 years of age ≥5 days
- Usual dosage: 300mg (150mg x 2 tablets) of nirmatrelvir with 100mg (50mg x 2 tablets) of ritonavir every 12 hours
- Renal dosing (CID ≥ 30mL/min to ≤60mL/min): 150mg (75mg x 2 tablets) of nirmatrelvir with 100mg (50mg x 2 tablets) of ritonavir every 12 hours

**Follow up in 2 days**
- Yes
- No warninging
- Yes

**Access here if there been any improvement?**
- No worsening

**Complete treatment course**
- Yes
- NERF 12/21

**Worsening/more severe symptoms**
- Yes
- Refer to Emergency
Management of adult patients [18 years and older] hospitalized with COVID-19 infection is stratified based on severity of illness:

Severely Ill Patients
Therapies that are recommended with demonstrated benefit in patients meeting detailed eligibility criteria:

1. Dexamethasone 6 mg PO/IV Daily for 10 days (or until discharge from hospital).
2. Prophylactic-intensity dosing of LMWH is recommended for VTE prophylaxis.
3. Tocilizumab 400 mg IV (single dose) in patients on recommended doses of dexamethasone or equivalent corticosteroid and within 14 days of symptomatic COVID-19 infection.
4. Sarilumab 400 mg IV (single dose) may be automatically substituted for tocilizumab due to global medication shortages (NOTE: Sarilumab currently unavailable in SHH as of January 2022).
5. Baricitinib 4 mg PO Daily for eGFR greater than or equal to 60; OR 2 mg PO daily for eGFR 30 to 59; OR 1 mg PO daily for eGFR 15 to 29) for 14 days is available as an alternative therapy if both tocilizumab and sarilumab are unavailable due to global medication shortages.

Therapies that are NOT currently recommended due to uncertain benefit and/or potential harm:

1. Monoclonal antibodies with supportive data in hospitalized adults (casirivimab/infusevum) are not presently being used due to in vitro resistance with the dominant circulating Omicron variant.
2. Remdesivir has not demonstrated benefit in existing trials of hospitalized patients with COVID-19. The Recovery Trial is actively recruiting patients to assess sotrovimab in hospitalized adults.
3. Therapeutic anticoagulation is not recommended in patients with a clear clinical indication or high suspicion.
4. Empiric antivirals are not recommended unless there is concern for bacterial co-infection.

Moderately Ill Patients
Therapies that are recommended with demonstrated benefit in patients meeting detailed eligibility criteria:

1. Dexamethasone 6 mg PO/IV Daily for 10 days (or until discharge from hospital).
2. Prophylactic-intensity dosing of LMWH is recommended for VTE prophylaxis.

Therapies that may be considered despite limited benefit in patients meeting eligibility criteria:

1. Remdesivir 200 mg IV x 1 dose followed by 100 mg IV Daily x 4 days may be considered for patients on low-flow supplemental oxygen. Administration may reduce the need for mechanical ventilation but has not demonstrated reduction in mortality or clinical benefit in severely ill patients already requiring advanced organ support.
2. Therapeutic anticoagulation may be considered in patients without other indications, not requiring advanced organ support, and at low risk of bleeding. Impact on survival is uncertain but it may reduce the need for organ support and thrombotic events while increasing risk of major bleeding events. Given small benefit and known potential harms, definitive recommendations cannot be made until further evidence is available.

Therapies that are NOT currently recommended despite demonstrated benefit due to limited medication supply:

1. Tocilizumab/Sarilumab have demonstrated benefit in patients on low-flow oxygen with elevated CRP (>25) but should be reserved for patients with severe illness to maximize benefit during global medication shortage of anti-IL-6 agents.

Therapies that are NOT currently recommended due to uncertain benefit and/or potential harm:

1. Monoclonal antibodies with supportive data in hospitalized adults (casirivimab/infusevum) are not presently being used due to in vitro resistance with the dominant circulating Omicron variant.
2. Remdesivir has not demonstrated benefit in existing trials of hospitalized patients with COVID-19.

The following therapies are NOT currently recommended for hospitalized adults:

- Chloroquine
- Hydroxychloroquine
- Lopinavir/Ritonavir
- Ivermectin
- Docetaxel
- Interferon
- Ribavirin
- Fluvoxamine
- Ceftriaxone
- Dexamethasone
- ACE-I/ARB
- NSAIDs
- Vitamin D

Information regarding detailed clinical guidance for specific therapies is available.
Our “Personal Risk Assessment”

What if we applied “risk assessment” in the community, in public settings?

1. Before going out, let’s assess the following:

**The individual**
- Are you sick right now? do you have symptoms?
- Can you practice respiratory etiquette and hand hygiene?

**The Task**
- Is it necessary to go out, or can the task wait until you are better?
- Will I be interacting with others, will I come into contact?
- Are you a care provider that will have contact with others, & unable to maintain physical distancing?

**The Environment**
- Will you be in a public space?
- Is it indoors?
- Can physical distancing be maintained?
- Are there compromised people around me? (Keep in mind, you likely don’t know everyone!)

2. Decide if you need a mask, to protect others from getting your virus!
- Try to stay home if unwell
- Wear a medical mask if you’re sick
- Follow respiratory etiquette
- Try to maintain physical distancing
- Carry some hand gel with you
THANKS FOR LISTENING!

ANPANMAN  BAIKINMAN