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PHO Rounds: Prioritizing Pathogens for Genomics

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PHO Rounds

CONFLICT OF INTEREST

- I do not have a conflict of interest to declare

OBJECTIVES

- Describe how microbial genomics can impact decision-making in public health during outbreaks
- Explore the impact and benefits of using microbial genomics in public health practice
- Explain the importance of prioritization exercises in public health organizations

POLL - QUESTION 1. HOW OFTEN DO YOU USE OR INTERPRET GENOMIC DATA FOR OUTBREAK INVESTIGATION OR SURVEILLANCE?

- Often (i.e., once to a few or more times per week)
- Sometimes (i.e., once to a few times per month)
- Rarely (i.e., once to a few times per year)
- Never
- Not applicable (i.e., I do not work in a role that requires this)

POLL - QUESTION 2. CHOSE WHAT PATHOGEN YOU THINK WOULD BE MOST IMPORTANT TO SEQUENCE FOR PUBLIC HEALTH AND INFECTION CONTROL.

- *Acinetobacter* (HAI)
- *Candida spp.* (HAI)
- *C. difficile* (HAI)
- Influenza virus (Influenza)
- *N. meningitidis* (meningitis)
- *M. tuberculosis* (TB)
- *Salmonella* spp. (Salmonellosis)
- *Staphylococcus aureus* (MRSA)
- SARS-Cov-2 (COVID-19)
- *Treponema pallidum* (Syphilis)

PLAN

- Genomics and Genomic epidemiology
- Literature
  - Genomics and Decision-making
  - Genomics and Impact on PH
  - What pathogens should we sequence based on the evidence
- Public health prioritization
  - WHO – resistant bacteria
  - For genomics
- PHO Genomic Pathogen Priority List Approach
- <u>We will not present the exact ranking as the validation is in progress</u>

BACKGROUND

- **Pathogen Genomics**
  - Decrypting the nucleic acid codes of the pathogens to produce sequences (e.g. TATG)
  - Technology: Next-generation sequencing allows for high sequencing capacity and resolution
- **Genomic epidemiology**
  - Microbes evolve by the acquisition of new mutations and other phenomena
  - These changes in the genome can be identified by sequencing
  - E.g. 1) TATGTATG → 2) T**T**TGTATG → 3) TT**T**A**A**TATG → 4) TTTATATG
  - Comparing pathogen genome sequences can help understand the spread of an infectious diseases

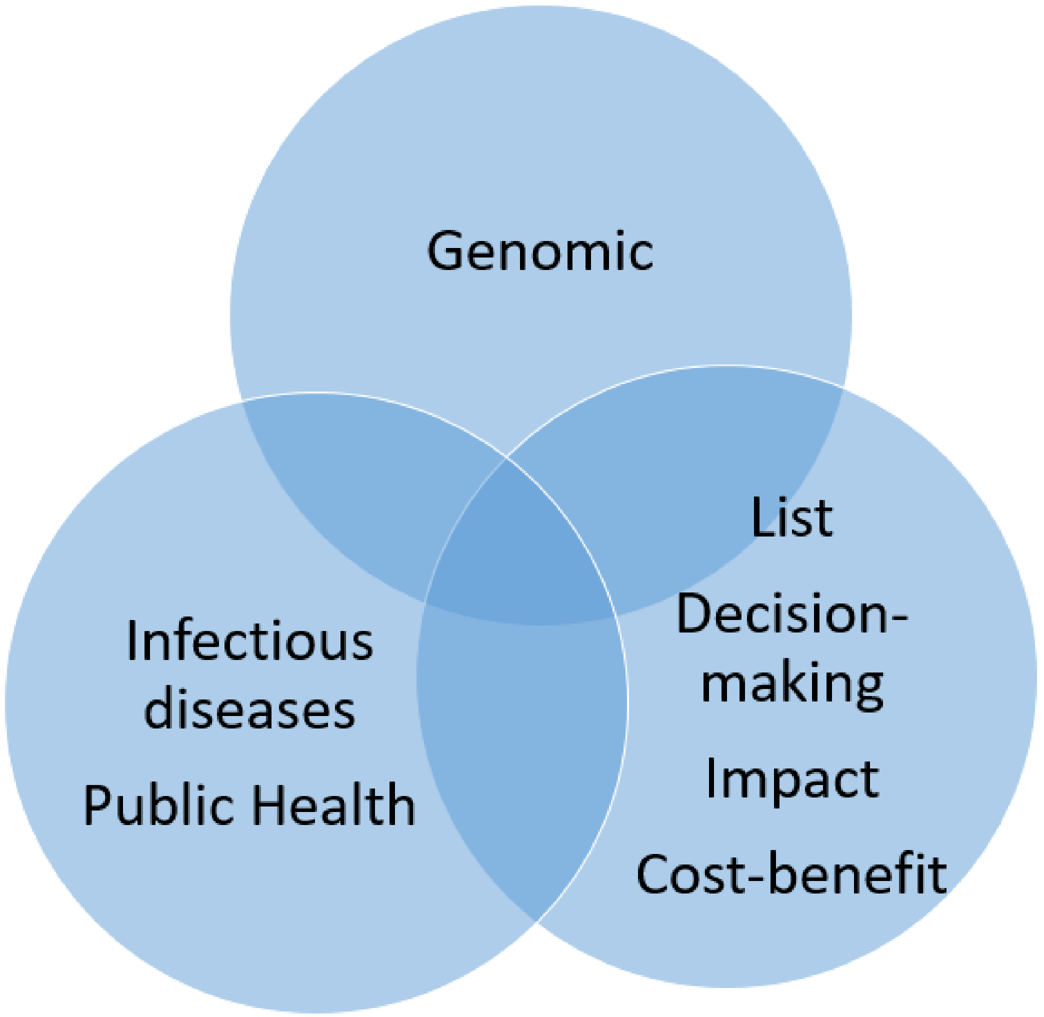
BACKGROUND

- Microbiology labs are incorporating pathogen genomics (e.g. PulseNet for foodborne pathogens, SARS-CoV-2)

- How does pathogen genomics
  - influence decision-making in public health?
  - impact public health?
  - cost?

- What pathogens have been selected for genomics by other public health organizations and why?

SCOPING REVIEW AT PHO – STRATEGY AND RESULTS



- Indexed and grey literature databases, search since 2005
- English and French
- COVIDENCE and MetaQAT

- 990 abstract screened
- 212 full text review
- 114 papers extracted
- Added 83 papers for specific pathogens

Example Genomics Prioritization - Australia

- Carbapenemase-producing *Enterobacteriaceae* (CPE) and other antibiotic-resistant pathogens
- *Candida auris*
- *Corynebacterium diphtheriae* (toxin producing)
- Enteric pathogens:
  - *E. coli* STEC, *Listeria monocytogenes*, *Salmonella* spp., *Shigella* spp.
- Hepatitis A virus
- *Legionella pneumophila*
- *Mycobacterium tuberculosis*
- *Neisseria meningitidis*

Australia Government. Implementation plan for the national microbial genomics framework, 2021-2022. Canberra: Commonwealth of Australia as represented by the Department of Health; 2021. Available from: https://www.health.gov.au/sites/default/files/documents/2021/02/implementation-plan-for-the-national-microbial-genomics-framework-2021-2022.pdf

KEY PAPERS – DECISION MAKING/IMPACT FOR PUBLIC HEALTH

- >30 salmonellosis cases in 3 hospital sites and the community over 3 weeks (typical 5-8/month) in the UK
- Unclear spread or multiple importations in the hospital→ Rapid sequencing in the hospital
- Identified the source (food distribution, food trolley & staff), closed 2 wards
- Ruled out the relationship with concomitant childcare cases
- Led to more precise intervention for infection control (food distribution)

Quick J, Ashton P, Calus S, Chatt C, Gossain S, Hawker J, et al. Rapid draft sequencing and real-time nanopore sequencing in a hospital outbreak of Salmonella. Genome Biol. 2015;16:114. Available from: https://doi.org/10.1186/s13059-015-0677-2

KEY PAPERS – DECISION MAKING/IMPACT FOR PUBLIC HEALTH

- Outbreak of hepatitis A in men-having-sex-with-men in Europe (2016-2018)
- Vaccine shortage in many countries→ reduction of antigen doses/doses
- Hepatitis A in vaccinated individuals - Emergence of hepatitis A antigenic variants
- Barcelona: 159 cases, compared sequences of 5 vaccinated and 8 not vaccinated cases
- Higher diversity in the epitope-coding regions for the vaccinated cases
- Led to recommendations on vaccination to avoid escape variants

Sabrià A, Gregori J, Garcia-Cehic D, Guix S, Pumarola T, Manzanares-Laya S, et al. Evidence for positive selection of hepatitis A virus antigenic variants in vaccinated men-having-sex-with men patients: implications for immunization policies. EBioMedicine. 2019;39:348-57. Available from: https://doi.org/10.1016/j.ebiom.2018.11.023

KEY PAPER – ECONOMIC ANALYSIS

- Modelling of cost-effectiveness of TB PCR and WGS
- PCR and WGS (diagnostics and transmission)
- Low-burden setting (England and Wales) over 10 years
- Estimated incremental net benefit for TB with the strategy was £14.4-16.6 million
- Quality-adjusted life-years of £20,000

- Mugwagwa T, Abubakar I, White PJ. Using molecular testing and whole-genome sequencing for tuberculosis diagnosis in a low-burden setting: a cost-effectiveness analysis using transmission-dynamic modelling. Thorax. 2021;76(3):281-91. Available from: https://doi.org/10.1136/thoraxjnl-2019-214004

SUMMARY OF SCOPING REVIEW FINDINGS

- In the literature, there is evidence that pathogen genomics can
  - influence decision-making in public health
  - impact public health
  - be cost-effective
- The level of evidence differs for different pathogens
  - More literature on some pathogens: e.g. *Salmonella*, *Listeria*, TB, *Enterobacterales* with broad-spectrum resistances
  - Very little or no literature on many pathogens: specific search, added 83 papers

WHAT PATHOGEN SHOULD WE SEQUENCE?

- Lists of pathogens sequenced by different public health organizations differ
- There is no pathogens ranking for genomics in the literature
- Let’s look at other prioritization efforts

PRIORITIZATION FOR PUBLIC HEALTH

- Is no small task
- Examples – Criteria
  - E.g. WHO List of Bacteria with Resistance
- What are methodologies used
  - E.g. Multicriteria decision analysis

WHO ANTIBIOTIC-RESISTANCE PRIORITY WORK

- PRIORITIZATION OF PATHOGENS TO GUIDE DISCOVERY, RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS FOR DRUG-RESISTANT BACTERIAL INFECTIONS, INCLUDING TUBERCULOSIS

World Health Organization (WHO). Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: WHO; 2017. Available from: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12

WHO ANTIBIOTIC-RESISTANCE PRIORITY WORK - CRITERIA

Table 5. Criteria selected for the prioritization exercise

Criterion	Definition
Mortality	Pooled prevalence of all-cause mortality in patients with infections caused by antibiotic-resistant bacteria
Health-care burden	Need for hospitalization and increase in length of stay in patients with infections caused by antibiotic-resistant bacteria compared to patients infected by susceptible strains
Community burden	Prevalence of resistance and type of infections in community settings
Transmissibility	Isolation and transmission among three sectors: animal-human, food-human, and human-human in community and hospital settings
Prevalence of resistance	Pooled prevalence of resistance in clinically significant isolates[a], stratified by WHO region
10-year trend of resistance	Linear increase in 10-year prevalence of resistance in clinically significant isolates[a], stratified by WHO region
Preventability in community and health-care setting	Availability and effectiveness of preventive measures in community and health-care settings
Treatability	Availability of effective treatments (number of antibiotic classes, residual activity of antibiotics, and oral and paediatric formulations)
Pipeline	Likelihood of future development (5-7 years) of new antibiotics based on the current drug development pipeline

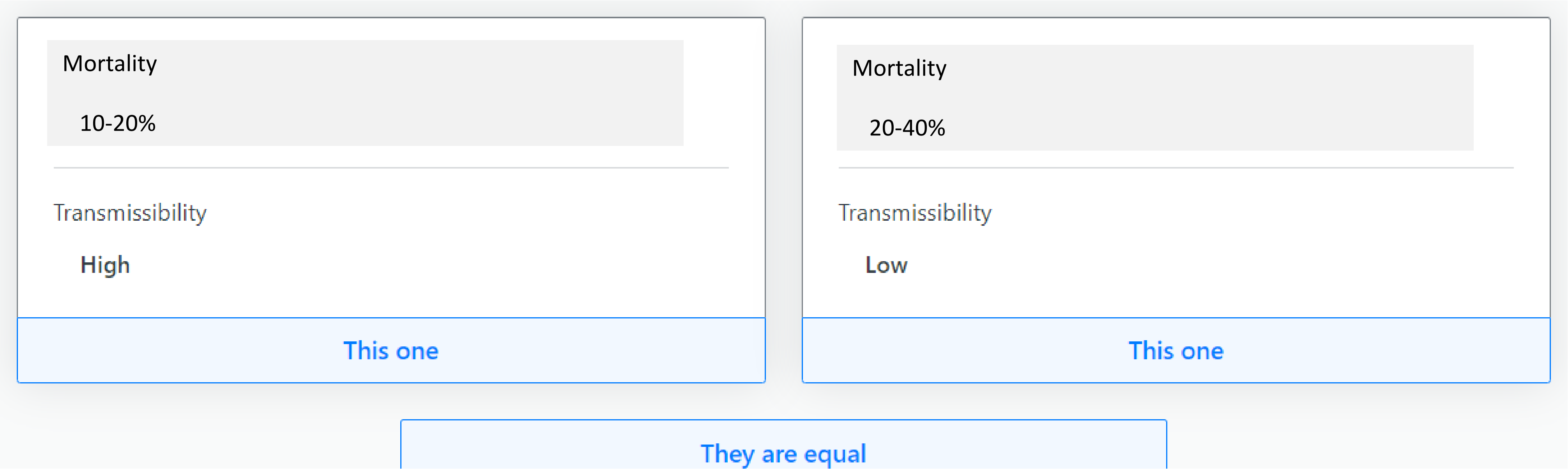
[a] Clinically significant isolates: isolates from blood and cerebrospinal fluid for bacteria commonly causing invasive infections; other samples were included (i.e. stools for Campylobacter spp. or swabs for Neisseria gonorrhoeae) depending on the most common clinical diseases.

World Health Organization (WHO). Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: WHO; 2017. Available from: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12

WHO ANTIBIOTIC-RESISTANCE PRIORITY WORK – WEIGHT ATTRIBUTION

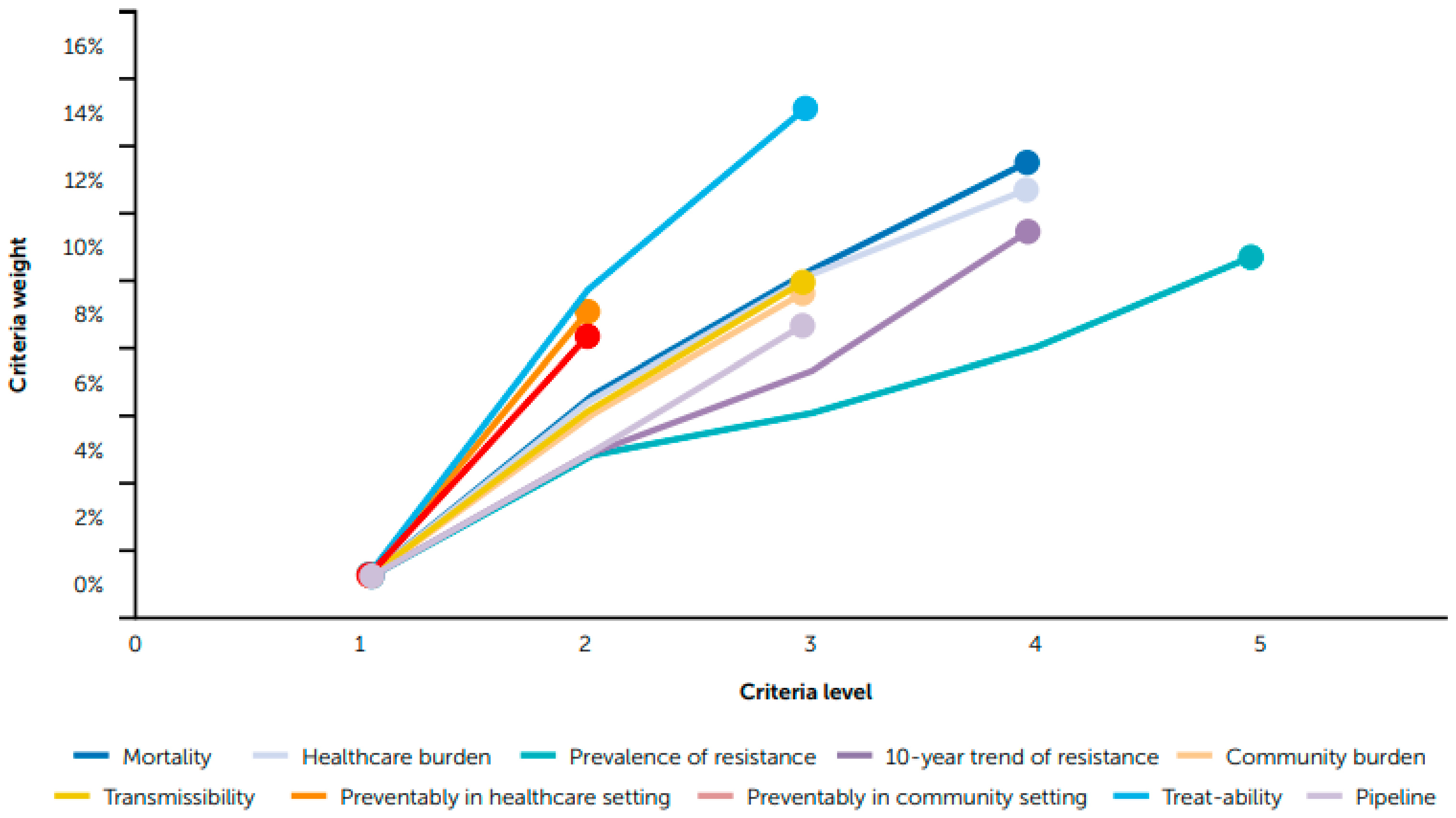
- Requires experts
- PAPRIKA method (Potential All Pairwise RanKings of all possible Alternatives)

Simplified example. Which of these 2 unnamed bacteria should be prioritized?



WHO ANTIBIOTIC-RESISTANCE PRIORITY WORK – NON-LINEARITY

Fig 19. Criteria value functions computed by the survey software



World Health Organization (WHO). Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: WHO; 2017. Available from: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12

WHO ANTIBIOTIC-RESISTANCE PRIORITY WORK – RESULTS

Fig 20. Final ranking of other antibiotic-resistant bacteria (mean weight and standard deviation)

AmpR: ampicillin-resistant, CR: carbapenem-resistant, ClaR: clarithromycin-resistant, FQR: fluoroquinolone-resistant, MR: methicillin-resistant, PNS: penicillin non susceptible 3GCR: third-generation cephalosporin-resistant, VR: vancomycin-resistant

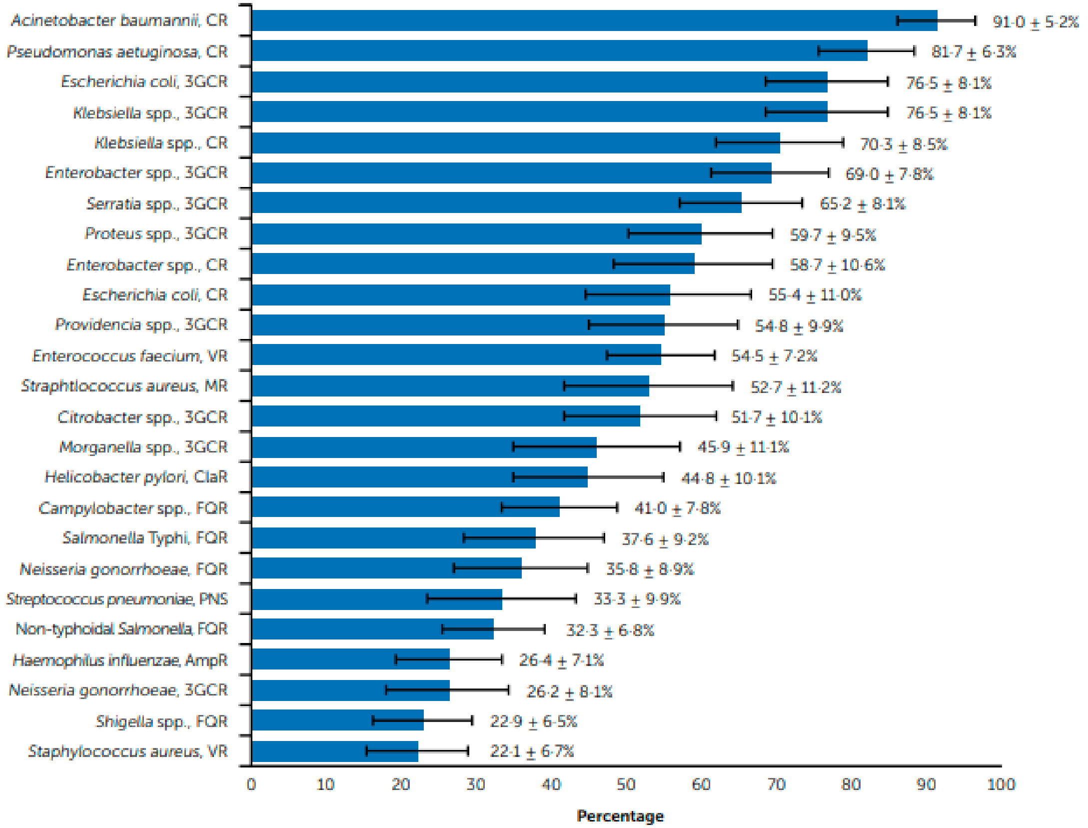
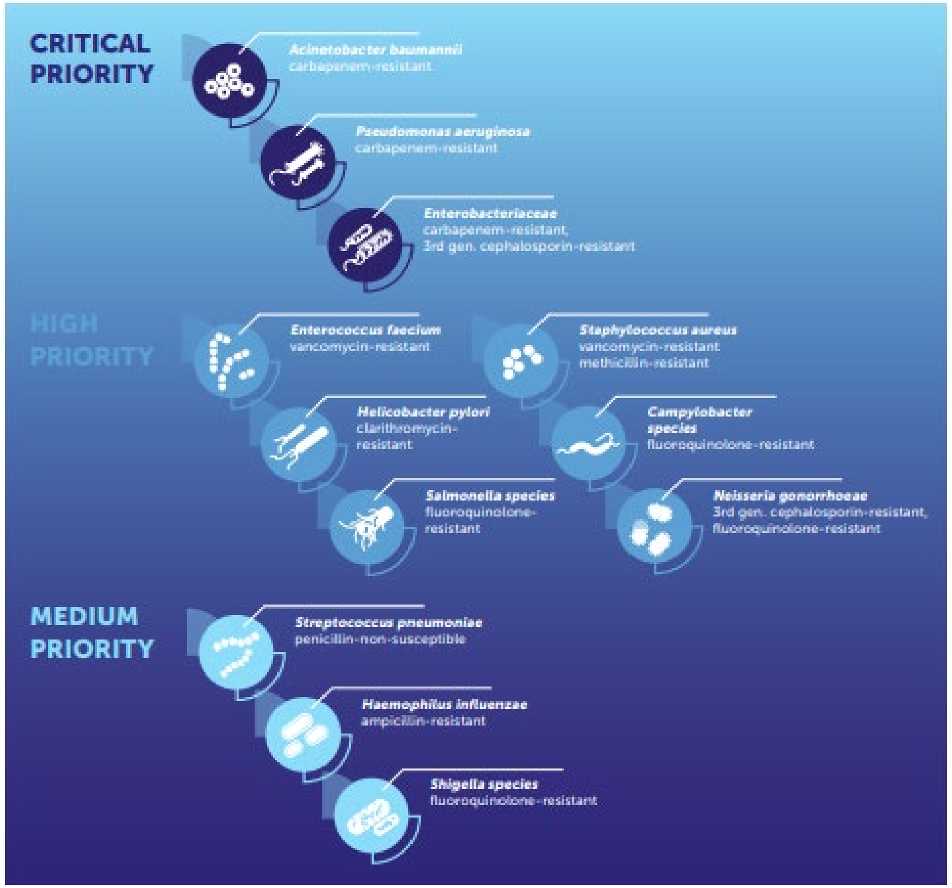


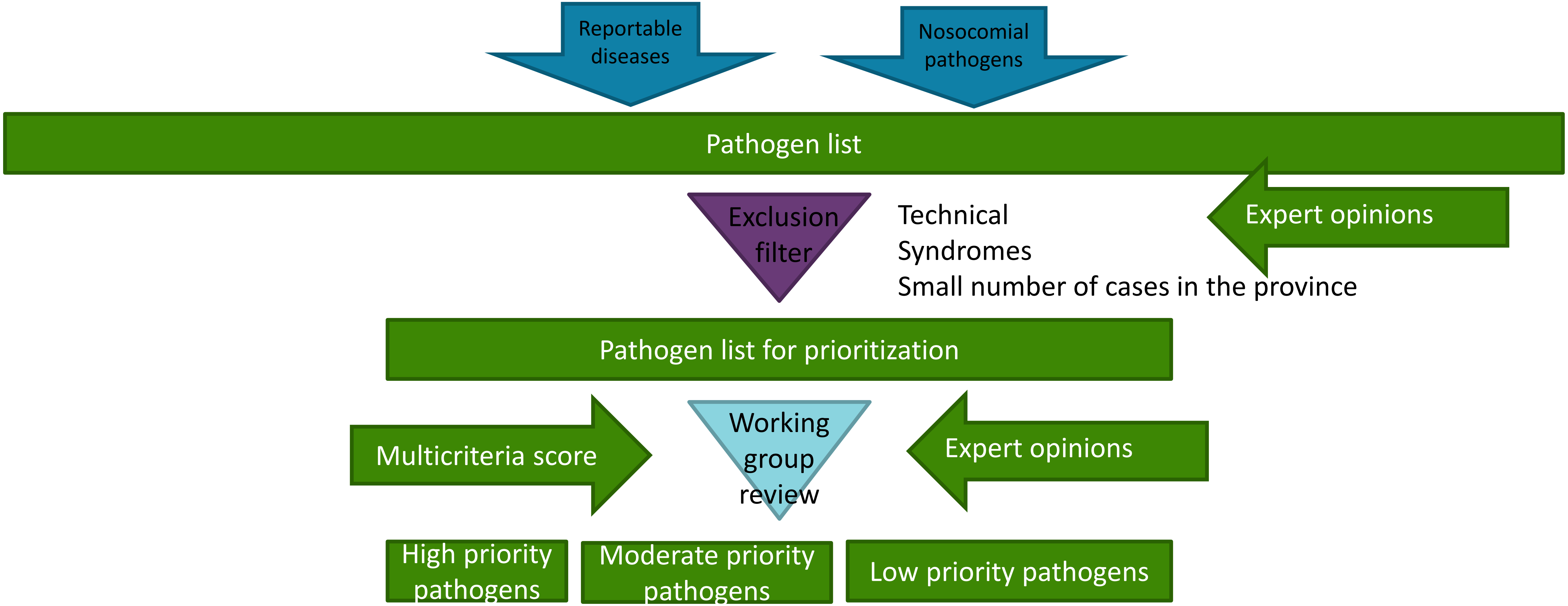
Fig 23. Priority pathogens for R&D of new antibiotics



World Health Organization (WHO). Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: WHO; 2017. Available from: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12

PHO GENOMIC PATHOGEN PRIORITY LIST

PHO GENOMIC PATHOGEN PRIORITY LIST - ALGORITHM



Design: Isabel and Duvvuri

PHO GENOMIC PATHOGEN PRIORITY LIST – PATHOGENS (54)

Category	Subcategory	Pathogen
Reportable diseases in Ontario included	**Blood borne infections**	Hepatitis B virus
		Hepatitis C virus
		Human immunodeficiency virus
	Enteric diseases and food-borne diseases	Campylobacter spp.
		Clostridium difficile
		Listeria monocytogenes
		Salmonella spp.
		Shigella spp.
		Escherichia coli (Verotoxin-producing)
		Yersinia enterocolitica & *Y. pseudotuberculosis*
		Cryptosporidium spp.
		Hepatitis A virus
		Norovirus
		Rotavirus

PHO GENOMIC PATHOGEN PRIORITY LIST – PATHOGENS (54)

Category	Subcategory	Pathogen
Reportable diseases in Ontario included	**Respiratory diseases**	*Corynebacterium diphtheriae*
		Streptococcus pyogenes
		Streptococcus agalactiae
		Legionella spp.
		Mycobacterium tuberculosis
		Blastomyces dermatitidis
		SARS-CoV-2
		Influenza A virus
		Influenza B virus
		Adenovirus
		Seasonal Coronaviruses
		Enterovirus A, B, C, D
		Human metapneumovirus
		Human parainfluenza virus
		Rhinovirus A, B, C
		Respiratory syncytial virus

PHO GENOMIC PATHOGEN PRIORITY LIST – PATHOGENS (54)

Category	Subcategory	Pathogen
Reportable diseases in Ontario included	**Sexually transmitted infections**	*Chlamydia trachomatis*
		Neisseria gonorrheae
		Treponema pallidum
	Vaccine preventable diseases	*Haemophilus influenzae*
		Neisseria meningitidis
		Streptococcus pneumoniae
		Bordetella pertussis
		Human poliovirus serotypes 1-3
		Measles virus
		Mumps virus
		Monkeypox virus
		Varicella Zoster Virus
	Vector-borne and zoonotic diseases	*Brucella* spp.
		Coxiella burnetii
		West nile virus

PHO GENOMIC PATHOGEN PRIORITY LIST – PATHOGENS (54)

Category	Subcategory	Pathogen
Not in the list of reportable diseases in Ontario	**Health care-associated infections (HAI)**	*Acinetobacter* spp. MDR/carbapenem resistant
		Burkholderia cepacia
		Enterobacterales ESBL/carbapenem resistant
		Staphylococcus aureus MRSA
		Nontuberculous Mycobacteria (NTM), including *Mycobacterium chimerae*
		Pseudomonas spp. MDR/carbapenem resistant
		Enterococci, vancomycin resistant
		Candida spp., including *Candida auris*
		Aspergillus spp.

Other pathogens that can cause HAI are in the list of reportable diseases during outbreaks and presented above: *C. difficile*, respiratory viruses, gastro viruses. Carbapenemase-producing *Enterobacteriales*.

PHO GENOMIC PATHOGEN PRIORITY LIST – CRITERIA (6)

CRITERIA (EPIDEMIOLOGICAL)	CRITERIA LEVELS
TRANSMISSIBILITY	Low
	Moderate
	High
POTENTIAL FOR OUTBREAK	Low
	Moderate
	High
INCIDENCE IN ONTARIO	Low, or no case in recent years
	Moderate
	Moderate-High
	High
	Critical (1 case would warrant immediate action)

PHO GENOMIC PATHOGEN PRIORITY LIST – CRITERIA (6)

CRITERIA (GENOMIC)	CRITERIA LEVELS
WGS POWER TO UNDERSTAND TRANSMISSION	No evidence that WGS can rule out/in transmission
	Can rule out transmission
	Can enable cluster analysis
	Can infer relatedness/transmission
	Can identify unrecognized transmission/outbreak
IMPACT OF WGS ON PUBLIC HEALTH AND INFECTION CONTROL	No evidence that WGS influences decisions
	WGS can lead to more precise investigations
	WGS can lead to more precise interventions
WGS COST-EFFECTIVENESS	No evidence of cost-saving
	Cost-effective in the laboratory
	Cost-effective for investigations
	Cost-effective at the population level

PHO GENOMIC PATHOGEN PRIORITY LIST – EVIDENCE GATHERING

- 54 pathogens/pathogen groups
- ~ 200 papers were reviewed
- Criteria levels were determined for each pathogen/group

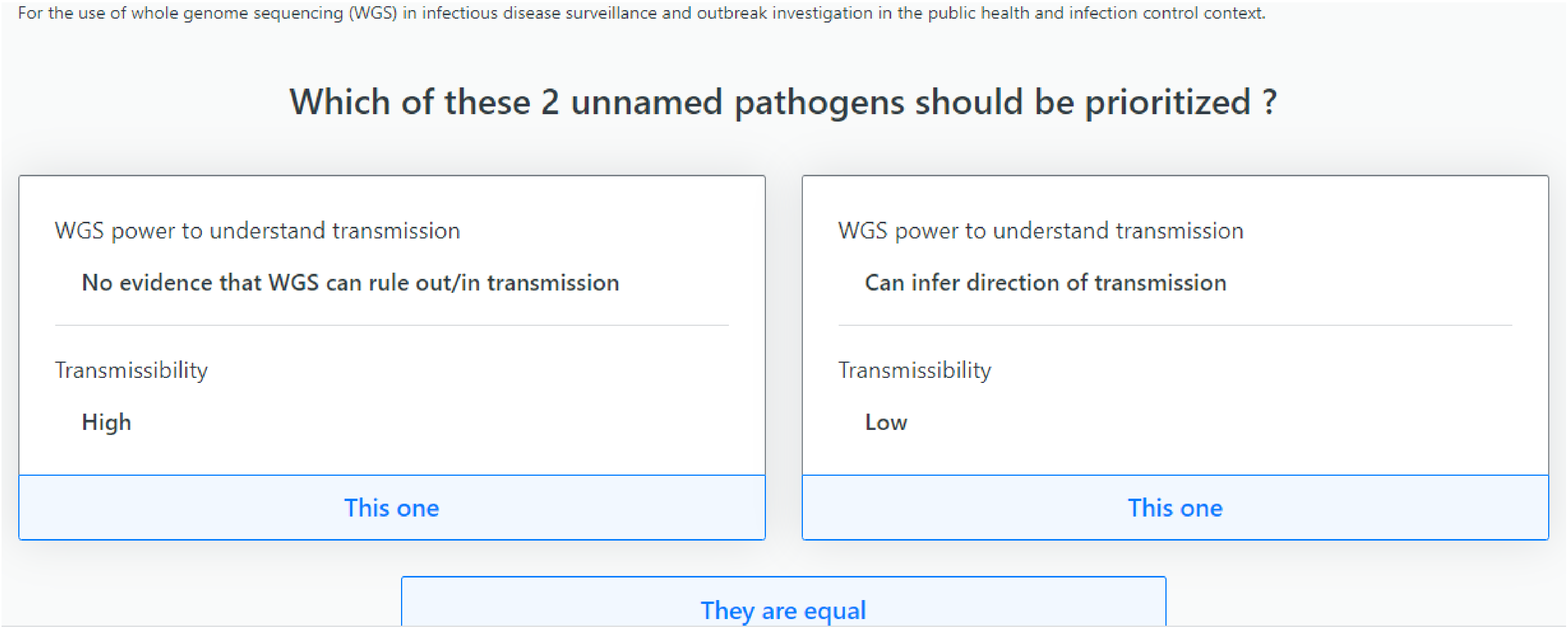
PHO GENOMIC PATHOGEN PRIORITY LIST – EVIDENCE GATHERING

- Example of *Mycobacterium tuberculosis*

CRITERIA	CRITERIA LEVEL
TRANSMISSIBILITY	High
POTENTIAL FOR OUTBREAK	Moderate
INCIDENCE IN ONTARIO	Moderate-High
WGS POWER TO UNDERSTAND TRANSMISSION	Can identify unrecognized transmission/outbreak
IMPACT OF WGS ON PUBLIC HEALTH AND INFECTION CONTROL	WGS can lead to more precise interventions
WGS COST-EFFECTIVENESS	Cost-effective at the population level

PHO GENOMIC PATHOGEN PRIORITY LIST – STAKEHOLDER OPINIONS

- PAPRIKA method (Potential All Pairwise RanKings of all possible Alternatives) on the 1000minds platform

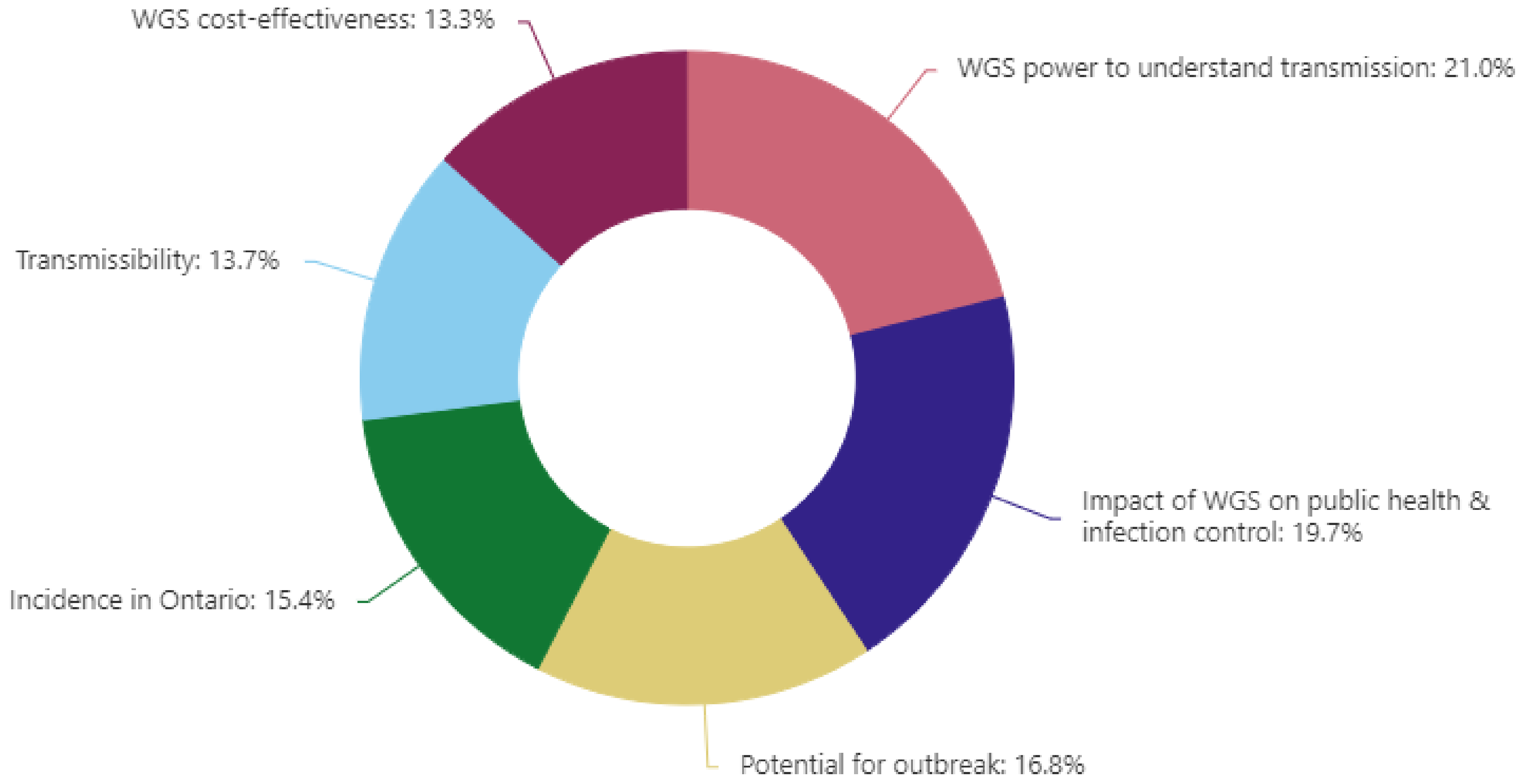


Isabel et al.

PHO GENOMIC PATHOGEN PRIORITY LIST – STAKEHOLDER OPINIONS

- Survey of stakeholders (provincial and national) and PHO experts was launched on September 22nd and closed on October 19th.
- 71 stakeholders completed the survey
  - Bioinformatic and genomic specialists
  - Clinical or medical microbiologists
  - Data analysts, epidemiologists
  - Infectious diseases specialists
  - Public health physicians
  - Public health investigators
  - Academic

PHO GENOMIC PATHOGEN PRIORITY LIST – STAKEHOLDER OPINIONS



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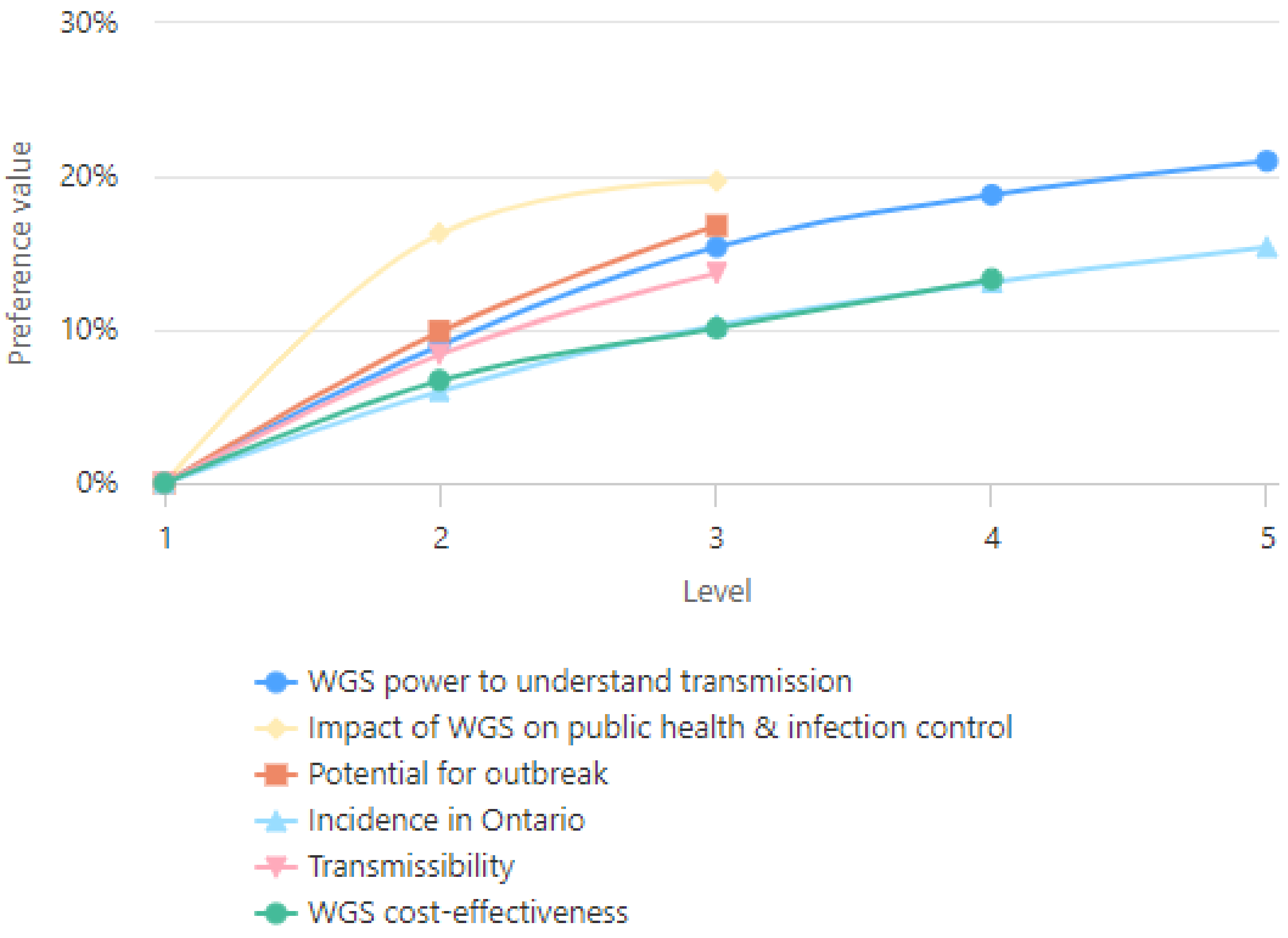
PHO GENOMIC PATHOGEN PRIORITY LIST – STAKEHOLDER OPINIONS



Isabel et al.

PHO GENOMIC PATHOGEN PRIORITY LIST – STAKEHOLDER OPINIONS

- PRELIMINARY RESULTS

- Kendall's W of the alternative rankings = 0.917
- Spearman rank correlation = 0.915

- Analysis is in progress with an added statistical validation

- Examples of top ranking pathogens

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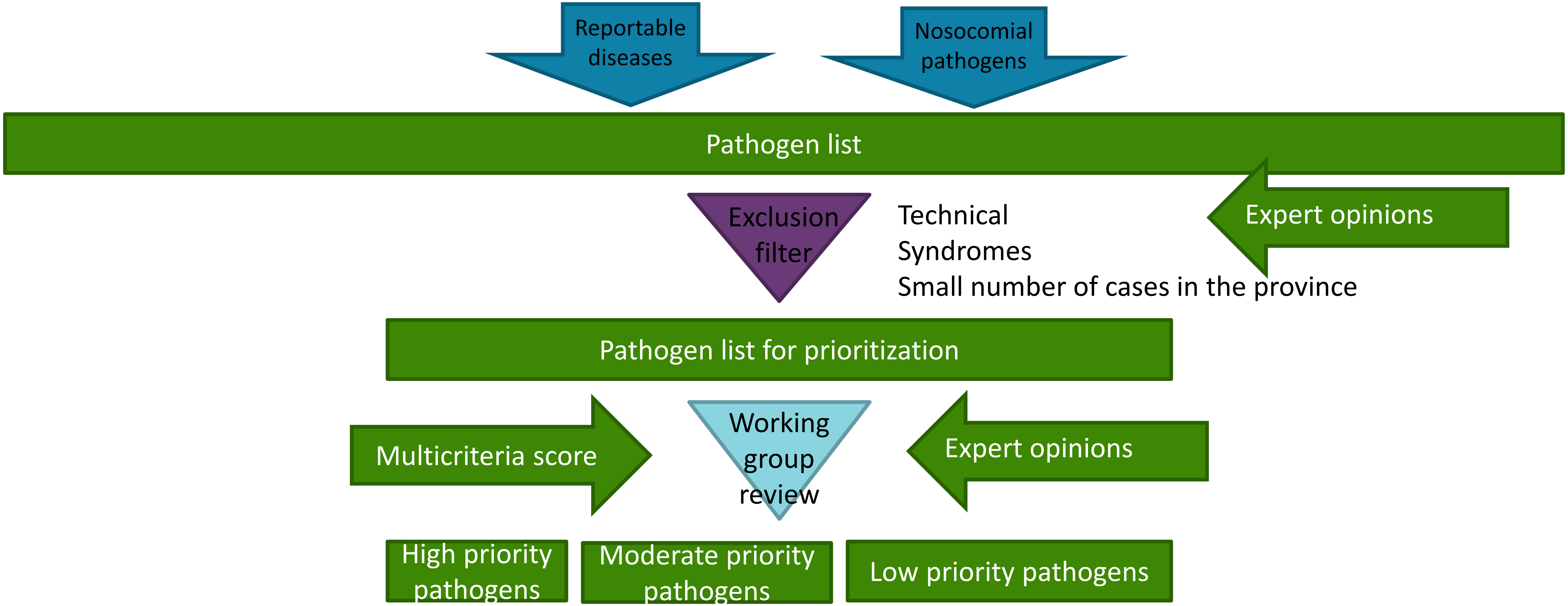
PHO GENOMIC PATHOGEN PRIORITY LIST - ALGORITHM



Design: Isabel and Duvvuri

SUMMARY

- Microbial genomics can impact public health investigations and interventions
  - E.g. *Salmonella* and Hepatitis A

- Prioritization exercises for public health is complex and important

- We presented the approach for the PHO Genomic Pathogen Priority List

- It was unbiased toward pathogens

PERSPECTIVES: PHO GENOMIC PATHOGEN PRIORITY LIST

- Statistical and expert validations in progress
- Ranking of the pathogens in 3 categories (high, moderate, low) to follow
- Help to focus WGS resources on pathogens with the highest potential benefits
- Adaptability of the method: The ranking can be reassessed and adjusted for different pathogens as genomic evidence arises or as the epidemiological situation changes

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- Our collaborators at NML
  - Catherine Yoshida, Andrea Tyler
- Colleagues that contributed to the scoping review on WGS
  - Jennifer Tat, Melissa Greenblatt-Richards, Shawn Clark, David Poon, Maxime Billick, Mohammed Sarhan, Stone Li, Mohsin Ali, Kevin Davies, Martin Grunnill, Venkata Duvvuri
- Jessica Hopkins and Samir Patel

Thank you

- QUESTIONS?