Pathogen prioritization for pathogen genomics

WORKSHOP PARTNERS

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

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CENTRE FOR PATHOGEN GENOMICS

Sydney Infectious Diseases Institute
Centre for Infectious Diseases & Microbiology
WHO Southeast Asia Regional Office (SEARO)
WHO Western Pacific Regional Office (WPRO)
WHO International Pathogen Surveillance Network (IPSN)

Considerations prior to genomic surveillance

How does genomics within existing surveillance programs

TUBERCULOSIS

AFB Smears
TB culture
GeneXpert

ARBOVIRAL DISEASE

Serology, molecular tests
Human – Vector samples

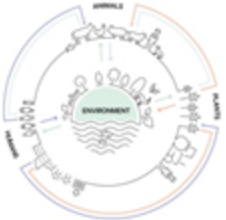
INFLUENZA CONTROL

SEVERE ACUTE RESPIRATORY INFECTION

Respiratory samples
Culture – Molecular testing

MICROBIOLOGY

Antimicrobial
Sensitivity Testing



ONE HEALTH

Human-animal
interface

POLIO GLOBAL ERADICATION INITIATIVE

Wastewater
samples

Screening tests help target and interpret genomics

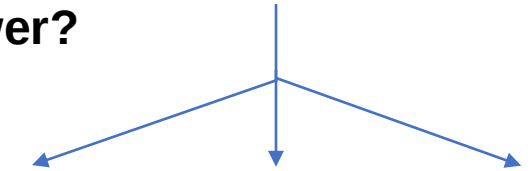
Where and how frequently to sample?

- Representative sample
- High-risk setting ie. wet market, migrant settlement

Link between genomics and conventional testing

- Antimicrobial resistance
- Genotype – Serotype ie. Dengue

What question does genomics answer?

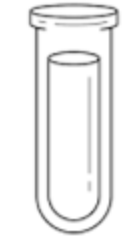


Rare or novel pathogen
Polio, Nipah, outbreak investigation

Track existing variants
COVID, influenza, MDR-TB

Assess intervention effects
Vaccination, isolation/travel restrictions, Wolbachia (Dengue)

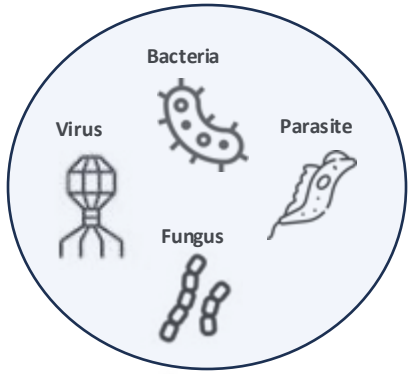
Benefits of pathogen genomic sequencing



Laboratory sample

NGS

WHAT INFECTION IS CAUSING DISEASE?



- **Single test** can identify **any infectious cause** of disease
- **More sensitive and timely** than bacterial/TB cultures
- Can detect bacteria **even if antibiotics present**
- **Viral/fungal difficult to detect** any other way
- Critical information for **public health action**
- Can inform **patient care**

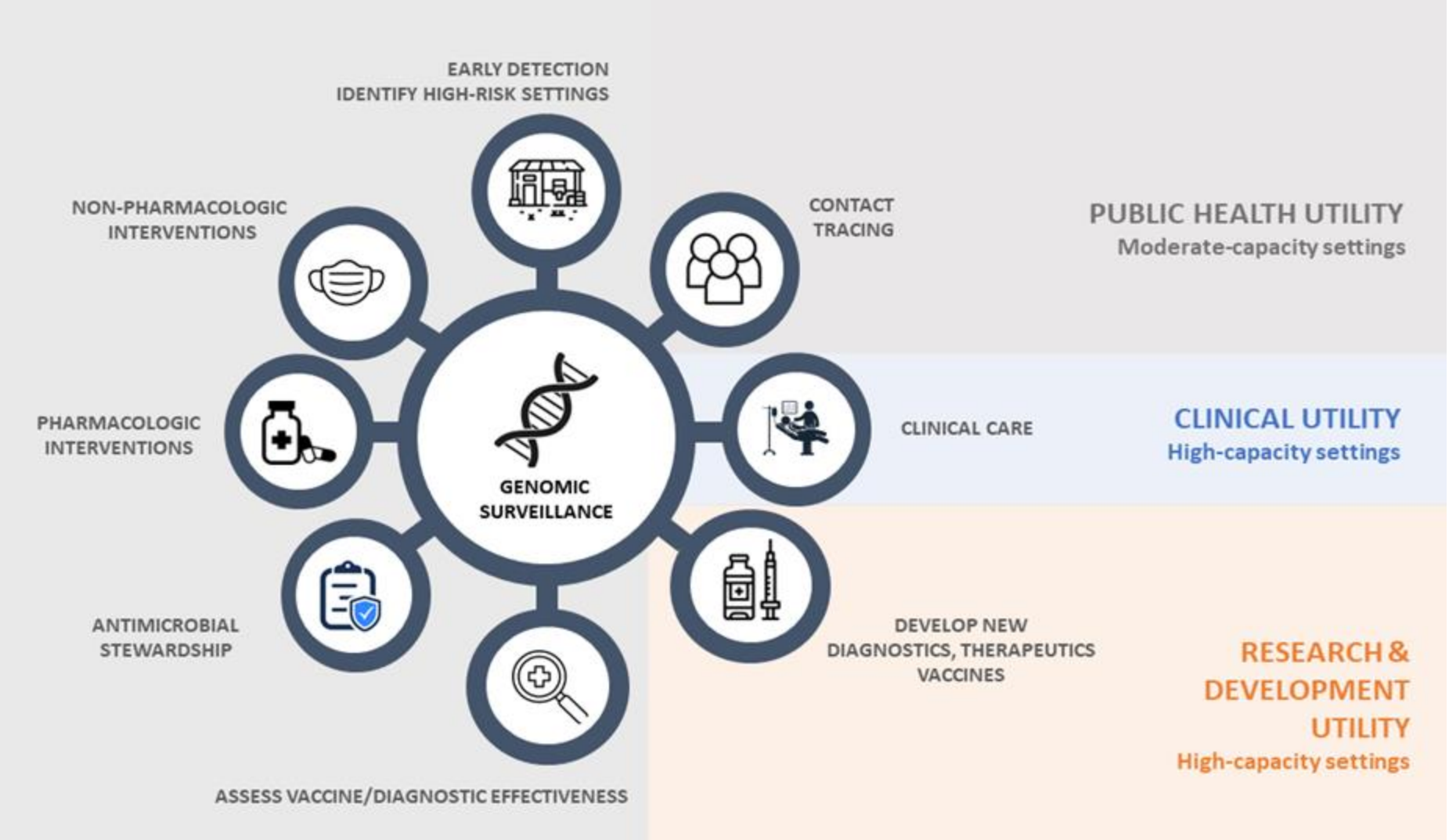
IS IT A KNOWN OR UNKNOWN PATHOGEN?

Only approach to identify a **rare or unknown** infectious disease

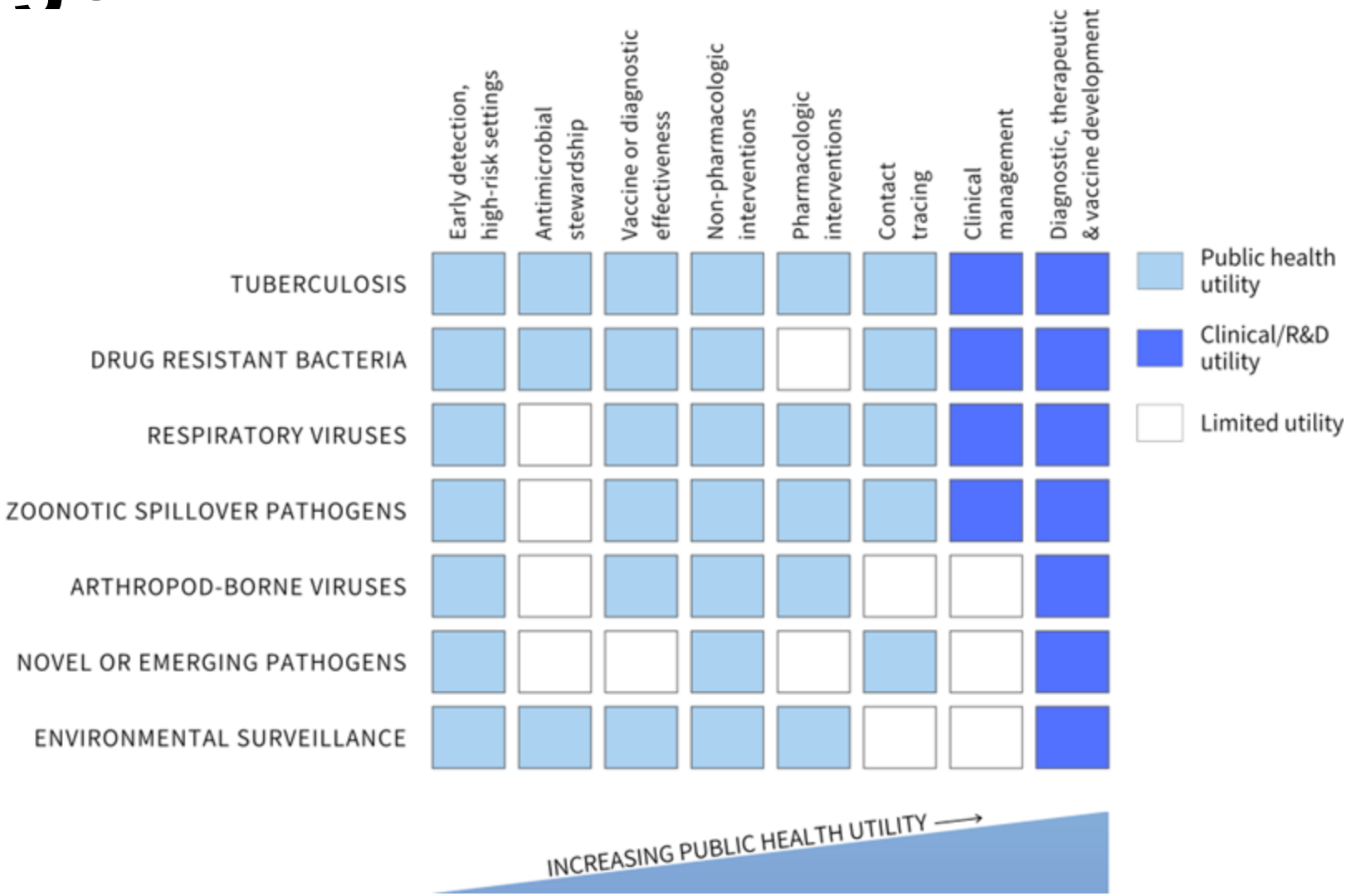
GENETIC DIFFERENCES BETWEEN PATHOGENS?

- **Drug or vaccine resistance**
- **Link a pathogen between individuals** (contact tracing, source identification of an outbreak)
- **Identify high-risk settings** for transmission and/or drug resistance
- **Importation**: Was resistance imported or did it originate independently
- **Variant detection** – may be linked to transmission or clinical severity
- **Are screening tests effective?**

Pathogen genomics utility



The utility of genomics differs by pathogen



Review

Advancing pathogen genomics in resource-limited settings

Cell Genomics 2023

Tuberculosis

Key considerations: MDR-TB costs 25x more to treat and takes 3x longer than regular TB

- TB culture and sensitivity testing can take 6 weeks; GenXpert widely deployed but misses some DR-TB
- Strong correlation between TB mutations and drug-resistant (DR) TB
- Can use Whole Genome Sequencing on cultured specimens or tNGS on sputum
- Many recent innovations in tNGS and TB bioinformatics that are simpler and less costly
- **WHO Guidance** (2023): tNGS is accurate and cost-effective for detecting drug-resistant TB; detects wider DR than GeneXpert

MODERATE CAPACITY

TB control: Incidence >50/100,000
Sequence guidance: Population sample to assess resistance profile

- Sequence all GeneXpert DR cases; relapses; a portion of GeneXpert (-) cases
- Sequence during outbreaks and among high-risk populations: paediatric, HIV-positive

ACTIONS

- **Antimicrobial stewardship**: Inform optimal programmatic TB/DR-TB treatment regimens
- **Characterise high risk populations –** transmission and drug resistance
- **Non & Pharmacologic interventions**: Active case finding, transmission tracking, contact tracing; treatment and preventive therapy
- **Assess diagnostic and vaccine effectiveness:** Monitor resistance missed by commercial tests; Monitor vaccine effectiveness and immune escape
- **Economic significance**: Reduce DR-TB transmission

HIGH CAPACITY

TB elimination: Incidence <50/100,000
Sequence guidance: All TB cases

ACTIONS

- **Enhanced program performance monitoring**:
  - Understand transmission dynamics and define imported vs locally acquired cases with aim of zero local TB transmission
  - Identify lab contamination events
  - Ongoing comprehensive drug resistance surveillance
  - Differentiate de novo vs transmitted drug resistance, relapse vs re-infection
- **Better clinical care**: Optimal personalized treatment of drug- resistant cases
- **New tools**: Inform the development of more sensitive molecular diagnostics and more effective TB medications

Drug resistant bacteria

Key considerations: Major global health threat; higher rates of AMR in LMICs despite less antiobiotic use

- Sequencing should be embedded within AMR surveillance programme with diagnostic and/or reference labs conducting antimicrobial sensitivity testing
- Cultures tell you if there is resistance. Sequencing tells you how and why it has emerged
- Important to understand baseline AMR situation in population

MODERATE CAPACITY

Sequence guidance: Conduct retrospective baseline where feasible

- Prospective sampling of susceptible and resistance isolates; Targeted sequencing during outbreaks

ACTIONS

- **Antimicrobial stewardship**
- **High risk settings**: Early detection of high-AMR risk settings; identify nosocomial threats to inform IPC measures; early identification & non/pharmacologic response to food borne outbreaks
- **Vaccine effectiveness**
- **Economic significance:** Food security, etc

HIGH CAPACITY

Sequence guidance: Known baseline

- Prospective sampling of susceptible and resistance isolates; Targeted sequencing during outbreaks

ACTIONS

- **Antimicrobial stewardship**
- **Rapid outbreak investigation**
- **Contact tracing:** Sequencing can identify transmission routes (de novo emergence, imported, transmitted)
- Implications for IPC or other measures
- **Clinical care**: For those not responding to treatment
- **Develop new tools**: Novel drug testing, new mechanisms of AMR, vaccine development

Respiratory pathogens

Key considerations

- Disease burden (including morbidity and mortality) in LMICs 10-50x greater than HICs. 80% viral
- Respiratory specimens contain large amounts of host genetic material and organisms not causing disease
- Conventional microbiology +/- molecular diagnostics (PCR) initial screen
- Targeted NGS on pathogens-of-concern; metagenomics if suspect sample negative

MODERATE CAPACITY

Sequence guidance: Positive samples containing pathogen of interest; Negative samples for metagenomics (undetected pathogen)

ACTIONS

- **Early detection**:
  - Define local causes of respiratory infections
  - Outbreak detection and public health measures
- **Antimicrobial stewardship**
- **New tools**: Influenza – influence vaccine development
- **Vaccine effectiveness**

HIGH CAPACITY

Sequence: Positive samples containing pathogen of interest; Negative samples for metagenomics (undetected pathogen)

ACTIONS

- **Early detection:** Rapid outbreak investigation
- **Antimicrobial stewardship**
- **Contact tracing:** Sequencing can identify transmission routes
- **Clinical care**: For those not responding to treatment
- **Develop new tools**: Novel drug testing, vaccine development

Zoonotic spillover

Key considerations

- Most human infectious diseases originate in animals - known and unknown pathogens
- Resource-limited settings at highest risk
- Risk-environment worsening due to climate change, species loss, population density/movement, human-animal interaction
- One Health approach essential – human & animal labs, environmental risk assessments
- Still a major issue in high-income countries (salmonella, brucella, leptospirosis, etc)

MODERATE CAPACITY

Molecular diagnostics: first step to detect known pathogens; serology in high-risk settings (i.e. wet-markets, domestic farms)

Sequence guidance: Clinical cases in high-risk settings with tNGS or metagenomics; Active sentinel surveillance; Emerging airborne sampling - Serology as complementary strategy

ACTIONS

- **Early detection/identify high-risk settings:** outbreak investigation; assess human-to-human transmission
- **Pharmacologic interventions:** drug treatment and/or human/animal vaccination
- **Non-pharmacologic interventions:** based on transmission route; food safety/food export measures; domestic wildlife culling
- **Assess vaccine/diagnostic effectiveness**

HIGH CAPACITY

Molecular diagnostics: first step to detect known pathogens; serology in high-risk settings

Sequence guidance: All suspected clinical cases; close contacts; domestic animals

ACTIONS (additional)

- **Contact tracing:** Rapid outbreak investigation and containment; pinpoint animal source
- **Clinical care:** Where effective treatment exists
- **New tools:** Diagnostic, therapeutic, vaccine development for new pathogens/variants

Arboviral disease

Key considerations:

- Arboviral disease: 60% of world's population at-risk – Climate change creating new vector habitats
- High genetic diversity with limited understanding of links between genotype and transmission dynamics/pathogenicity
- Limited understanding of genetic drivers of transmission and pathogenicity
- Vaccines available for some (i.e. Dengue) - Few clinical management options for arboviral disease
- Wolbachia introduction requires monitoring

MODERATE CAPACITY

- High arboviral disease burden
- **Detection**: Serology testing, PCR testing, NS1 Protein for current infection
- **Sequence guidance**: tNGS or WGS from portion of clinical cases and pooled mosquito sampling

HIGH CAPACITY

- Low burden with the risk of re-emergence due to climate change
- **Sequence guidance**: Additional active case finding and sampling of household contacts

ACTIONS

- **Early detection:** circulating strains; potential outbreaks; global transmission patterns; recognition of recent importation/exportation
- **Identification of high-risk settings/populations**
- **Non-pharmacologic interventions**: Early initiation of interventions (community awareness, fogging)
- **Intervention effectiveness**: Assess effectiveness of vaccines/Wolbachia
- **New tools**: R&D for new tool development

Wastewater and environmental surveillance

Key considerations:

- **Novel early detection strategy –** detect pathogens in advance of clinical cases
- **Ease of sample collection** - potential to represent populations / high-risk settings
- **Laboratory techniques:** Beneficial effects of culture-enrichment for bacterial pathogens; filtration/centrifugation vs Nanobead concentration methods
- **More difficult to interpret findings**: Clinical-Environmental correlates; human-animal contamination; advanced bio-informatic requirements
- **Limited number of pathogens** (+/- 30): Feasible to detect and where public health action clear

MODERATE CAPACITY

Existing systems: Can leverage established polio systems to establish multi-pathogen approaches

Sequence guidance: PCR or tNGS screen for known pathogens; metagenomics for novel pathogens; human-animal interface sampling; focus on pathogens that are both feasible to detect and where public health action is clear

HIGH CAPACITY

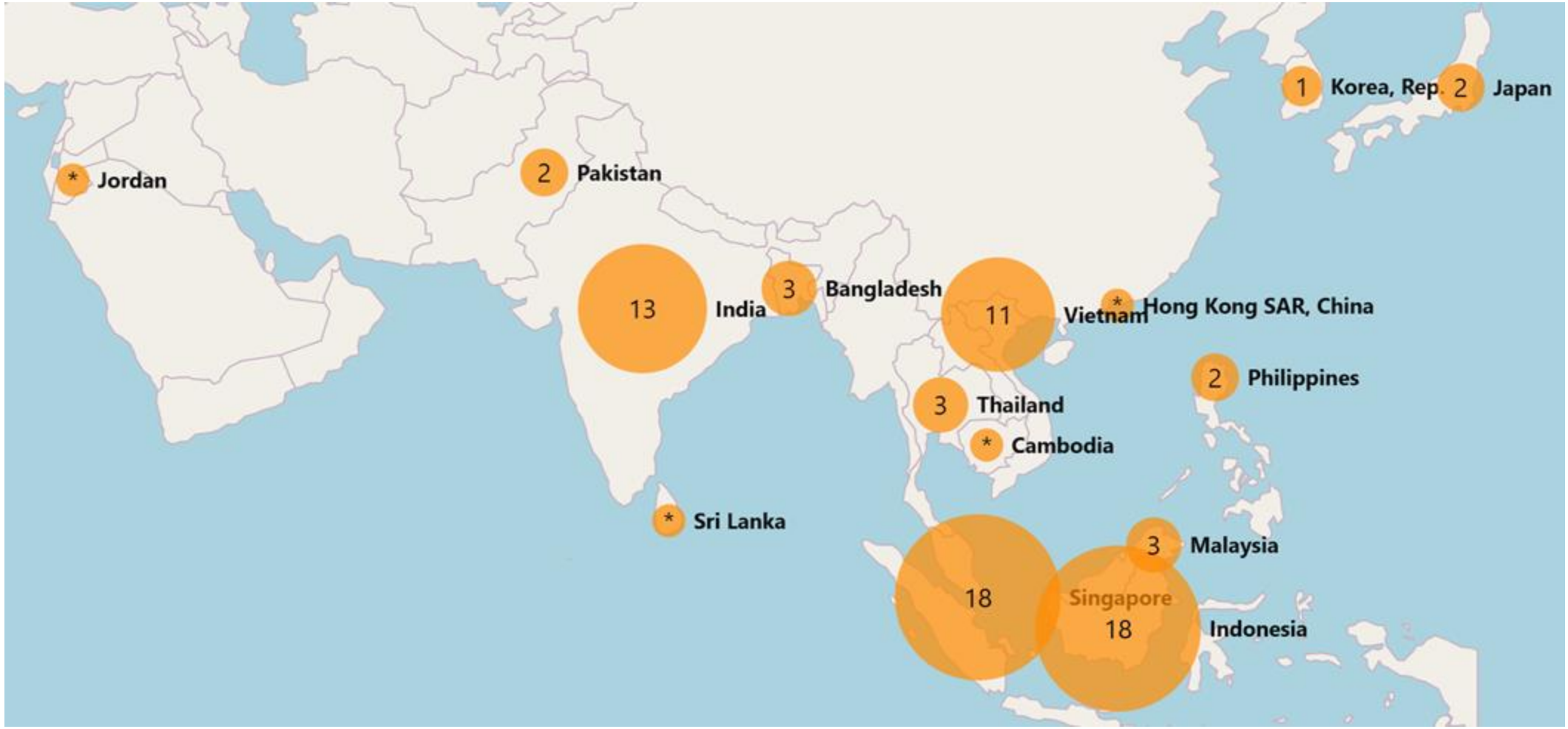
Potential innovation focus: Link to climate effects / water-salinity; automation; Aircraft-based wastewater surveillance; active air sampling

New tools: Potential to influence new tool development

ACTIONS

- **Early detection** of new pathogens
- **Identify high-risk settings**
- **Shape early pharmacological/non-pharmacological interventions**
- **Antimicrobial stewardship**: Early AMR identification
- **Vaccine effectiveness**

Recent surge in wastewater surveillance programs across Asia



ASIA

76 Projects

15 Countries

Bacterial and viral pathogens: Feasible to detect in wastewater and actionable

Pandemic potential

Vaccine-preventable

- Yellow fever virus*
- SARS CoV-2^
- Respiratory Syncytial Virus
- Polio virus
- Dengue virus
- Ebola virus* ^
- Hepatitis A & B
- Hepatitis E
- Highly Pathogenic Avian Influenza*
- Seasonal Influenza
- Measles
- Rotavirus
- Rubella virus
- Japanese encephalitis virus*
- Human Papilloma Virus
- M-Pox
- Varicella zoster virus
- Salmonella Typhi
- Tuberculosis*
- Vibrio cholerae

Drug-treatable

- Seasonal Influenza
- Ebola virus*
- SARS CoV-2^
- HIV
- Tuberculosis*
- Salmonella
- AMR bacteria

Vector control

- Japanese encephalitis virus*
- Dengue virus
- Yellow fever virus*
- West Nile Virus*
- Zika virus
- Alphaviruses* ^

Non-pharmaceutical

- SARS Co-V2^
- Respiratory Syncytial Virus
- Astrovirus
- Enterovirus
- Norovirus
- Parainfluenza virus
- Seasonal Coronavirus
- Salmonella
- E. coli (EHEC O157:H7)

Pandemic potential

- Other filiovirus *
- Henipahviruses * ^
- Nairoviruses
- Phleboviruses * ^
- Arenaviruses * ^
- MERS ^
- Picornoviruses
- Hantaviruses
- Influenza C virus

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Unique pathogens / pathogen-groupings

Pathogens appearing in more than one grouping

* Potential BSL 3 or above requirement

^ CEPI priority pathogen list