# ANTIMICROBIAL RESISTANCE CASE STUDY

*SOUTH & SOUTHEAST ASIA*

*PATHOGEN GENOMICS PRIORITIZATION & IMPLEMENTATION WORKSHOP*

*September 9-13, 2024*
*Bangkok, Thailand*

WORKSHOP PARTNERS

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

DukeNUS Medical School
Asia Pathogen Genomics Initiative

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)

# Learning Objectives

- Identify utility of pathogen genomics for antimicrobial resistance (AMR)
- Explore approaches to implementing pathogen genomics for surveillance & investigation of AMR priority pathogens
- Explore how setting specific factors can be considered when implementing pathogen genomics for AMR

# Outline

- Background Information (~15 mins):
  - Uses of genomics for AMR
  - Examples from the literature
  - Considerations for implementation
- Interactive case study (~70 mins):
  - Scenario introduction
  - Investigation of an emerging AMR threat
  - Surveillance of AMR priority pathogens
- Summary (5 mins)

# Threat of AMR

- Infections with resistant bacteria are associated with:
  - Longer hospital stays
  - Increased treatment costs, often with increased side effects
  - Increased illness and death
- Considerable health and economic impacts:
  - In 2019, 1.27 million deaths (95% UI 0·911–1·71) attributable to AMR
  - Costs expected to exceed $1 trillion annually after 2030
- Asia Pacific is a hot spot for AMR emergence & impact

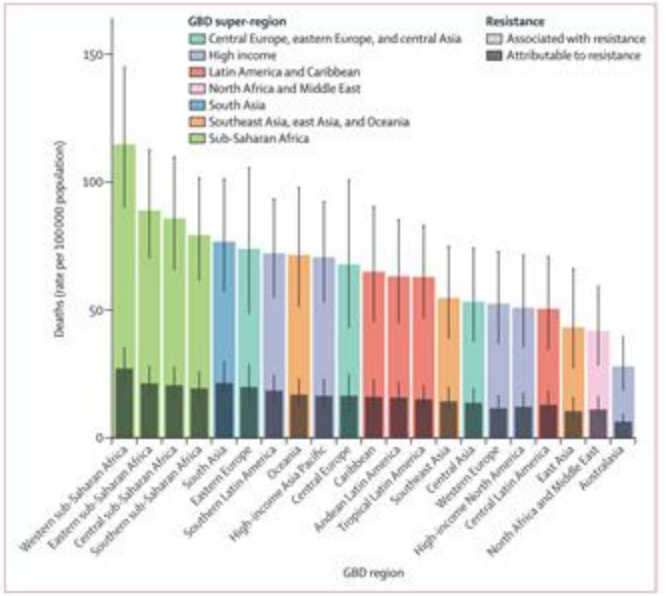
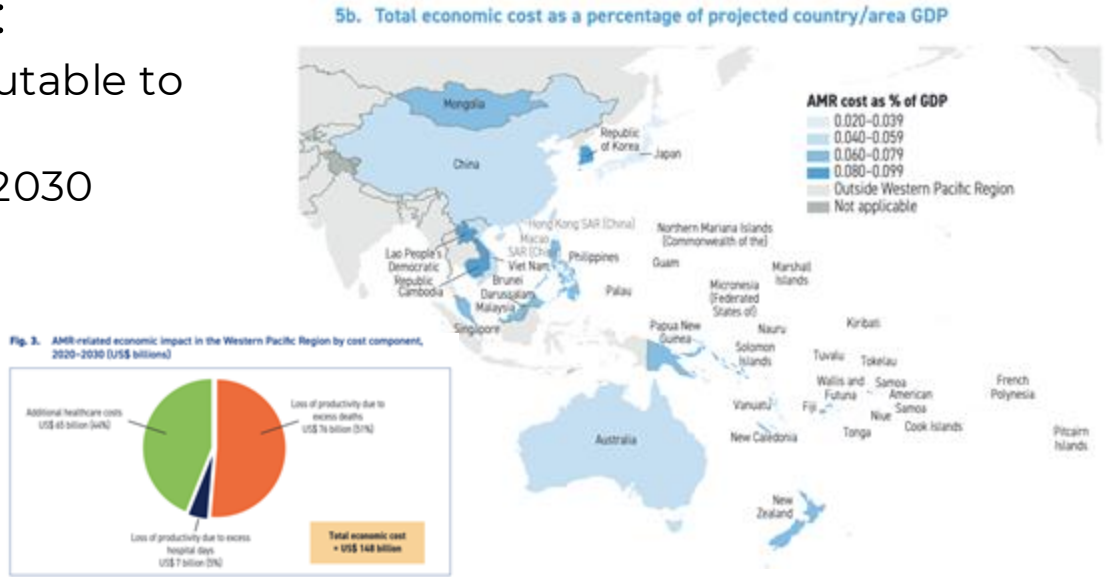



*Figure 2:* **All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019**
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Source: 10.1016/S0140-6736(21)02724-0

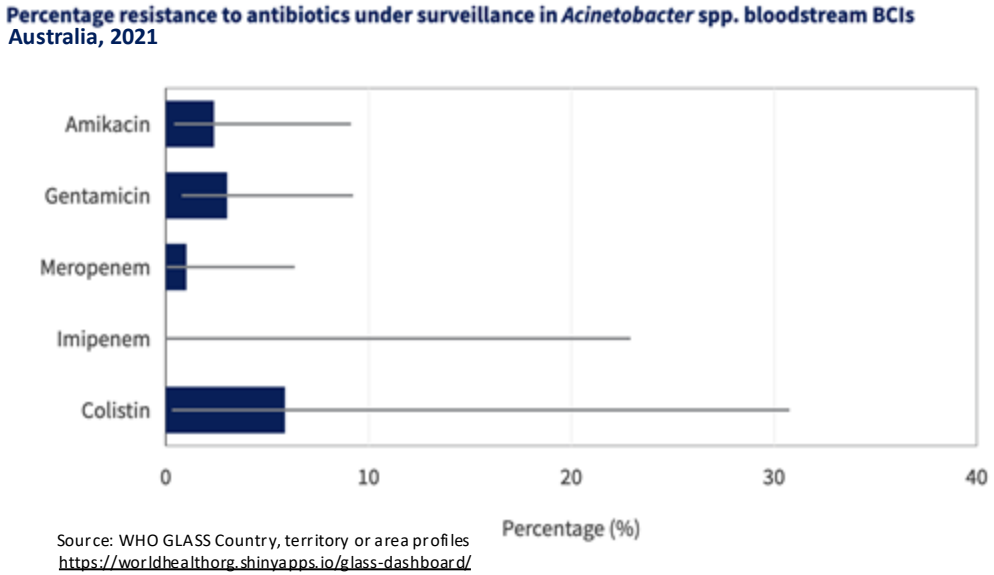



Source: https://www.who.int/publications/i/item/9789290620112

# AMR Surveillance

- Not a single pathogen, transmission route, setting
- “Layered & connected” surveillance approaches
  - Often integrated into other, existing surveillance systems

Passive isolate/sample surveillance, with denominator data (often sentinel)

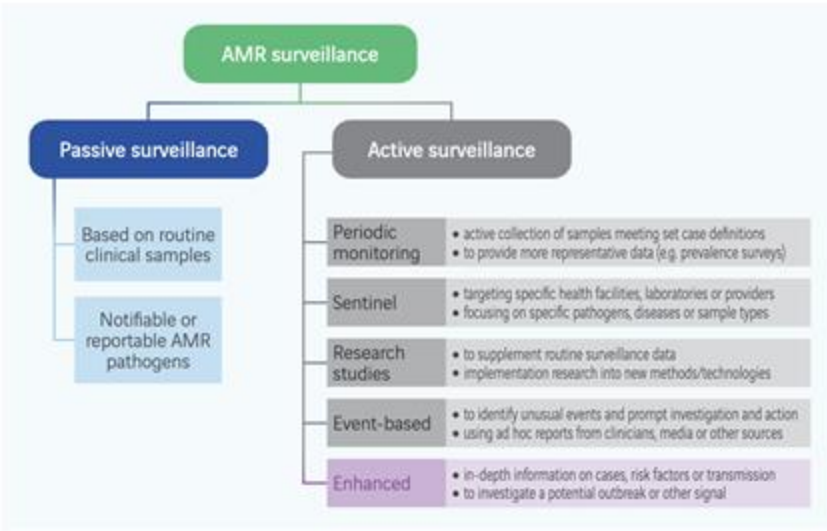



Source: WHO GLASS Country, territory or area profiles
https://worldhealthorg.shinyapps.io/glass-dashboard/

Case-based surveillance of priority AMR pathogens


Source: https://www.who.int/publications/i/item/9789240093461

Supplemented by others




Source: https://www.who.int/publications/i/item/9789290620365

# Uses of Pathogen Genomics for AMR

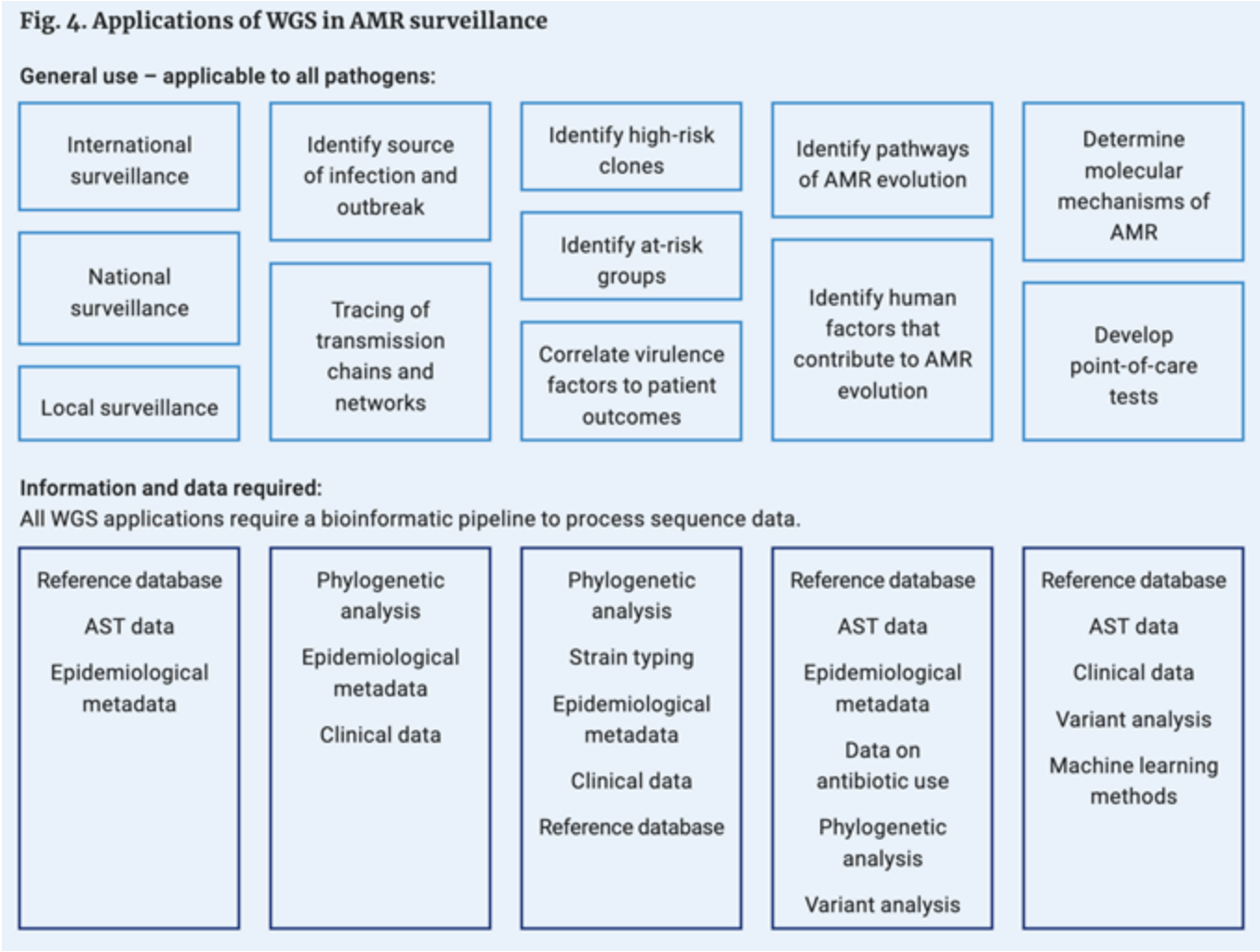
GLASS
Whole-genome sequencing for surveillance of antimicrobial resistance

Global Antimicrobial Resistance and Use Surveillance System (GLASS)

World Health Organization

Source: https://www.who.int/publications/i/item/9789240011007

**Fig. 4. Applications of WGS in AMR surveillance**



# Uses of Pathogen Genomics for AMR

Adapted from:


& Baker *et. al* 10.1186/1471-2458-10-332

*Selected objectives using pathogen genomics*

**Public health investigation**

Reactive investigation in response to event

- Support/refute source of infection(s) & outbreaks
- Tracing of transmission chains and networks

**Surveillance**

Systematic, ongoing collection of data on pathogen or syndrome

Control-focused

- Detect cases & outbreaks of priority AMR pathogens
- Identify high-risk clones & at-risk groups

Strategy-focused

- Monitor circulating resistance mechanisms & strains
- Investigate pathogen factors associated with severity, outcome & transmissibility

**Research**

Targeted data to drive knowledge

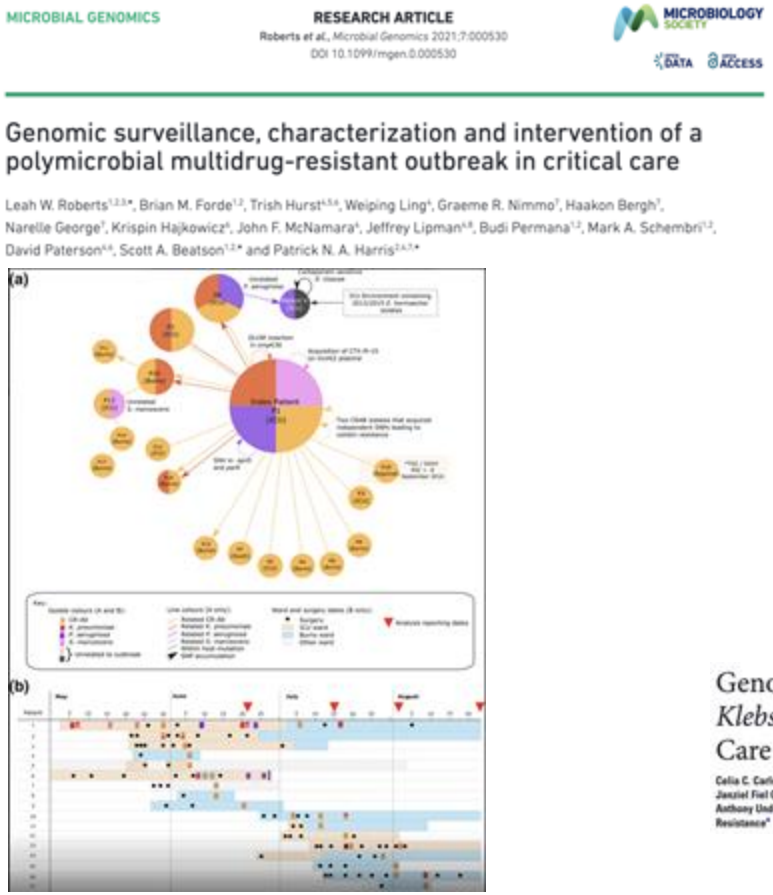
- Identify pathways & drivers of AMR evolution
- Characterise new mechanisms of resistance
- Develop point of care tests

Inform direct control measures

Inform prevention, treatment & other policies

# Examples: Investigation

- Support/refute source of infection(s) & outbreaks
- Tracing of transmission chains and networks





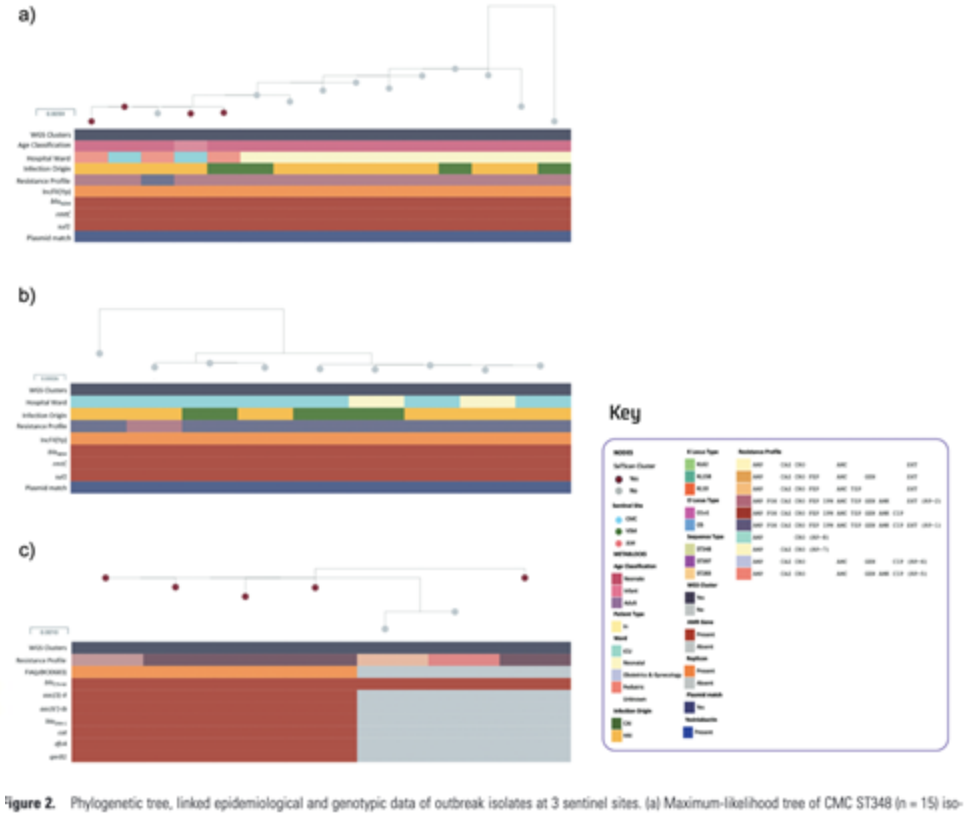



Figure 2. Phylogenetic tree, linked epidemiological and genotypic data of outbreak isolates at 3 sentinel sites. (a) Maximum-likelihood tree of CMC ST348 (n = 15) iso-

# Examples: Surveillance

- Detect cases & outbreaks of priority AMR pathogens

**Genomic characterisation of multidrug-resistant *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* in two intensive care units in Hanoi, Viet Nam: a prospective observational cohort study**

Leah W Roberts, Le Thi Hoi, Fahad A Khokhar, Nguyen Thi Hoa, Tran Van Giang, Cuong Bui, Tran Hai Ninh, Dao Xuan Co, Nguyen Gia Binh, Hoang Bao Long, Dang Thi Huong, James E Bryan, Archie Herrick, Theresa Fothwell, Behzad Nadjm, H Rogier van Doorn, Julian Parkhill, Nguyen Vu Trung, Nguyen Van Kinh, Zamin Iqbal*, M Estée Török*

**Summary**

**Background** Viet Nam has high rates of antimicrobial resistance (AMR) but little capacity for genomic surveillance. This study used whole genome sequencing to examine the prevalence and transmission of three key AMR pathogens in two intensive care units (ICUs) in Hanoi, Viet Nam.

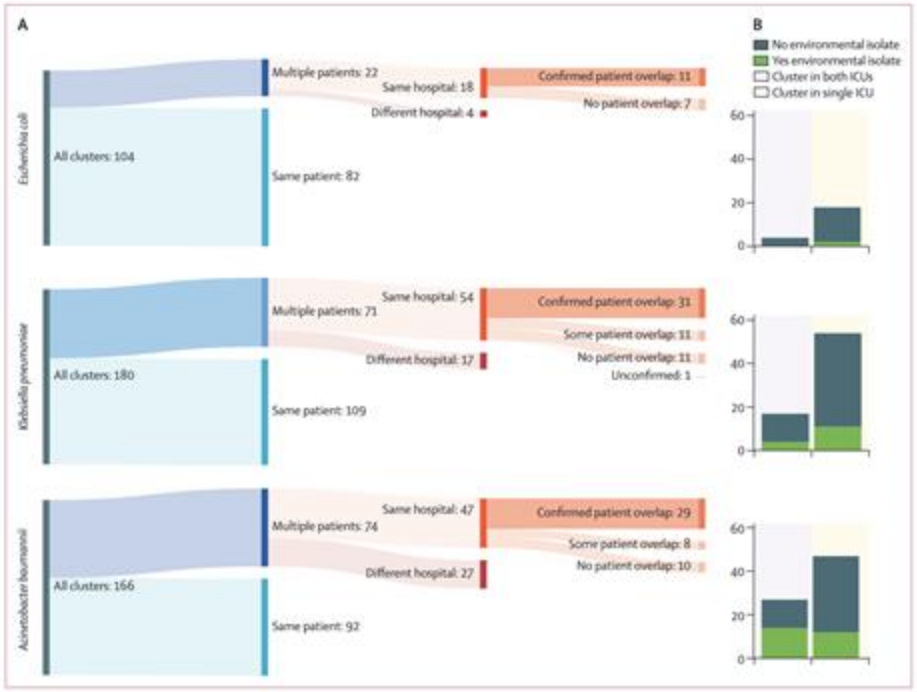


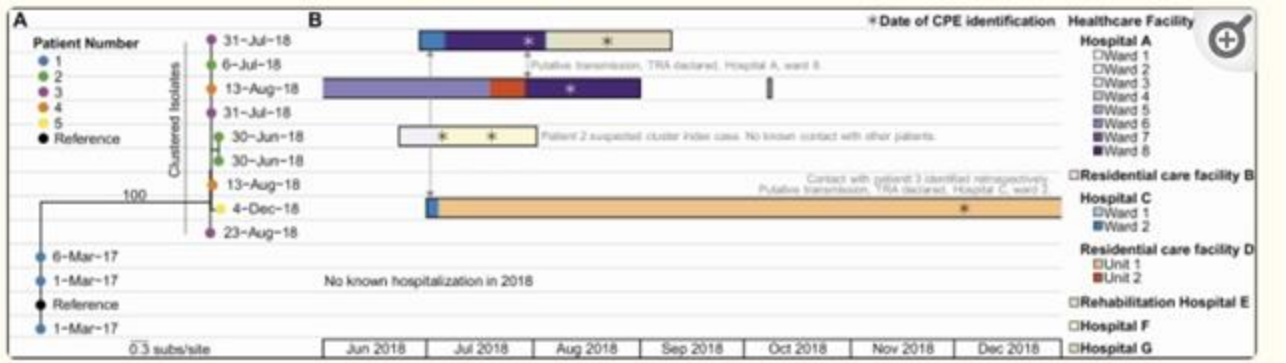

***Figure 3*: Summary of zero SNP clusters in all species**

(A) Clusters were defined as multiple patients (samples were derived from at least two different patients) or same patient (isolates were derived from the same patient, or only a single patient and the environment). Epidemiological evidence to support clusters was defined as confirmed patient overlap (all patient ICU stays overlap with another in the same cluster), some patient overlap (at least two patient ICU stays overlap), and zero patient overlap between all patients in cluster. (B) Environmental isolates in clusters were counted if an environmental isolate was found in that cluster. SNP=single nucleotide polymorphism. ICU=intensive care unit.

*Clinical Infectious Diseases*

MAJOR ARTICLE

**Search and Contain: Impact of an Integrated Genomic and Epidemiological Surveillance and Response Program for Control of Carbapenemase-producing *Enterobacterales***




*Clinical Infectious Diseases*

MAJOR ARTICLE

Clinical Implementation of Routine Whole-genome Sequencing for Hospital Infection Control of Multi-drug Resistant Pathogens

**Multi-site implementation of whole genome sequencing for hospital infection control: A prospective genomic epidemiological analysis**

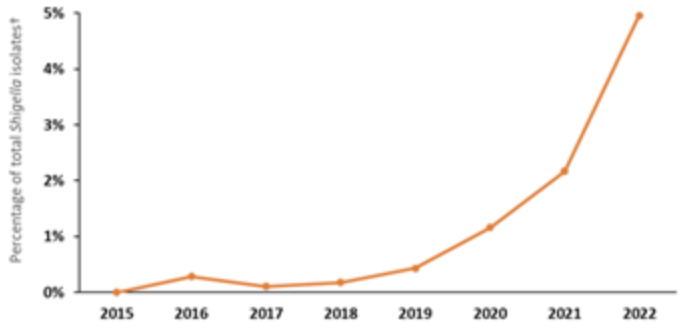
Building a genomic framework for prospective MRSA surveillance in the United Kingdom and the Republic of Ireland

Sandra Reuter,[1,2] M. Estée Török,[1,3,4] Matthew T.G. Holden,[2,5] Rosy Reynolds,[6,7] Kathy E. Raven,[1] Beth Blane,[1] Tjibbe Donker,[8] Stephen D. Bentley,[2] David M. Aanensen,[9] Hajo Grundmann,[8,10] Edward J. Feil,[11] Brian G. Spratt,[9] Julian Parkhill,[2] and Sharon J. Peacock[1,2,3,4,12]

# Examples: Surveillance

- Identify high risk clones & at-risk groups

Figure: Percentage of *Shigella* isolates that showed an extensively drug resistant (XDR)* phenotype or genotype in the United States, by year, 2015–2022†




Increase in Extensively Drug-Resistant Shigellosis in the United States

Print

HAN

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
February 24, 2023, 11:30 AM ET
CDCHAN-00486


Figure 2. Countries in the WHO European Region which have reported extensively drug-resistant *Shigella sonnei* in 2020-2022 as of 17 March 2022


nature communications

Article

https://doi.org/10.1038/s41467-023-37672-w

## The evolution and international spread of extensively drug resistant *Shigella sonnei*


Received: 12 September 2022

Accepted: 24 March 2023

Published online: 08 April 2023

Check for updates



Lewis C. E. Mason[1,2], David R. Greig[3], Lauren A. Cowley[4], Sally R. Partridge[5,6,7,8], Elena Martinez[7,9], Grace A. Blackwell[7,9], Charlotte E. Chong[2], P. Malaka De Silva[2], Rebecca J. Bengtsson[2], Jenny L. Draper[7,9], Andrew N. Ginn[7,8,9,10], Indy Sandaradura[6,7,9], Eby M. Sim[5,6,8], Jonathan R. Iredell[5,6,7,8], Vitali Sintchenko[5,6,7,8,9,11], Danielle J. Ingle[12], Benjamin P. Howden[12], Sophie Lefèvre[13], Elisabeth Njamkepo[13], François-Xavier Weill[13], Pieter-Jan Ceyssens[14], Claire Jenkins[3] & Kate S. Baker[1,2]

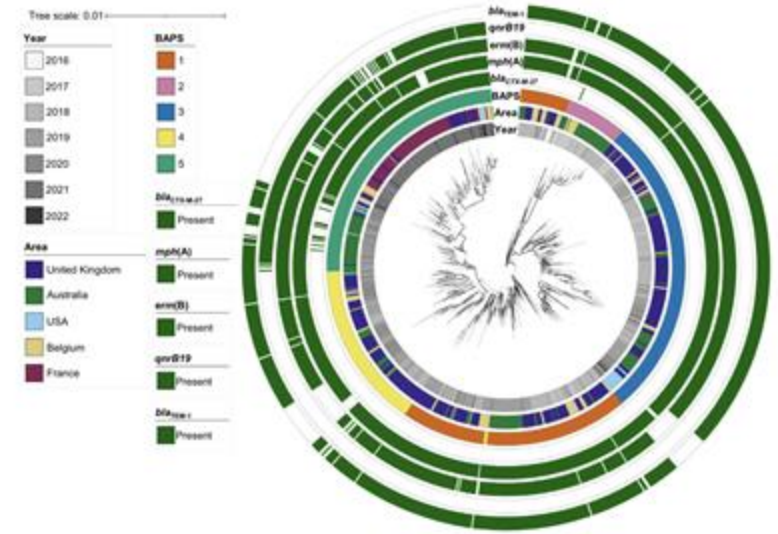




**Fig. 2 | The evolution and international spread of MSM-associated XDR *S. sonnei*.** A midpoint rooted maximum likelihood phylogenetic tree shows the distribution of UK isolates (belonging to both CipR.MSM5 and the t10,377 outbreak cluster, $n = 468$) and relevant related international isolates belonging to CipR.MSM5 (Supplementary Fig. 1, $n = 475$). Metadata tracks show year and country (area) of isolation, BAPS subtype, and the presence of selected AMR genes according to the inlaid keys. The scalebar is provided by IQTree, and represents expected number of substitutions per site across a 1717 bp alignment. Bold branches represent a bootstrap value of ≥ 70 out of 100.

# Examples: Surveillance

- Monitor circulating resistance mechanisms & strains

## Bacterial Genomics for National Antimicrobial Resistance Surveillance in Cambodia

Christina Yek,[1,2,✉] Chanthap Lon,[1] Sophana Chea,[1,✉] Sreyngim Lay,[1] Meng Heng Oum,[1] Gechlang Tang,[1] Chansothea Lon,[1] Andrea R. Pacheco,[1] Ian Drobish,[3] Reagan Stuehser,[1] Sokna Ly,[1] Ratanak Sath,[1] Malin Srouen,[4] Chamrouen Bin,[5] Chanthou Chak,[6] Sosorphea Seang,[6] Viso Srey,[7] Bunna Chhor,[7] Somary Nhem,[8] Sivhour Chiek,[9] Rina Dork,[9] John P. Dekker,[10] Heng Seng,[11] Sidonn Krang,[11] Sovann Ly,[11] and Jessica E. Manning[1,2,✉]

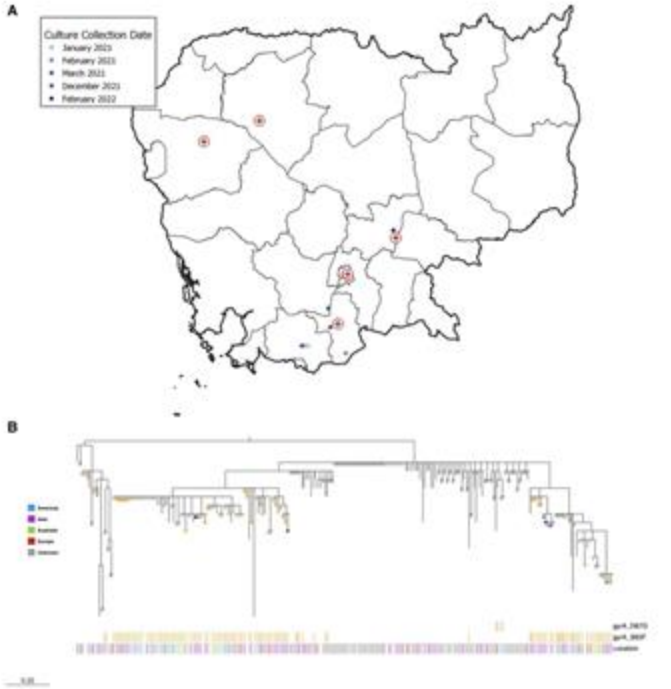


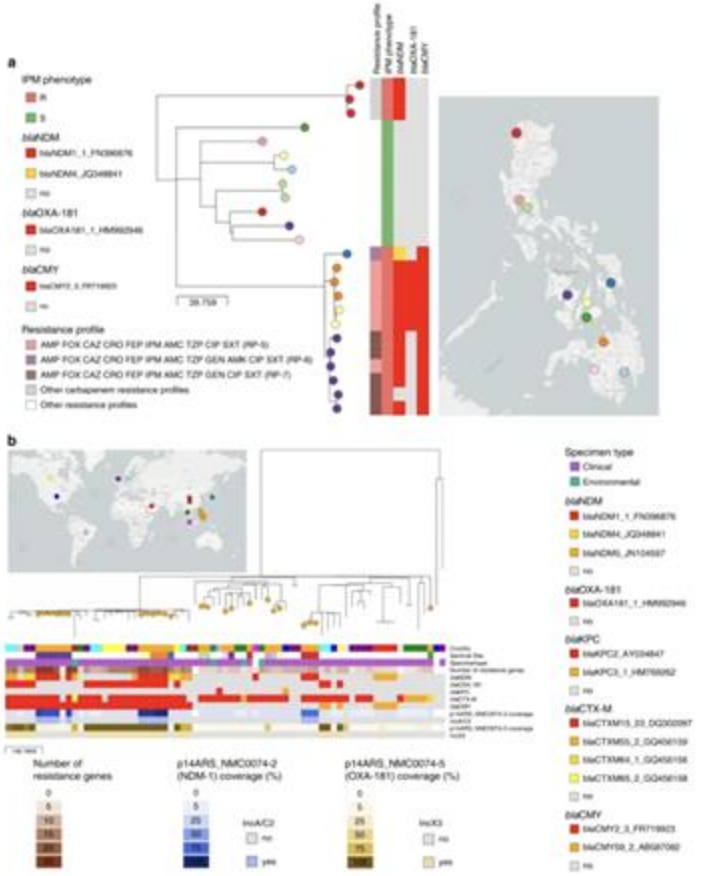

**Figure 3.** *A*, Geographic map of 7 *Salmonella enterica* serovar Paratyphi A isolates collected across 6 Cambodian hospitals, denoted by a red cross within a red bordered circle. Filled circles denote individual cases, with fill color scaled by date of sample collection (ranging from 3 January 2021 to 21 February 2022). *B*, Phylogenetic tree of all 7 *S. enterica* serovar Paratyphi A isolates in this cohort and closely related isolates (<25 allelic difference) in the Pathogen Detection repository, reconstructed from single-nucleotide polymorphisms within whole-genome multilocus sequence type clusters using maximum compatibility criteria. Branch ends indicate individual genomes, with the 7 cohort isolates denoted by circles with blue-purple spectrum fill colors corresponding to the time scale (legend shown alongside geographic map). Other isolates within the cluster are represented by orange filled circles (if from Cambodia) and unlabeled branch ends (other locations). Metadata bars indicate presence (orange) of gyrase A mutations gyrA-D87G and gyrA-S83F, along with reported isolate location.

## Integrating whole-genome sequencing within the National Antimicrobial Resistance Surveillance Program in the Philippines

Silvia Argimón, Melissa A. L. Masim, June M. Gayeta, Marietta L. Lagrada, Polle K. V. Macaranas, Victoria Cohen, Marilyn T. Limas, Holly O. Espiritu, Janziel C. Palarca, Jeremiah Chilam, Manuel C. Jamoralin Jr., Alfred S. Villamin, Janice B. Borlasa, Agnettah M. Olorosa, Lara F. T. Hernandez, Karis D. Boehme, Benjamin Jeffrey, Khalil Abudahab, Charmian M. Hufano, Sonia B. Sia, John Stelling, Matthew T. G. Holden, David M. Aanensen ✉ & Celia C. Carlos ✉

Nature Communications 11, Article number: 2719 (2020) | Cite this article

**Fig. 6: Phylogeographic analysis of *E. coli* ST410 from the Philippines.**




**a** Phylogenetic tree and linked epidemiological and genotypic data of 24 retrospective ST410 genomes. The imipenem (IPM) phenotype was either resistant (R) or susceptible (S). The three-letter

# Examples: Research

- Characterise new mechanisms of resistance

**Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study**

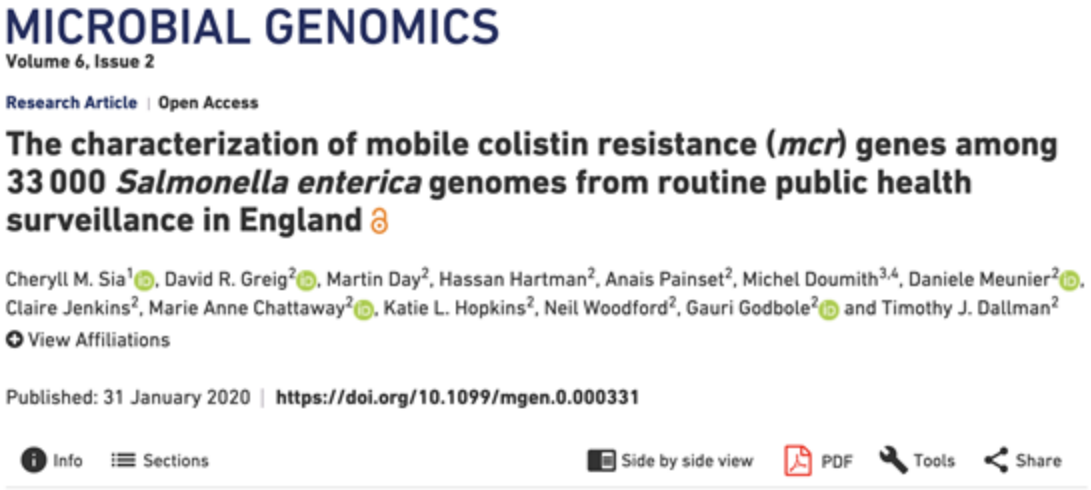
Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

**Summary**

**Background** Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Lancet Infect Dis 2015
Published Online
November 18, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00424-7
See Online/Articles
http://dx.doi.org/10.1016/

And rapidly screen for them….



MICROBIAL GENOMICS
Volume 6, Issue 2
Research Article | Open Access

**The characterization of mobile colistin resistance (*mcr*) genes among 33 000 *Salmonella enterica* genomes from routine public health surveillance in England**

Cheryll M. Sia[1], David R. Greig[2], Martin Day[2], Hassan Hartman[2], Anais Painset[2], Michel Doumith[3,4], Daniele Meunier[2], Claire Jenkins[2], Marie Anne Chattaway[2], Katie L. Hopkins[2], Neil Woodford[2], Gauri Godbole[2] and Timothy J. Dallman[2]
View Affiliations

Published: 31 January 2020 | https://doi.org/10.1099/mgen.0.000331

Info Sections Side by side view PDF Tools Share

# Particular considerations for AMR

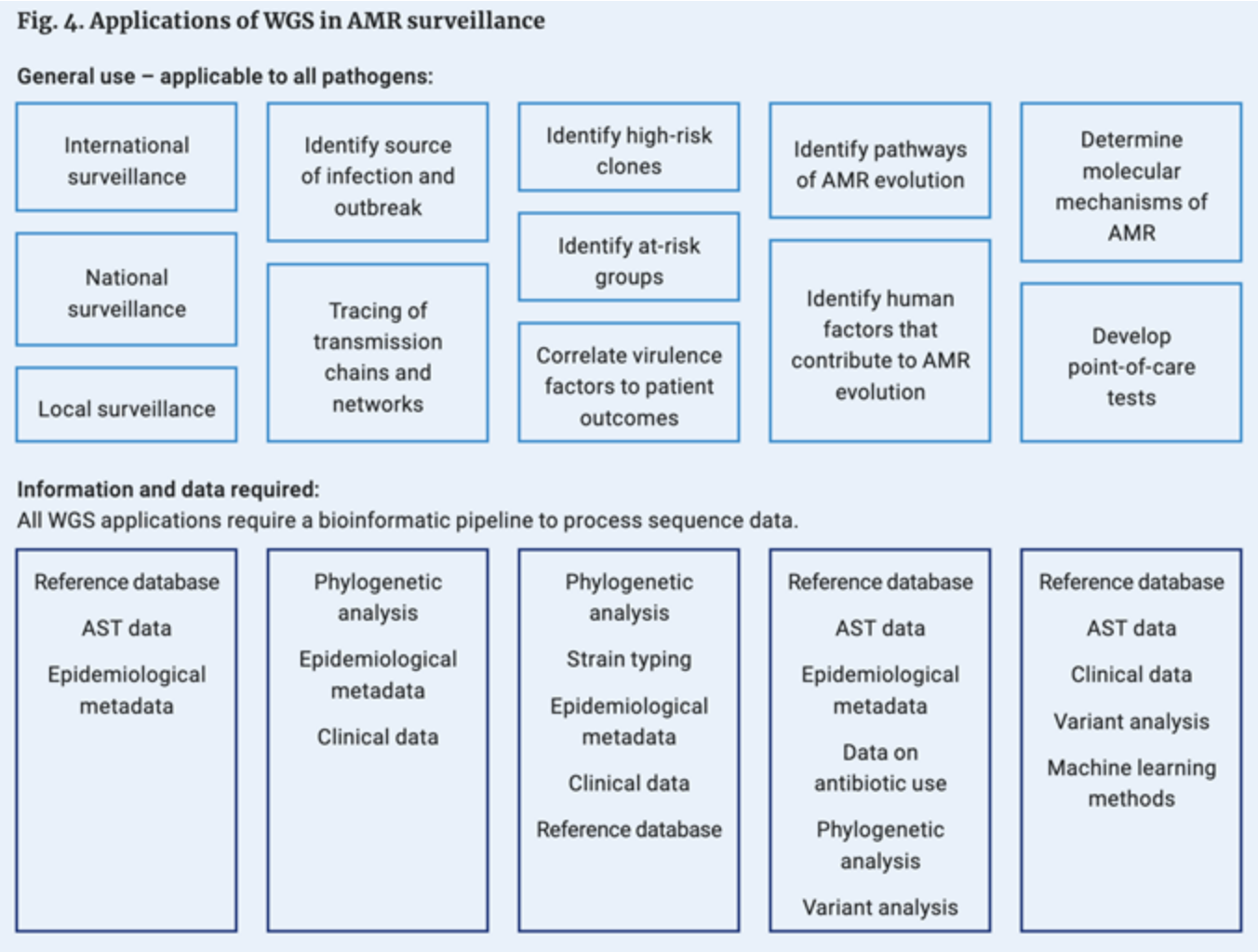
- Multi-pathogen, multi-layered
  - Multiple pathogens, transmission routes, settings
- Often intersects with other surveillance systems
  - Sentinel AMR surveillance, notifiable diseases
- Complex governance
  - Can sit across clinical/HAI surveillance & public health
  - One health
- Complex responses
  - Hospital infection control & Public health
- Interpretation can be complicated by long term colonisation

# Requirements for WGS in AMR surveillance

GLASS
Whole-genome sequencing for surveillance of antimicrobial resistance

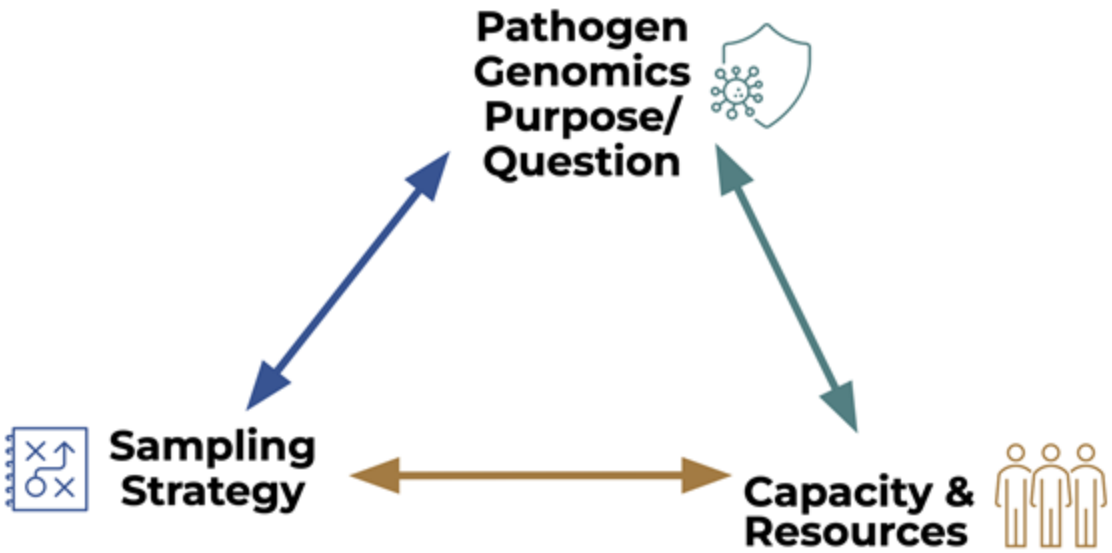
Global Antimicrobial Resistance and Use Surveillance System (GLASS)

World Health Organization




- Integration with other data:
  - Phenotypic AST
  - Epidemiological
  - Clinical
- Reference databases
- Accredited pipelines

# Recap: Sampling



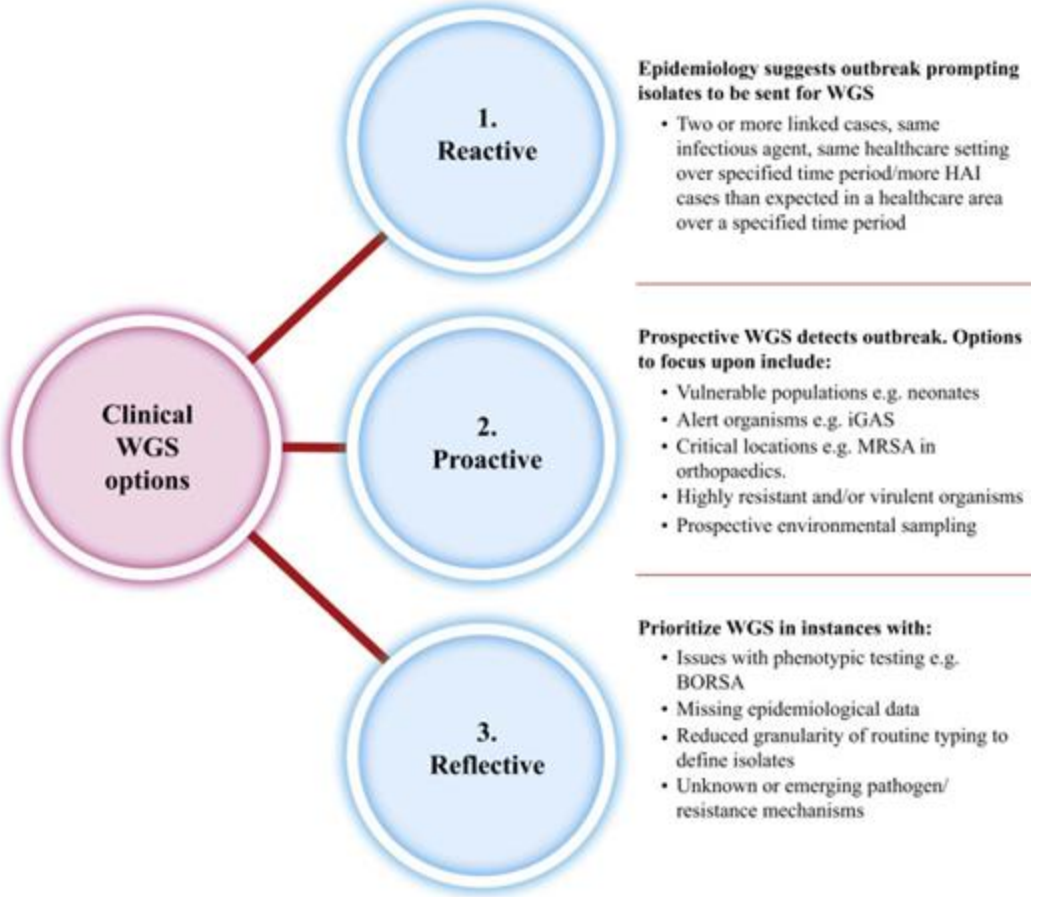




Figure 3. Recommendations for using whole-genome sequencing (WGS) for the detection of nosocomial outbreaks. HAI, hospital-acquired infection; MRSA, meticillin-resistant *Staphylococcus aureus*; BORSA, borderline oxacillin-resistant *S. aureus*.

Source: 10.1016/ j.jhin.2020.11.001

# INTERACTIVE CASE STUDY

# Interactive case study

Three parts:

| | |
|---|---|
| Part 1 (10 mins) | Scenario Introduction |
| Part 2 (25 mins) | An emerging AMR threat: Investigation & response |
| Part 3 (35 mins) | What now? Surveillance & monitoring |

Two settings:

- Country A: Moderate genomics capacity
- Country B: High genomics capacity

# Instructions

- Your group has been allocated a hypothetical country (A or B)
  - Odd number groups – Country A
  - Even number groups – Country B

- Slides will be quite dense with information - you may want to refer back (don't read ahead!)
- A page of additional details about your country has been provided in the online materials

- You will be presented with questions to discuss among the group
- Facilitators will guide the discussion

- Nominate a group member to:
  - take notes on butchers paper
  - report back to the wider group

# Scenario Settings

| Setting | Country A | Country B |
|---|---|---|
| Sequencing capacity | Moderate<br>• Some sequencing for COVID-19<br>• Fragmentation of sequence data across labs<br>• Limited dedicated staff/expertise<br>• Dedicated resourcing for scale up<br>• Strong partner support | High<br>• Comprehensive sequencing across a range of pathogens<br>• Extensive local expertise<br>• Integration of genomics into surveillance & response plans, decision making |
| Governance | • Notifiable disease legislation, but not AMR priority pathogens<br>• Limited supporting instruments | • Notifiable disease legislation, but not AMR priority pathogens<br>• Supported by data sharing agreements, surveillance & response guidelines, & genomics strategies |
| Response capacity | • Dedicated infection control and rapid response teams<br>• Limitations in the built environment (few isolation rooms) | • Dedicated infection control and rapid response teams<br>• Sufficient capacity for isolation, contact precaution & screening |

**Familiarise yourself with the additional information about your setting**

# Scenario: An emerging AMR threat

Staff in your country's largest hospital have called to report a rapid rise in the number of Carbapenem-resistant *Acinetobacter* (CR-Ab) bacteria.

A quick literature review identifies the following facts about CR-Ab:

- Carbapenem resistance is associated with a range of acquired resistance genes
- CR-Ab is a "critical" AMR priority pathogen, associated with increased mortality, length of hospital stay & treatment costs
- Most reported outbreaks have been in hospitals, particularly ICU
- Person-to-person transmission & contaminated hospital environments have been implicated
- Transmission can be reduced using infection control interventions
- Patients can have prolonged asymptomatic carriage & colonised people can be infectious, complicating investigation & control

You call other local hospitals and many report either cases or outbreaks of CR-Ab.

You decide an investigation may be warranted.

**During your literature review, you noted many investigations used pathogen genomics, and wonder if you should too.**

**Discuss in your group: What questions might genomics help you answer? (5 mins)**

# Investigating a Suspected CR-Ab Outbreak

You decide to go ahead with a national investigation into CR-Ab.

You want to know:

- Is there local transmission of CR-Ab?
- If so, what are the settings and extent of transmission?
- Are there any opportunities for intervention?

After hearing such fantastic applications of pathogen genomics, you have decided to use it to help answer these questions.

**Thinking about your setting, discuss in your group (15 mins):**

1. What do you need to consider before starting?
    - Think about enablers & barriers
2. What data do you want to collect and why?
3. What samples would you sequence and why?
4. What types of analyses might you consider?

Please take notes to report back.

# What You Found

You conducted a timely and comprehensive outbreak investigation, but unfortunately what you discovered isn't great news.

It appears that there has been undetected spread of CR-Ab within and between hospitals in your country.

You now know also know that:

| Country A | Country B |
|---|---|
| • Screening has revealed a high prevalence of CR-Ab<br>• You have environmental contamination across multiple hospitals<br>• Treatment is complicated by lack of access to appropriate antimicrobials & extended AST, leading to delayed treatment & increased mortality<br>• Availability of epi data is limited | • Screening has revealed a relatively low overall prevalence of CR-Ab<br>• Importation events appear very frequent<br>• Hospitalisation history & genomic data revealed colonised patients are driving unrecognized spread<br>• Environmental contamination appears limited<br>• Many sequences had no known resistance mechanisms |

# What now?

You have reported your findings to all stakeholders, and there is now significant pressure to implement ongoing surveillance & response for CR-Ab in your country.

You have been tasked with designing CR-Ab surveillance that is appropriate to your setting.

**In your group, outline how surveillance for CR-Ab could be implemented, with a particular focus on (30 mins):**

1. What would be the key objectives of CR-Ab surveillance?
2. Would you incorporate genomics into your system, and if so, how & why?
3. How would it interact with existing surveillance systems?
4. What are the data and sample flows?
5. What are the key challenges you would need to address?

Please take notes to report back.

# Back to the real world

Now that you have provided such a comprehensive and sustainable genomic surveillance system for your hypothetical country, let's bring it back to the real world.

In your groups, discuss:

- If you have AMR priority pathogen surveillance in your country, how is it similar or different to your hypothetical example?
- What additional factors are present in your country that weren't in the two we discussed?

Complete the pathogen prioritization tool CR-Ab for your country:

- Much is context specific, but may be tricky due to limited information in many settings
- The 2024 AMR priority pathogens list may help for global data: https://www.who.int/publications/i/item/9789240093461

# Summary

- AMR surveillance needs layered & connected surveillance approaches
- Genomics for AMR incorporates almost all use cases
  - due to multiple pathogens, transmission routes & settings
- Surveillance of priority AMR pathogens in hospital settings is a common use of genomics for AMR
  - due to impact, sample availability & difficulties with traditional epidemiological investigation
- As always, genomic utility is informed by surveillance objectives, capacity & resourcing
  - for AMR often must consider capacity for response across infection control and public health

# THANK YOU!

WORKSHOP PARTNERS

CDC
U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

DukeNUS Medical School
Asia Pathogen Genomics Initiative

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)