Applying genomics to outbreak investigations

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Outline

• Using genomics in outbreak investigations:
  • One Health investigations
  • Investigating outbreaks of resistant pathogens
  • Emerging outbreaks
• Implementing WGS into Public Health Microbiology
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An outbreak of livestock-associated MRSA
Livestock-associated MRSA

- Livestock, most notably swine, poultry and veal calves, can act as reservoirs of MRSA
- The most commonly reported LA-MRSA strains are those that belong to clonal complex 398 (CC398)
- First reported in the Netherlands in 2003 with spread across Europe
- Highest incidence in countries with industrial pig production

Rapid Communications

Detection of livestock-associated meticillin-resistant Staphylococcus aureus CC398 in retail pork, United Kingdom, February 2015

Emergence and molecular characterization of clonal complex 398 (CC398) methicillin-resistant Staphylococcus aureus (MRSA) in New Zealand

- June 2013: 9 patients with CC398 MRSA infection
CC398 MRSA in NZ, 2016

- 36 patients with CC398 MRSA
- 23 patients from the South Island of NZ (Canterbury; Otago)
- 14/23 cases from South Island pig farmers / dairy workers / abbatoir workers
- Questions:
  - Is there an outbreak of CC398 MRSA in the South Island, or multiple introductions of this clone?
  - Where did this clone come from, and how is it spreading?

Global phylogeny of CC398

Microbial Genomics, 2017
Spatiotemporal and cross-species evolutionary origins of CC398 *S. aureus*

- A phylogenetic reconstruction of the NZ CC398 lineage, and the global CC398 collection was performed
- Parameters used:
  - **Geographic region** (NZ, UK, Western Europe, Eastern Europe, North America, South America, and China)
  - **Host** (human, pig, cattle, horse, and turkey)

*Microbial Genomics, 2017*
CC398 in NZ

- A distinct clade of CC398 MRSA was circulating in humans in the South Island of NZ
- Resembles LA CC398 MRSA from animals in other settings
- Strong epidemiological association with pigs / rural location
- There have also been multiple introductions of CC398 into NZ
- Would not have been identified using ‘conventional’ typing

A sustained outbreak of multi-resistant *Staphylococcus capitis* in a neonatal care unit

James Ussher
Glen Carter
Anders Gonçalves Da Silva
Sarah Baines
Background

- *S. capitis* has emerged as an important opportunistic neonatal pathogen
- Sustained outbreak in Dunedin NICU despite intensive infection control interventions (screening; decolonisation; contact precautions)
- Jan 2007 – July 2016: 40 /127 (34%) CoNS bloodstream infections
- Isolates typed by PFGE:
  - Pulsotype most similar to globally disseminated NCRS-A clone, but emergence and evolution poorly understood

Wide geographical dissemination of the multiresistant *Staphylococcus capitis* NRCS-A clone in neonatal intensive-care units

M. Butin\(^1,2,3\), J-P. Rasigade\(^1,2,3\), P. Martim-Simões\(^1,2,3\), H. Meugnier\(^1,2\), H. Lemire\(^3\), R. V. Goering\(^4\), A. Keane\(^5\), M. A. Deighton\(^6\), O. Denis\(^6\), A. Brahimi\(^6\), O. Claris\(^6,7\), F. Vandenesch\(^2,3,4\), J-C. Picaud\(^2,3,4\) and F. Laurent\(^1,2,3,4\)

Worldwide Endemicity of a Multidrug-Resistant *Staphylococcus capitis* Clone Involved in Neonatal Sepsis

Marine Butin, Patricia Martins-Simões, Jean-Philippe Rasigade, Jean-Charles Picaud, Frédéric Laurent

EID, 2016
140 isolates (115 NZ; 25 international)

Two major groups

Group 1

Dunedin NICU bloodstream isolates (outbreak group)

Environmental isolates (stethoscopes; incubators)

International NICU isolates

Group 2

Dunedin NICU staff screening isolates

The core genome of NZ *S. capitis* is similar to other NICU-associated *S. capitis*
Local adaptation and accessory genome differences

- NICU-associated NZ S. capitis has undergone local adaptation
- Majority of NZ NICU blood and environmental isolates harbour fusB, qacA, blaZ andaadD on a ~28kb plasmid

Chlorhexidine
Fusidic acid

- Genomics provided insights far beyond conventional typing methods
- Plausible that NICU clone disseminated by HCW movement or point-source outbreak of contaminated medical devices
- Subsequent local adaptation and microevolution
- Genomic analyses informed subsequent work investigating phenotypic traits of this clone
AMR and public health

- Recognition of AMR as a public health issue
- ‘Public Health’ genomics increasingly applied to outbreak investigations (and surveillance) of antimicrobial-resistant pathogens

Antimicrobial Stewardship and Infection Control:
Limiting the burden of antimicrobial resistance in New Zealand

New Zealand College of Public Health Medicine Policy Statement

Policy statement
The New Zealand College of Public Health Medicine (NZCPHM) recognises that antimicrobial resistance (AMR) is an increasing health threat of significance, both globally and to New Zealand.

NZCPHM Antimicrobial Resistance Policy Statement | August 2016

- Routine genomics for characterisation of CPE isolates in Victoria
- Contributes to decisions regarding determination of risk status and interventions
- Newly established Antimicrobial Reference and Research Unit within MDU
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Mycobacterium chimaera and cardiac surgery infections
**Mycobacterium chimaera** and cardiac surgery infections

- Recent studies have reported patients with post-cardiac surgery infections due to a non-tuberculious mycobacterial (NTM) species, *Mycobacterium chimaera*.
- Infections publicly reported in at least seven different countries, including Australia (five patients).
- All infected patients had undergone cardiac bypass using heater-cooler units (HCUs) produced by a single manufacturer.
- Epidemiological investigation suggested a single point-source contamination.

*Sax et al., CID, 2016*
• 48 presumptive *M. chimaera* isolates were obtained from four states in Australia and five sites in NZ
• 43 from HCUs (from the same manufacturer), and five patient samples
Global phylogeny of *M. chimaera*

Note: branch lengths transformed
• Genomic analysis provided (necessary) validation of an epidemiological association

• Highlighted requirement for:
  • Coordination nationally and internationally in multidisciplinary outbreaks
  • Rapid, collegial and actionable data sharing and dissemination
  • Allowed development of a rapid PCR assay
  • Ongoing application in environmental investigations and case classification
Outline

- What is public health microbiology?
- Using genomics to effect public health action:
  - Outbreak investigations
  - Tracking and reducing AMR
  - Applying genomics to source investigations
- Implementing WGS into Public Health Microbiology in Australia

Can we replace traditional methods with WGS?

- *Salmonella* spp.
- STEC
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Neisseria gonorrhoeae*
- *Legionella pneumophila*
- *Streptococcus pyogenes*

https://github.com/MDU-PHL
Communicable Diseases Genomics Network, Australia

- Recently established Communicable Diseases Genomics Network in Australia
- Provides nexus for national coordination of communicable diseases genomics
- Specific focus on:
  - Workforce training in communicable diseases genomics
  - Laboratory, analytical and reporting standardisation of genomics applied to public health microbiology
  - Phased implementation of national genomic surveillance
  - National framework for secure data access, storage and sharing

Recent initiatives

- Report to Commonwealth on challenges and opportunities related to communicable diseases genomics
- Data sharing pilot projects between PHLs
- Cross-disciplinary symposia (industry; epidemiologists; policy)
- Establishment of national genomic repositories, including high-quality reference genomes
- Planned workshop on implementation
Conclusions

- Genomic surveillance will transform infectious diseases epidemiology and public health microbiology
- The (quality) metadata is just as important as the (quality) sequence data
- Implementation challenges include:
  - Infrastructure / workforce (re)training / cost
  - Significant upskilling / resource required
  - Privacy / legal concerns
  - Accreditation and standardisation
  - Data sharing

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Biofilm formation differs by subspecies
A Model for Nationally Coordinated Genomic Data Flow