Whole genome sequencing to inform infection control practice

Dr Nick Brown
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The current situation: Outbreak identification and investigation

- Identification often (usually) relies on intuition rather than technology
- Simple lab methods remain most useful (colonial morphology, susceptibility patterns)
- Slow turn around time of typing techniques
- Current typing techniques have varying and often species-dependent ability to discriminate
The current situation: Whole genome sequencing

- Improvements in sequencing technology are reducing turn around time and cost
- Potential roles for WGS
  - Species identification and antimicrobial resistance;
  - Epidemiological typing;
  - (Early) identification of outbreaks;
  - Ruling out outbreaks
- Need to demonstrate how this can influence actions and improve outcomes
- Challenges for implementation
What is a single nucleotide polymorphism (SNP)?
What is a phylogenetic tree?

Slide: Ed Cartwright
The application of WGS to study MRSA reservoirs and transmission

Macro-epidemiology

- Inter-continental

- National

- Hospital-wide
  - Long SW et al. 2015. *mBio*.

- Household/community
  - Alam et al. 2015. *mBio*. (Household, USA300, USA).
  - Toleman MS et al. 2016 *JID*.

- Individual wards

- Targeted outbreak investigation

Micro-epidemiology
Rapid Whole-Genome Sequencing for Investigation of a Neonatal MRSA Outbreak


Köser CU et al. NEJM 2012; 366: 2267-75
Phylogenetic analysis

- Phylogenetic tree of 10 MRSA isolates and reference ST22 genome
- Seven outbreak isolates – six clustered closely together
- One outbreak isolate (6C) found to have a mutation in the $\textit{mutS}$ gene
- Three non-outbreak isolates (15C, 19B and 20B) were located distant from the outbreak cluster

Köser CU et al. NEJM 2012; 366: 2267-75
Whole-genome sequencing for analysis of an outbreak of meticillin-resistant Staphylococcus aureus: a descriptive study

Outbreak extended beyond the SCBU

New case and screening of staff members

Longitudinal genomic surveillance of MRSA in the UK reveals transmission patterns in hospitals and the community

Francesc Coll, Ewan M. Harrison, Michelle S. Toleman, Sandra Reuter, Kathy E. Raven, Beth Blane, Beverley Palmer, A. Ruth M. Kappeler, Nicholas M. Brown, M. Estée Török, Julian Parkhill, Sharon J. Peacock

12-month prospective observational cohort study (April 2012 - April 2013)

Samples processed by the Clinical Microbiology & Public Health Laboratory at the Cambridge University Hospitals NHS Foundation Trust.

3 hospitals and 75 GP practices in Cambridgeshire

Screening strategy:

All individuals screened for MRSA on admission to hospital and repeated weekly in critical care units.

Additional clinical specimens were taken as part of routine clinical care.

In the community, specimens were taken by GPs or community nursing teams for clinical purposes.

Study period
April 2012 – April 2013

Number of sequenced MRSA isolates (patients)
2345 (1465)

Source of MRSA isolate collection
Hospital A 1306 (890)
Hospital B 275 (187)
Hospital C 245 (179)
GP 457 (387)
EoE 62

Number of patients with MRSA

<table>
<thead>
<tr>
<th>Type</th>
<th>Hospitalised</th>
<th>Primary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>955</td>
<td>119</td>
</tr>
<tr>
<td>Clinical</td>
<td>120</td>
<td>232</td>
</tr>
<tr>
<td>Both</td>
<td>150</td>
<td>36</td>
</tr>
</tbody>
</table>
Methodology

Integration of genomic and epidemiological data

Legend:
- ● MRSA isolate from non-clustered patient
- □ MRSA isolate from clustered patient, no epidemiological links
- ● MRSA isolate from clustered patient, community-contact
- ○ MRSA isolate from clustered patient, ward-contact
- Purple Same hospital ward
- Gray Different hospital ward

Hospital-linked transmission chain:
- Pt1
- Pt2
- Pt3
- Pt4
- Pt5
- Pt6
- Pt7
- Pt8

Community-linked transmission chain:
- Pt1
- Pt2
- Pt3

Legend:
- ○ Negative MRSA screen
- House Community epidemiological contact
- Building Hospital epidemiological contact
- Cluster of MRSA isolates under 50 SNPs
- Community-linked transmission chain
- Hospital-linked transmission chain
## Epidemicological classification of cases

### Overall

<table>
<thead>
<tr>
<th>Epidemiological classification of cases</th>
<th>Overall</th>
<th>CC22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetically unrelated</td>
<td>680</td>
<td>462</td>
</tr>
<tr>
<td>Genetically clustered with other cases</td>
<td>785</td>
<td>578</td>
</tr>
<tr>
<td>Genetically clustered and epi contacts</td>
<td>598 (173)</td>
<td>449 (127)</td>
</tr>
<tr>
<td>Only community contacts</td>
<td>72 (27)</td>
<td>50 (17)</td>
</tr>
<tr>
<td>Shared GP practice</td>
<td>14 (3)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Household</td>
<td>25 (11)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>LTCF</td>
<td>22 (8)</td>
<td>20 (7)</td>
</tr>
<tr>
<td>Different addresses</td>
<td>2 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Unresolved</td>
<td>9 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Only hospital contacts</td>
<td>371 (118)</td>
<td>296 (91)</td>
</tr>
<tr>
<td>Ward contact</td>
<td>255 (64)</td>
<td>212 (52)</td>
</tr>
<tr>
<td>Hospital A</td>
<td>125 (41)</td>
<td>101 (35)</td>
</tr>
<tr>
<td>Hospital B</td>
<td>48 (14)</td>
<td>32 (10)</td>
</tr>
<tr>
<td>Hospital C</td>
<td>8 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Multiple hospitals</td>
<td>75 (5)</td>
<td>75 (5)</td>
</tr>
<tr>
<td>Hospital-wide contact</td>
<td>118 (54)</td>
<td>85 (39)</td>
</tr>
<tr>
<td>Hospital A</td>
<td>97 (45)</td>
<td>70 (33)</td>
</tr>
<tr>
<td>Hospital B</td>
<td>6 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hospital C</td>
<td>8 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Multiple hospitals</td>
<td>8 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Both hospital and community contacts</td>
<td>156 (28)</td>
<td>104 (19)</td>
</tr>
<tr>
<td>Shared GP practice</td>
<td>13 (2)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Household</td>
<td>37 (9)</td>
<td>17 (3)</td>
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<tr>
<td>LTCF</td>
<td>56 (9)</td>
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</tr>
<tr>
<td>Different addresses</td>
<td>17 (3)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Unresolved</td>
<td>33 (5)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Neither hospital nor community contacts</td>
<td>193</td>
<td>134</td>
</tr>
<tr>
<td><strong>Total number of cases</strong></td>
<td><strong>1465</strong></td>
<td>1040</td>
</tr>
</tbody>
</table>

### CC22

53.6% genetically linked
(173 clusters: 2 to 44 cases)

40.8% genetically + epidemiologically linked

71% of total
(9 other clonal complexes (CC) were identified)
Zooming out

Transmission clusters coloured-coded on the CC22 phylogeny (71% of patients)
For clusters with epidemiological links (transmission clusters) involving five or more cases, we attempted to identify the most plausible transmission route by integrating:

- Patients’ movement data and postal codes
- MRSA sampling dates
- MRSA screen results
- Genetic relatedness of MRSA strains (phylogeny)
Zooming in

Unrecognised hospital transmission (ward-centric) - CC22

6/8 cases MRSA isolated at later admissions (3 cases at different hospitals)
Unrecognised hospital transmission (patient-centric) - CC22

388 as the index/source case
Unrecognised hospital transmission (community-origin) - CC30

815 and 725 as the index/source case
6/8 cases shared the same postal code (elderly nursing home). 3 samples from the same GP (GP21), other samples isolated in hospital A.
3/5 are members of the same family (household transmission). 2/5 acquired at the hospital after entry of patient 715.
Zooming out again

Transmission clusters coloured-coded on the CC22 phylogeny (71% of patients)
Investigation of a Cluster of Sequence Type 22 Methicillin-Resistant *Staphylococcus aureus* Transmission in a Community Setting

Michelle S. Toleman,1,2,3a Emmeline R. Watkins,4a Tom Williams,1 Beth Blane,1 Belinda Sadler,5 Ewan M. Harrison,1 Francesc Coll,6 Julian Parkhill,2 Bernadette Nazareth,3 Nicholas M. Brown,7 and Sharon J. Peacock1,2,3,6

1University of Cambridge, 2Wellcome Trust Sanger Institute, Hinxton, 3Cambridge University Hospitals NHS Foundation Trust, 4Health Protection Team, Public Health England–East of England, Thetford, 5Infection Prevention and Control, Cambridgeshire and Peterborough Clinical Commissioning Group, 6London School of Hygiene and Tropical Medicine, and 7Clinical Microbiology and Public Health Laboratory, Public Health England, Cambridge, United Kingdom
Flow diagram summarising patient identification

2012-2013 WGS study
Patients: 1465

Community Cluster
Patients: 13

Retrospective laboratory record review
Patients: 4

2014-2015 Post Infection Reviews
Patients: 2

Prospective lab surveillance
Patients: 3

Genotypically confirmed cluster strain
Patients: 15

1 patient withheld consent
1 patient records not available

Patients: 13

Phylogenetic analysis of 29 MRSA ST22 isolates from 15 patients linked to a GP surgery.

Coloured bars represent spa genotype

Annual incidence of MRSA at the cluster GP practice and four other practices of similar size and characteristics

Date of first known MRSA isolate (black stars), the preceding six month window for analysis of healthcare links (grey boxes) and dates of isolates sequenced (red circles)
Timeline summarising healthcare contact in the six months before first known MRSA isolate
## Conclusions (I of III)

<table>
<thead>
<tr>
<th>Current understanding/practice</th>
<th>Study findings</th>
<th>Infection control implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain MRSA lineages are hospital-adapted (e.g. CC22 in the UK) whereas others community-adapted.</td>
<td>All MRSA lineages identified in this study including hospital-associated (CC22 and CC30) and community-associated (all the others) are found equally capable of transmitting in the community including instances of transmission in households, nursing homes and GP practices.</td>
<td>Postcodes and GP registration information, combined with hospital admission data, should be extracted routinely from hospitalised patients to identify transmission hot spots in the hospital and the community.</td>
</tr>
<tr>
<td>As CC22 is the predominant MRSA lineage in the UK (~70%), it is presumed that hospitals are responsible for the majority of MRSA transmission.</td>
<td>Postcodes and GP registration information are strong epidemiological markers.</td>
<td>Infection control could allocate resources to investigate those with a greater number of cases and/or worse clinical manifestations.</td>
</tr>
<tr>
<td>Routine screening and infection control efforts in the UK are focused on hospital settings.</td>
<td>Repeated introduction of MRSA strains from the community into the hospital, and vice versa, was identified.</td>
<td></td>
</tr>
</tbody>
</table>
## Conclusions (II of III)

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<tr>
<td>An outbreak is defined as transmission to two or more patients on a unit/ward within a short time period (usually 1-2 weeks). Unless two patients are within the same location when they are screened or in the very recent history, they probably will not be linked.</td>
<td>Transmitted MRSA strains can be isolated in later hospital admissions, away from where people had putatively acquired them</td>
<td>Epidemiological investigations should not restrict their search to admissions and hospital locations where people were first detected as MRSA positive and ensure that ward visits in previous admissions (even if in different hospitals) are considered as potential sources of MRSA acquisition. Failing to control MRSA spread in a particular niche will place pressure on neighbouring health-care institutions, particularly if patient sharing is high.</td>
</tr>
</tbody>
</table>
## Conclusions (III of III)

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<tbody>
<tr>
<td>Conventional hospital epidemiology is focused on identifying MRSA outbreaks in wards/units (i.e. single ward outbreaks).</td>
<td>A critical role of persistent MRSA carriers in disseminating MRSA, regardless of the hospital and MRSA lineage, has been identified (i.e. patient-centric longitudinal outbreaks). The patient journey through the health-care system determines the extent to which their MRSA strain becomes disseminated.</td>
<td>Conventional infection control would generally fail to detect patient-centric transmission. Identifying and targeting persistently colonised carriers (e.g. use of side-rooms) will limit the spread of MRSA in the hospital.</td>
</tr>
</tbody>
</table>

| Nosocomial outbreaks of MRSA increase the incidence of MRSA carriage and infection among hospitalised patients. | The bulk of MRSA transmission may not be attributable to a single outbreak clone but can be the result of multiple discrete transmitting clones. | Conventional hospital epidemiology may fail to identify the drivers of endemic (background) acquisition that does not reach the threshold for an outbreak investigation (despite the fact that these often constitute the majority of cases). |