Exploiting Whole-Genome Sequencing for enhanced surveillance of methicillin-resistant *Staphylococcus aureus* bacteraemia in England

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INTRODUCTION

The Methicillin-resistant *Staphylococcus aureus (*MRSA) bacteraemia prevalence in England has been stable at ca. 9% since 2012. Data gathered through mandatory surveillance indicate a reservoir in hospital and community settings but information on the clonal distribution is lacking because <40% of the isolates are sent to the national reference laboratory for analysis.

In April 2017 a new initiative was established, aiming to improve the national surveillance of MRSA bacteraemia by expanding existing data collection systems to include whole-genome sequencing (WGS) based analysis of isolates from all cases in England and to monitor for potential changes in epidemiology.

Aim: to retrospectively evaluate the first nine months of an enhanced MRSA surveillance system in England from April to December 2017.

Objectives:

1. Calculate the WGS coverage within the new MRSA surveillance system.
2. Describe molecular epidemiology.
3. Compare the new surveillance molecular epidemiology results with the data obtained from a prior study (September 2012- October 2013).

METHODS

Public Health England national mandatory surveillance from 1st April to 31st December 2017

Mandatory report:
Personal data
Hospital-onset (HO-MRSA): ≥3 days from admission
Community-onset (CO-MRSA): <3 days from admission
Clinical information

National reference laboratory report:
Personal data
Sample/onset date
WGS:
MLST
SCC*mec* type
Gene profile: toxin and antimicrobial resistance markers

1. The two datasets were matched and compared by a patient identifiers.
2. The proportion of linked cases was calculated.
3. Analysis of WGS data including: multilocus sequence type (MLST), clonal complex (CC), staphylococcal cassette chromosome *mec* (SCC*mec*) type, toxin and antimicrobial resistance (AMR) profiles.
4. The onset setting (hospital onset, HO-MRSA vs community onset, CO-MRSA) was derived for all linked cases.
5. The proportion of multi-drug resistant (MDR) cases (defined as resistance to β-lactams plus ≥3 other classes of antibiotic) was calculated.
6. The Panton-Valentine leukocidin (PVL) positive rate was calculated.
7. The molecular epidemiology of MRSA bacteremia in England during this study period (April-December 2017) and a previous study (September 2012- October 2013) was compared.

RESULTS

During the study period, 602 MRSA bacteraemia cases were reported through the national mandatory surveillance system (Figure 1).

Overall, 464 isolates were deterministically linked to the paired report, with a **total coverage of 77% of all MRSA bacteraemia** cases reported in England during the study period (Figure 1).

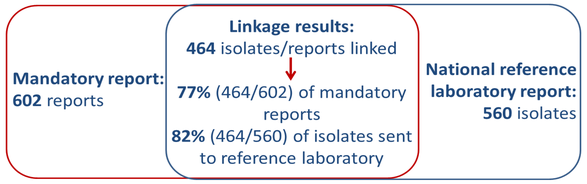

Figure 1: scheme of the total number of MRSA bacteraemia mandatory reports and isolates collected from April to December 2017 in England. In the middle are reported the linkage results.

The majority of the 464 linked cases were male (68%), significantly more than female (68% *vs* 32%; p<0.0001).

The median age of linked population was 69 years (age range: 0-102 years, inter quartile range -IQR- 35 years).

The majority of linked cases were reported as CO-MRSA, significantly more frequent than HO-MRSA (65% *vs* 35%, p<0.0001).

The primary site of infection was known for 32% (150/464) of linked cases. The most common site of infection was skin/soft tissue (55/150, 36%), followed by pneumonia (15%) and urinary tract infection (UTI, 8%).

Linked cases: WGS-based findings

18 MLST clonal complexes were identified; the majority (81%) carried SCC*mec*IV.
CC22 was identified in 48% (225/464), representing the most common clone (Figure 2b), most of which (69%, 156/225) harbored SCC*mec*IVh (EMRSA-15).
CC5 encoding various SCC*mec* types was the second most common MRSA clone (18%, 85/464).

CC22 and CC5 were the most common clones, both among CO-MRSA (44% and 22% respectively) and HO-MRSA (57% and 12% respectively).
Overall, the genotypic MDR rate was 41%.
Among the 295 CO-MRSA cases, 121 (41%) were MDR, such as among HO-MRSA (70/169).
39 (8%) were PVL positive, most of which (10/39; 26%) belonged to the USA300 clone (CC8-IVa).

Molecular epidemiology comparison of linked cases: Sep 2012- Oct 2013 study *vs* Apr- Dec 2017

The number of isolates collected during the 2017 surveillance period increased by 45% compared with the 2012-2013 data (560/602, 93% *vs* 433/903, 48%).
The percentage of linked cases was similar over the two study periods (362/433, 84% *vs* 464/560, 83%).
The coverage of linked cases in 2017 was 77% (464/602), representing a 37% increase compared to 2012-2013 (Table 1).

MRSA bacteraemia in England: comparison 2012-13 vs 2017

Study period	No. MRSA reported	No. isolates collected	No. linked cases	% linked cases
Sep 2012-Oct 2013	903	433	362	40%
Apr-Dec 2017	602	560	464	77%

Table 1: Number of MRSA bacteraemia mandatory reports and isolates collected and linked during the two study periods.

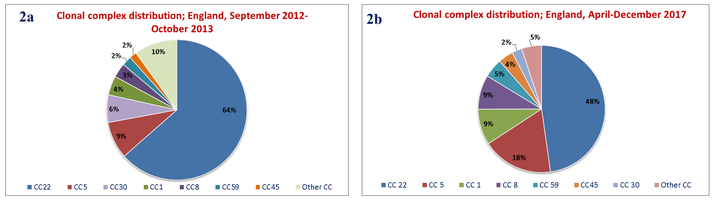

Figure 2: Clonal complex (CC) distribution in Sep 2012 - Oct 2013 (2a) and Apr-Dec 2017 (2b)

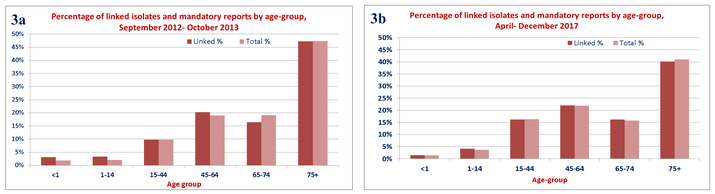

Figure 3: Percentage of linked isolates and mandatory reports by age-group in Sep 2012- Oct 2013 (3a) and Apr-Dec 2017 (3b)

Among linked cases in 2017, the CO-MRSA cases were significantly more frequent than in 2012-2013 (64% vs 47%, p=0.0003) when most were HO-MRSA (53%).
In both 2017 and 2012-2013 study periods, CC22 was the most common clone, representing 48% and 64% respectively (p=0.0006; Figure 2).
CC5 was the second most common lineage in both periods, increasing its circulation from 9% in 2012-2013 to 18% in 2017 (p=0.239; Figure 2); 75% were CO-MRSA.
CC30 decreased from 6% in 2012-2013, to 2% in 2017 (p=0.598).
In both study periods, the linked cases age-group distribution was representative of the age distribution reported in mandatory surveillance (Figure 3).
In both periods, patients aged >75 years comprised the majority of cases: 47% in 2012-2013 *vs* 40% in 2017 (p=0.130).

DISCUSSION

The enhanced surveillance of MRSA bacteraemia in England combined with WGS proved successful with 77% cases linked, representing 37% improvement compared with previous initiatives.

The overall demographics of the study population in 2017 did not differ from previous studies.

In 2017, the percentage of community onset cases increased, comprising 64% cases, contrary to what observed in 2012-2013 when the majority of the cases were HO-MRSA. This trend has been observed elsewhere (1), indicating a reservoir in the community setting and highlighting the switch from healthcare-associated to community-associated MRSA infection.

Changes in the clonal distribution were apparent over time, with an increase in CC5 and a decrease in CC30 between 2012-2013 *vs* 2017.

In conjunction with changes in molecular epidemiology, the genotypic MDR rate was 41% which has implications for choice of therapeutic agent and attendant public health concern regarding AMR rates.

These data provide evidence to support the development of interventions aimed at reducing the incidence of MRSA bacteraemia.

Efforts are ongoing to further maximise case ascertainment to obtain a more complete overview of MRSA bacteraemia cases in England.

CONCLUSIONS

The enhanced surveillance system established in England offers the promise of a better understanding of the circulating MRSA clones, rapid detection of high risk clones and outbreaks.

Moreover, this initiative will help provide evidence for future public health decision making, including patient management strategies and national policy.

REFERENCE

1. David MZ, Daum RS. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 2010; 23: 616–87

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