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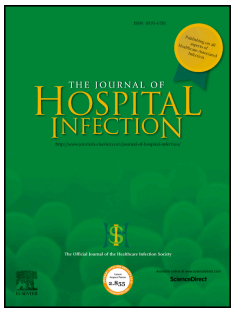

Comparison of national strategies to reduce methicillin-resistant *Staphylococcus aureus* (MRSA) infections in Japan and England

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Title: Comparison of national strategies to reduce methicillin-resistant *Staphylococcus aureus* (MRSA) infections in Japan and England

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Running title: MRSA strategies in Japan and England

Structured summary

Background: National responses to healthcare-associated infections vary between high-income countries but when analysed for contextual comparability, interventions can be assessed for transferability.

Aim: To identify learning from country-level approaches to addressing meticillin-resistant *Staphylococcus aureus* (MRSA) in Japan and England.

Methods: A longitudinal analysis (2000-17), comparing epidemiological trends and policy interventions. Data from 441 textual sources concerning infection prevention and control (IPC), surveillance, and antimicrobial stewardship interventions were systematically coded for: *type* - mandatory requirements, recommendations, or national campaigns; *method* - restrictive, persuasive, structural in nature; *level of implementation* - macro (national), meso (organisational), micro (individual) levels. Healthcare organisational structures and role of media were also assessed.

Findings: In England significant reduction has been achieved in number of reported MRSA bloodstream infections. In Japan, in spite of reductions, MRSA remains a predominant infection. Both countries face new threats in the emergence of drug-resistant *Escherichia coli*. England has focused on national mandatory and structural interventions, supported by a combination of outcomes-based incentives and punitive mechanisms, and multidisciplinary IPC hospital teams. Japan has focused on (non-mandatory) recommendations and primarily persuasive interventions, supported by process-based incentives, with voluntary surveillance. Areas for development in Japan include resourcing of dedicated data management support and implementation of national campaigns for healthcare professionals and the public.

Conclusion: Policy interventions need to be relevant to local epidemiological trends, while acceptable within health system cultures and public expectations. Cross-national learning can help inform the right mix of interventions to create sustainable and resilient systems for future infection and economic challenges.

Keywords

Meticillin-resistant *Staphylococcus aureus*; antimicrobial resistance; infection prevention and control; healthcare-associated infections

Introduction

Antimicrobial resistance (AMR) and healthcare-associated infections (HCAIs) remain a critical global challenge[1]. While a standard template for National Action Plans for AMR has been suggested, countries have adopted different interventions to address AMR and HCAIs. A better understanding of what has been attempted at the national level can offer improved contextualisation for the often challenging implementation of large-scale interventions such as National Action Plans. By comparing international responses across different countries, a look at the wider policy setting can help transfer of learning. Global transfer of learning has influenced UK initiatives in the past (e.g. primary care organisational development [2]) but for infection prevention and control (IPC), England has deviated from its European neighbours in policy approach and particularly the amount of information available in the public domain [3]. International collaboration and cross-border learning from innovative models tackling AMR are encouraged by the UK Department of Health (DH)[4] and Japan Ministry of Health Labour and Welfare (MHLW)[5]. High-income countries, such as Japan and UK, face a further challenge arising from ageing populations, which require careful consideration of sustainable approaches.

The AMR National Action Plans in both countries cover similar overarching themes. The Japanese government formulated its plan in April 2016, aiming to cut total antibiotic usage by 33% of the current level by 2020 [5]. However, the UK, in its Five Year AMR Strategy (2013-2018), has approached the setting of AMR targets differently [4]. The UK is implementing continuous yearly review and revised targets using baselines, starting with ten different drug-bug combinations [4]. MRSA is not included because of the earlier focus and achievement [6], [7]. Japan has implemented a reduction programme with a set target for achievement by 2020 for each one of six different drug-resistant bacteria, including MRSA [5].

This study addressed the question: What can be learnt from approaches for addressing MRSA between two high-income countries?

Methods

This study involved the collection and analysis of secondary data to systematically map and understand the trajectory of national-level interventions to address MRSA as follows.

(i) Observing the epidemiological setting

The most complete datasets (chronologically) in each country were accessed, data extracted and trends plotted (on MS Excel). For England, the publicly accessible Public Health England (formerly Health Protection Agency) data were used [8]–[12]. We included four infections for which NHS acute hospital trusts have been subject to mandatory surveillance and public reporting in England: methicillin-resistant *Staphylococcus aureus* (MRSA), meticillin-sensitive *S. aureus* (MSSA), and *E. coli* bloodstream infections (BSIs), and *Clostridium difficile* infection. The financial year 2001/2 was the start point of the analysis in line with initiation of mandatory surveillance, and public reporting of MRSA. Other Gram-negative organisms, *Psedomonas aeruginosa* and *Klebsiella* species, which became subject to mandatory surveillance and public reporting only in 2017, were not included in this study.

In Japan, since 1999 MRSA infections have been the subject of sentinel surveillance with 500 designated hospitals required to report their monthly number of patients with MRSA infection [13]. This covers approximately 6% of 8000 hospitals in Japan. In 2000, The Japan Nosocomial Infections Surveillance (JANIS), organised by the MHLW, was launched to collect data on multidrug-resistant organism (MDRO) nosocomial infections such as MRSA on a voluntary basis. JANIS member hospitals are required to submit surveillance data monthly. The JANIS system provides anonymous 'Open Reports' for the public (quarterly & annually) and 'Feedback Reports' for member hospitals (monthly & annually). Data from the divisions of Antimicrobial-Resistant Bacterial Infection (ARBI) and Clinical Laboratory (CL) at JANIS were accessed [14]. These data represent 10% and 19.5% of hospitals (2016) respectively [15]. The CL division reports prevalence of bacteria amongst clinical isolates based on microbiological data [14]. Whilst ARBI data have less coverage, they are used here as capture the incidence of seven different (multi)drug-resistant infections associated with six bacteria, including MRSA, amongst hospitalised patients. The ARBI data are more comparable with England data on MRSA BSI rather than the CL data. The CL data are included as supplementary data (Appendix A, **Figure A.1**) as include additional pathogens. Pre-2007 data for Japan were excluded, as longitudinal comparison is inappropriate due to different data collection systems. Across the countries, there is a difference in the denominators for epidemiological data due to different data collection methods.

(ii) Assessment of the health policy setting

To map policy interventions for the period 2000-17, we purposefully sampled secondary data sources, concerning wider IPC, surveillance, antimicrobial stewardship as key areas to address AMR, including MRSA [16]. The start point of 2000 is used for both countries to align with publication of two key reports by the US Institute of Medicine [17], [18] pointing out prevalence of hospital

infections, harnessing national commitment to patient safety, followed by country actions globally. As a first study to provide a rapid, efficient, but in-depth comparison of approaches post-2000, between Japan and England, a decision to use secondary sources was taken; setting the ground for future interviews and surveys.

The sampling was informed by field experts, such as senior clinicians and policy makers in each country. For Japan, a total of 275 textual sources were analysed from four main categories: (a) policy documents, guidelines, and legislation produced by Japan's health bodies; (b) hospital human resource documents, board minutes, reports and strategies on IPC (for a sample of five hospitals in Japan); (c) documentary evidence from professional associations; (d) documentary material from outside healthcare, such as newspaper articles concerning HCAIs and AMR. For England, we supplemented archival data of previous research conducted by the research team [6], [19], which resulted in 322 textual sources being retrieved and analysed for (a)-(c). We did not conduct analysis for media materials for England in this study, as this has been captured elsewhere in recent years [20], [21] with a frequency of reporting 'AMR'/'antibiotic resistance' and 'superbug' in the media averaging at up to 4.7 per month in popular and broadsheet newspapers between 2010-15 [22].

Using keyword searches taking into account relevant key literature [7], [23]–[26], an inventory of interventions was compiled. This inventory was then refined through an iterative process, including a series of team virtual discussions and emails about its appropriateness. Data from 441 textual sources were then independently and systematically mapped and coded along three dimensions: a. type - mandatory requirements, recommendations, or national campaigns; b. method – restrictive, persuasive, and/or structural in nature [27], [28]; c. level of implementation - macro (national), meso (organisational), and/or micro (individual) levels. This was done independently and concurrently between the research teams. A further 156 materials were also analysed for role of media (for Japan) and healthcare organisational structures.

Examples for restrictive interventions include limits or required approvals, such as formulary restriction requiring prior authorisation of prescriptions by infectious diseases physicians. Persuasive interventions refer to education, training, local consensus processes, advice, audit and feedback. Structural interventions include shifting towards electronic records, provision of rapid laboratory testing and technology, and organisation of quality monitoring mechanisms. Two researchers independently coded all data for each country (SM - Japan, MI- England). A second, independent coding was carried out for Japan for 30% of the interventions (MI bilingual). A second, independent

coding was carried out for England for 30% of the interventions (RA & YK). A third level of independent coding was carried out for discrepancies arising (RA). Disagreements in the results were resolved through team (virtual) discussions (SM, SK, MI, RA).

(iii) Wider contextual analysis

For a broader contextualisation of policy interventions we gathered information based on a classic policy appraisal framework , namely *Leichter's*: (i) situational factors (i.e. change of government and national leadership, health, healthcare utilisation); (ii) structural factors (i.e. socio-economic indicators, health expenditures, health workforce, population); (iii) cultural factors (i.e. cultural values); and (iv) exogenous factors (i.e. influence of international institutions) [29].

The approaches above allowed a multi-dimensional comparison of approaches over time between Japan and England.

Results

(i) The Epidemiological Setting

MRSA remains highly prevalent in Japanese hospitals. Although MRSA infections have been decreasing over the last decade, the speed of decline appears to have slowed down after 2013, with 2016 rates at 311 per 100 000 hospitalized patients [15]. The trend of other (multi)drug-resistant bacterial infections based on ARBI data either showed a decline or did not change during the observed period (2007-2016) (**Figure 1**). CL data show *E. coli* and drug-resistant *E. coli* (cephalosporin, fluoroquinolone) isolates have rapidly increased in recent years, reaching similar levels to *S. aureus* isolates (Appendix A, **Figure A.1**).

In England, there was a sharp drop in the rates of MRSA BSIs between 2006/7 and 2009/10, and then the speed of decline slowed down between 2009/10 and 2011/12. MRSA levels have plateaued since 2011/12 with all reported cases per 100 000 bed days below 5. Not all trends are in the right direction despite being subject to mandatory surveillance since 2001 (later implementation for *E. coli,* MSSA – 2011/12) (**Figure 2**). *E. coli* represents a rapid increase and the most frequent cause of BSIs; 41% of these were resistant to co-amoxiclav (commonest antibiotic used in hospitals) in 2016 [30].

Regional variation is also reported between Europe and Asia as well as England and Japan. *S. aureus*'s resistance to methicillin was reported as 6.7% (invasive isolates, 2016) in the UK, 13.7% in EU/EEA [31], whereas Japan and Asian Network for Surveillance of Resistant Pathogens accounted for 53% (comprehensive, 2012) and 64% (blood isolates, 2012) respectively [32].

(ii) The Health Policy Setting

Since 1996, the Japanese government has promoted infection control in hospitals using a medical reimbursement system. Hospitals which have in place methods for developing staff and capacity building as well as taking part in surveillance, establishment of a hospital infection control department/committee, and associated activities, are eligible to apply for an additional fee through reimbursement systems. Those hospitals that do not have systems to monitor optimal use of antimicrobials are barred from applying for this fee. A key feature of monitoring must be either a notification or permission system for broad spectrum antibiotics.[33]

In England, IPC policy towards MRSA has evolved dramatically since 2001. It transformed from the under-resourced 'Cinderella model' [34], [35], and HCAIs being seen as unavoidable, to a vertical and largely top-down performance management model. Mandatory surveillance and public reporting of MRSA BSI cases in hospitals in 2001 was closely followed by national and local stretch targets, and then embedded as 'objectives' in NHS operating/outcomes frameworks. More recently, the approach has evolved to a 'zero tolerance' model strategically applied to avoidable HCAIs with IPC indicator basket (e.g. quality requirement, threshold, measurement methods, breach)[36]; and more specifically for MRSA with post infection reviews being required to investigate how an incidence occurred, and identify lessons and actions to prevent such instance from reoccurring in the future [37].

Political pressure generated through a series of critical independent reports (e.g. National Audit Office reports [35], Robert Francis Inquiry Reports into Mid-Staffordshire NHS Foundation Trust [38]), and public outcry through increased media stories about dirty wards and hospital superbugs all acted as drivers to this policy trajectory. Nurses and medical consultants within infection prevention teams are required to have specialist training in infection prevention and cleanliness, set out within the 2015 Code of Practice in IPC [39].

Table I shows the timeline of key national policies reports and campaigns for addressing MRSA.

(iii) Comparing approaces in Japan and England

Organisational structures

At the organisational level, in the five Japanese hospitals reviewed here, Infection Control Committees or Departments are positioned directly under the Hospital Director. In England, this varies and includes examples of large teaching university hospitals where the IPC Committee sits under the Clinical Effectiveness Committee, which in turns sits under the Hospital Board. In England, the Directors of Infection Prevention & Control (DIPCs) can be members of the Hospital Board, depending on their other organisational role. For example, if the DIPC is also Director of Nursing or Medical Director, they are part of the Board. In Japan, nurse leadership in infection control is yet to be seen.

England has developed multidisciplinary IPC teams, extending beyond health professionals, including data managers/analysts and more recently surgical site infection (SSI) surveillance nurses and in some cases decontamination leads, in alignment with the 2015 Code of Practice in IPC [39]. In Japan, infection control also comprises multidisciplinary teams of health professionals, supported by admin staff but unlike England do not also include dedicated data management support.

The role of media

Newspapers in Japan have often reported nosocomial infection cases which have resulted in deaths but with little emphasis on AMR. Since 2016, however, AMR has become a worldwide problem and has been taken up as an agenda at the G7 Summit, with national newspapers covering the topic. The print and e-media has been publishing articles on the proper use of antibiotics and carrying out awareness-raising activities for citizens [101]–[105].

Comparison of interventions within and between countries

The total number of interventions in the period 2000-17 was 322 in England, compared to 119 in Japan. In England, there were two major peaks in the number of interventions around the periods of 2007/08 – 2008/09 and 2012/13 - 2013/14. The second peak was linked to a refocus on MRSA through intense regulatory action combined with a series of persuasive, restrictive, and structural in nature interventions. These included zero tolerance, mandatory post infection review for all MRSA BSIs, financial penalties for hospitals breaching infection control standards, quality premiums (pay for performance framework), together with a national strategy (the UK Five Year AMR Strategy 2013-

2018). In Japan, we see two large waves of sets of interventions introduced in 2007 and 2016 respectively. The magnitude of peaks in England is about two-fold greater than in Japan (Figure 3).

In England, there has been consistent focus on mandatory interventions, even after MRSA BSI rates dropped significantly. In Japan, interventions were primarily recommendations with successive increases observed 2013 onwards. Intensive focus on mandatory interventions in Japan was seen in 2007 and 2014 (Figure 4).

In both countries, campaigns started around the same time, but in England this type of intervention peaked in the years 2007/8 -2008/9, while in Japan campaigns were concentrated in the years 2003-2004 and then ten years later.

The target of campaigns in England has been wide, including health professionals, cleaning staff, patients and the public. In Japan, national campaigns have been less prevalent, while the target audience has often been narrower compared to England. For example, the Central Hospital Infection Control Council launched a campaign in 2003 targeting medical professionals and municipalities, excluding patients. Since publication of the AMR National Action Plan, however, campaigns have broadened. This includes an informative website and educational activities for citizens using user friendly SNS in response to calls from public institutions and non-profit organisations. The Japanese government added new modules of drug-resistant bacteria and proper use of antimicrobials in the curricula of medical schools in 2017. Furthermore, clinical seminars for doctors and dentists have been held across the country. The government also established the National International Medical Research Centre Hospital AMR Clinical Reference Centre (AMRCRC) in 2017.

In England, interventions have been primarily structural, though in more recent years the picture has become more balanced with increasing emphasis also on persuasive and restrictive interventions. Japan has tended toward proportionally more persuasive interventions, with focused efforts on structural interventions in 2007 and 2014 (Figure 5).

England has implemented more interventions targeted at the national (macro) level than Japan. England has also consistently, though to a lesser extent, also included micro-level focused interventions, whereas Japan has focused primarily at interventions implemented at the organisational (meso) level (Figure 6).

(iv) Wider contextual analysis

Distinctive features in each country are identified in the wider contextual policy domain which may have impacted on the nature and scope of MRSA-related interventions and their implementation.

The speed of success in the reduction of MRSA infections may be explained by these factors and approaches but causation of course cannot be attributed (Table II).

Discussion

In England there has been a substantial decrease in hospital MRSA BSIs in the last two decades, though there is still no consensus in the literature about which types of interventions were primarily responsible for bringing about this improvement; particularly as any such evaluation must also consider effects on other organisms [3], [6], [116]. In Japan, despite multiple interventions introduced and a notable decrease observed during the studied period, the prevalence of MRSA infections in hospitals remains relatively high. It is helpful to take a longitudinal and contextually grounded approach to such high-level comparative analysis. When comparing the availability and feedback of data at the organisational level, there is a gap in the Japanese context with limited data visualisation for the participating hospitals in the voluntary JANIS programme. It is difficult however to predict the impact of a voluntary versus mandatory scheme of reporting. A preference for national-level, mandatory and structural interventions in England reflects strong government intervention and a mainly top-down approach. The public character of the NHS and its integrated nature allowed for such an approach and resulted in a more uniform outcome at system-level. In contrast, the Japanese health system being more decentralised and characterised by stronger presence of the private sector emphasised recommendations and persuasive interventions targeting hospitals. For example, the development of guidelines in Japan has been largely driven by academic and professional societies, though lacking the next step of reinforcement and implementation via government action (as is the case in England). The top-down enforced target setting and monitoring approach in England has had very mixed responses from the professionals working within hospitals [117].

Culturally, in Japan, the learning from the quality improvement movement in health and other sectors advocates internal (to the organisation) drivers and motivators [118]. This is seen also in the way that financial incentives (rather than punitive measures) for AMR interventions in Japan have been used (e.g. medical reimbursement system). In contrast in England, enforced policies mandate that the Chief Executive of the NHS Board is responsible for ensuring successful prevention and control of hospital infections; all NHS trusts need to appoint a DIPC, while Chief Executives are held personally responsible for the accuracy of infection data submitted by their trusts.

External international drivers seem to have influenced national activities particularly in Japan, whereas England, particularly with key opinion leaders such as Chief Medical Officers, have tended to take a leading role in a global scene influencing the development of Global Action Plan on AMR and World Alliance for Patient Safety (i.e. worldwide hand hygiene and surgical checklist campaigns). Alignment with WHO and other global interventions, such as the G7 Ise-Shima Summit 2016 and Japan's National Action Plan on AMR seem to have led to increased national commitment by Prime Minister, media attention, and citizen-targeted education.

It may be that an incremental approach to policy making [119] during short-term and unstable governments, and strong influence of vested groups helps to explain Japan as a late adopter of National Action Plans and other key policy interventions. In England, wider political windows of opportunity, political leaning of national governments, and the government's determination to combat MRSA appear to be reflected in the two peaks of interventions. For example, strong focus on campaigns combined with NHS trust chief executives legal responsibility in MRSA (and CDI) reporting, and more on mandatory requirements during 2007/8-2008/9 and 2012/13-2013/14 respectively.

In view of an increasing use of broad spectrum antimicrobials in Japan, some scholars suggest a restrictive approach to the use of fluoroquinolones [120]. Possible longer-term impacts of restrictive policy intervention on the reduction of MRSA through banning routine use of antibiotics has also been discussed in the UK context [121]. A way forward for Japan may be to further nurture intrinsic motivations and drivers with stable, supportive government combined with personal and professional stewardship [122] and regional governance [123], given the complex involvement of vested interest groups in policy making processes [124]. Addiitonally, if Japan were to shift from confidential to public reporting of MRSA, its unintended consequences should be monitored [125].

The methods of healthcare funding and reimbursement mechanisms can influence antibiotic prescription [126], hence consequently affecting AMR. In Japan, it is possible to induce the implementation of healthcare by revising medical fees every two years. However, such system would require commitment from hospital leads.

A higher level of healthcare utilisation and unique demographic shifts with falling birth rates to contribute to healthcare funding for increasing aging population in Japan are also a reminder of challenges which lay ahead. Addressing avoidable costs to healthcare are therefore a priority.

From a more sociological perspective, the relationship between national cultural values and behaviour change in relation to IPC and antimicrobial stewardship needs to be investigated in Japan

where there are relatively higher power distance and uncertainty avoidance scores and slow progress in the reduction of MRSA [127]–[129].

Strengths and Limitations of the study.

We looked at the trends and patterns of MRSA and the relevant interventions since 2000 in an attempt to build and compare epidemiological settings across Japan and the UK, however direct comparisons in numbers could not be made due to different reporting units used. We recognise the difficulty of assessing the genuine effect of one specific intervention due to the concurrent existence of interventions that are often multimodal. There are also limitations in capturing the degree, duration and timing of implementation of interventions. Policy change and availability of new diagnostic technologies are factors which may affect the volume of clinical specimens. These factors are relevant for both Japan and England. There has been a high intensity of interventions in England for antimicrobial stewardship and IPC compared to Japan. The very nature of surveillance comes with limitations, and systems where a review process to verify infections and why they have happened provides information for learning. Future research will address local level implementation and perceptions of the interventions presented here through primary data (e.g. interviews with key informants) to triangulate and/or understand local effects. Future work must also understand the profile and trends in the community and across the whole health economy.

As an initial analysis, Leichter's four main dimensions of contextual factors are helpful for understanding potential for transferability between countries, but a more detailed analysis of governance approaches would be beneficial [3]. The approach here neglects the reality of complex and dynamic social phenomena but provides a framework for future cross-national comparisions for mutual learning.

Conclusions

In Japan, international drivers seem to have led to increased national commitment, but nationally, the approach is characterised by voluntary surveillance and a more persuasive approach for clinical professionals rather than a mandatory approach for institutional management. England has reached the extremes of mandatory reporting and ever increasing information in the public domain. Interventions need to be temporally relevant to the epidemiological trend, but also acceptable within the health system, culture and public expectations. Lessons from other high-income countries can help inform the right mix of interventions to create sustainable and resilient systems for future infection and economic challenges.

Abbreviations

AMR, antimicrobial resistance; ARBI, Antimicrobial-Resistant Bacterial Infection; BSIs, bloodstream infections; CCGs, Clinical Commissioning Groups; *C. difficile*, *Clostridium difficile;* CL, Clinical Laboratory; CQUIN, Commissioning for Quality and Innovation; DH, Department of Health; DIPC, Director of Infection Prevention and Control; *E. coli, Escherichia coli;* HCAIs, healthcare-associated infections; ICT, infection control team; IPC, infection prevention and control; JANIS, Japan Nosocomial Infections Surveillance; MDROs, multidrug-resistant organisms; MHLW, Ministry of Health, Labour and Welfare; MRSA, methicillin-resistant *Staphylococcus aureus;* NHS, National Health Service; *S. aureus, Streptococcus aureus*; UK, United Kingdom.

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Conflict of interest statement

JAO is a consultant to Gama Healthcare, and has consulted for Pfizer in the past three years.

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TABLES

Table I

Comparison of the overview of key policies, guidelines, reports, and campaigns for MRSA and other relevant interventions between Japan and England.

Japan	Year	England
Introduction of nation-wide voluntary surveillance (JANIS) – MHLW [14].	2000	DH issued Health Service Circular 2000/002: The management and control of hospital infection: action for the NHS for the management and control of infection in Hospitals in England [40].
Revision of medical reimbursement system: Hospital without ICT would subtracted fees (0.5 US$ or £0.4) – MHLW [41].		DH issued UK antimicrobial resistance strategy and action plan [42].
First Infection Control Doctors were certified. [43]		DH issued, The NHS Plan - A plan for investment, a plan for reform. Star ratings to be introduced. National cleaning standards to be monitored by Patient Environment Action Teams (PEAT). 'Modern matrons' to have the authority at ward level to ensure hospital cleanliness and right care for patients. A trust board member to be nominated to assume responsibility to monitor hospital cleanliness and report regularly to the board. [44]
18 Nurses certified as first Infection Control Nurses [33].	2001	Introduction of mandatory surveillance for MRSA BSIs [45].
Inauguration of the MHLW.		NHS Estates issued National Standards of Cleanliness for the NHS for the first time [46].
Held an expert opinion meeting on hospital infection control [47].	2002	The first results for MRSA mandatory surveillance data (April 2001 - September 2001) published in February 2002.
		Infection control in the built environment: design and planning, published by NHS Estates. Emphasised the importance of involvement of health staff and infection control teams in designing and planning of health facilities.[48]
'Future measures for nosocomial infection control' was released by expert opinion meeting on hospital infection control - Construction of a grand design for nationwide nosocomial infection control. The organisation the tasks from each stakeholder [47].	2003	DH issued Winning ways: working together to reduce healthcare associated infection in England, a report from the Chief Medical Officer [49].
Revised Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases was released [50].		
'Central Conference on Infection Control in Hospital' was established as a permanent advisory body by MHLW [51].	2004	Mandatory surveillance of orthopaedic surgical site infections began in trusts.
		DH issued Towards cleaner hospitals and lower rates of infection: a summary of action [52]. Patients were concerned about poor hospital cleanliness and increasing MRSA infections.
		National standards, local action: Health and Social Care Standards and Planning Framework 2005/2006–2007/2008 [53].
		National Patient Safety Agency launched clean**your**hands campaign to implement near patient alcohol hand rubs [54]. First in the world.
		National target reduction for the number of incidents of MRSA BSIs by 50% over 3 year period (April 2005 – March 2008) compared to the 2003/04 baseline data [55]. Mandatory target introduced to hospitals in November 2004.
		All NHS trusts to appoint a DIPC, who has authority and responsibility for the reduction of HCAIs (e.g., directly reporting to the trust chief executive and trust board, writing and publishing an annual report on HCAIs).[49]
Revision of 'Regulation for Enforcement of Medical Care Act' – MHLW [56].	2005	DH issued Saving Lives: a delivery programme to reduce healthcare associated infection including MRSA [57]. The first version of Saving Lives programme. Saving Lives campaign, including High Impact Interventions based on the 'care bundle' principle.
'Prevention of in-hospital infection in medical facilities' was released by MHLW [58]. Points which regard nosocomial infection prevention based on the latest scientific evidence.		Introduction of Mandatory MRSA bacteraemia enhanced surveillance scheme [59]. Health protection Agency developed and introduced an enhanced MRSA reporting system, moving from aggregated acute trust level to patient-level data collection using web-based Data Capture

Japan	Year	England
		System with 'real-time' nature, and that enabled to identify the presence of the BSI on admission.
Mandatory assignment of dedicated infection control personnel at Advanced Treatment Hospitals [47], [56], [60].		
Revision of medical reimbursement system: Hospital with medical safety measures could receive additional fees (4.7 US$ or £3.3)[61].	2006	The Chief Medical Officer made chief executive of the NHS trust board personally responsible for the accuracy of infection data submitted by their trusts [62].
		DH issued Going further faster: implementing the Saving Lives delivery programme - Sustainable change for cleaner, safer care. Set out actions aimed to reduce MRSA, and in turn, support system-wide improvement in HCAIs (e.g. ensuring infection control (induction & ongoing) training for hospital staff, inclusion of infection control in job description).[63]
		Health Act 2006 (c.28), requirement for provider registration with regulator, legal requirement for providers to ensure protection against HCAIs [64].
		Health Act 2006: Code of Practice for the prevention and control of healthcare associated infections issued [65]. Known as The 'Hygiene Code', applied to all NHS healthcare providers. Improvement Notice from the regulatory body for failing to observe the Code, or special measures for significant failings.
		DH's Healthcare Associated Infection Improvement Team established, and paid visits to acute hospitals to help trusts reduce MRSA BSIs. Doubled the size of the expert Improvement Team by October 2007 when Lord Darzi's interim report released. [66]
Partial revision of Infectious Disease Act – Tuberculosis prevention law was integrated into this act [67].	2007	DH published Uniforms and workwear: an evidence base for developing local policy [68]. Known as the 'bare below the elbows' guidance.
Partial revision law for the revision of Medical Care Act enacted- This law was obligatory for all medical institutions to establish measures to prevent in-hospital infection [69].		The Secretary of State for Health announced a series of measures to combat HCAIs, including a legal requirement for NHS trusts chief executives to report MRSA BSIs (and CDI) to Health Protection Agency with fines for non-compliance; clean**your**hands campaign to be continued.
'Guide and training program of medical safety manger' was settled by MHLW – This document summarised the education programmes for medical safety mangers. It clarified the work for a medical safety manger [70].		DH issued Isolating patients with healthcare-associated infection: a summary of best practice [71].
'Measures to prevent in-hospital infection by drug-resistant bacteria and responses after occurrence'- MHLW – This document requests hospitals to change criteria of suspected an outbreak [72].		Improving cleanliness and infection control (Professional letter from Chief Nursing Officer/Director General of Finance). 5 key action areas in nursing (e.g. increasing the number of matrons to 5000 in acute NHS hospitals by May 2008, quarterly mandatory reporting on cleanliness and infection control by matrons and clinical directors to trust boards, etc.). [73]
JANIS Open Reports are available via internet since 2007 [14].		Deep clean campaign. The Secretary of State for Health announced Deep Clean initiative 'as part of the drive for a culture of cleanliness', an initial deep cleaning to have conducted by all NHS trusts before 31 March 2008. [66]
		DH issued The NHS in England: Operating Framework for NHS, 2008/2009 - locally agreed stretch targets alongside national targets for improving cleanliness and reducing MRSA & *C. difficile* were announced [74].
Japanese Society for Infection Prevention and Control started the Device-related infection surveillance [75].	2008	DH issued Clean, safe care: reducing infections and saving lives [76]. Promotion of innovations / new technologies and equipment was emphasised.
Board Certified Pharmacist in Infection Control, by the Japanese Society of Hospital Pharmacists.		Health and Social Care Act 2008 (c.14), required registration with the Care Quality Commission, and duty to protect patients against HCAIs [77]. New code of practice.

Japan	Year	England
		MRSA screening operational guidance 2. Supplementary guidance to support trusts in introducing MRSA screening for all elective patients in March 2009.[78]
	2009	MRSA objective 2010/11 – relative to the median, with the best performers setting their objectives locally; embedding a culture of zero tolerance of preventable infections across any organisation (DH)[79].
Revision of medical reimbursement system: Hospital with ICT could receive additional fees (12 US$ or £8.5) – MHLW [80].	2010	MRSA screening operational guidance 3 [81]. Supported NHS organisations in introducing MRSA screening for all relevant emergency admissions in December 2010.
MHLW issued the notification - About the establishment of ICT, the frequency and structure of ICT ward round, standards about outbreak [82].	2011	'Start Smart - Then Focus' launched - Guidance on antimicrobial stewardship in the secondary healthcare setting [83].
Revision of medical reimbursement system: Hospital with advanced infection control management could receive additional fees (12 to 48 US$ or £8.5 - 34) – MHLW [84].	2012	Everyone counts: planning for patients 2013/14 [37]. Zero tolerance approach to MRSA bloodstream infections and mandatory Post Infection Review. Introduced on 1st April 2013.
Guideline for treatment of MRSA infection was published by the Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy [85].	2013	The Chief Medical Officer's annual report on Infections and the rise of antimicrobial resistance [86].
		Locally set objectives for incidence of MRSA (& *C. difficile*) infection included in Quality Premium for CCGs, 12.5% (subject to the following achievements: no cases of MRSA bacteraemia assigned to the CCG). (In 2014/15, this was removed from Quality Premium). [87]
		DH issued UK Five year antimicrobial resistance strategy 2013 -2018 [4].
		Everyone counts: planning for patients 2014/15-2018/19 [88] - reiterates zero tolerance to MRSA (NHS England).
		NHS Standard Contract 2014/15 Particulars [89] issued in December 2013- National Quality Requirements for 2014/15 financial year – zero tolerance MRSA a national quality requirement (threshold 2014/15 is >0). Consequence of breach £10 000 in respect of each MRSA incidence in the relevant month (NHS England).
MHLW issued new definition of outbreak [47], [90].	2014	DH published Implementation of modified admission MRSA screening guidance for NHS [91]. Recommended 'a more focused, cost-effective approach to MRSA screening'.
		English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR), established by Public Health England. 1st repot published in September 2014 [92].
		Antibiotic Guardian Campaign, launched in association with European Antibiotic Awareness Day. Developed by various organisations, including Public Health England, and promotes everyone to pledge appropriate use of antibiotics.[93], [94]
MHLW issued recommendations on drug-resistant bacterial policy [95].	2015	National Risk Register of Civil Emergencies, 2015 edition, by Cabinet Office [96]. AMR was placed on the UK government risk register.
		Antibiotic Quality Premium (NHS England), aiming to improve antibiotic prescribing in primary and secondary care. CCGs rewarded for quality improvement, paid in the following financial year, and must be reinvested in quality or health outcome improvement.[97]
		DH issued The Health and Social Care Act 2008: Code of Practice on the prevention and control of infections and related guidance [39].
MHLW issued AMR National Action Plan [5].	2016	CQUIN Guidance for 2016/17, issued by NHS England [98]. AMR became one of 4 national indicators for CQUIN.
		AMR local indicators profile (including local surveillance data) on the 'Fingertips' data portal (publicly accessible interactive web tool and enhanced data visualisation), launched by Public Health England [99].
Guideline for treatment of MRSA infection, 2nd edition was revised by The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy [100].	2017	

Abbreviations: AMR, antimicrobial resistance; BSIs, bloodstream infections; CCGs, Clinical Commissioning Groups; *C. difficile*, *Clostridium difficile;* CDI, *Clostridium difficile* infection; CQUIN, Commissioning for Quality and Innovation; DH,

Department of Health; DIPC, Director of Infection Prevention and Control; HCAIs, healthcare-associated infections; ICT, infection control team; JANIS, Japan Nosocomial Infections Surveillance; MHLW, Ministry of Health, Labour and Welfare; MRSA, methicillin-resistant *Staphylococcus aureus;* NHS, National Health Service; UK, United Kingdom.

NB: CCGs are responsible for commissioning care for defined geographical populations (2013-).

Table II

Comparison of the wider contextual factors and approaches to MRSA reduction / quality improvement between Japan and England (/UK)

Factor	Component	Japan	England (/UK)
SITUATIONAL	**POLITICAL**		
	Change of government & national leadership	**Political leadership instability:** • 15 terms of office (7 general election since 2000) of an average length of 1.9 years between July 1998 – December 2017 (range 0.8 -5.4 years). • September 2006 - December 2012: frequent leadership changes with 6 different prime ministers occurred, but only one prime minister since December 2012. • 10 coalition governments – *primarily* led by Liberal Democratic Party (LDP, *Jiminto* - Conservative), and shifted to Democratic Party of Japan (DPJ, *Minshuto* - Centrist), and then back to LDP. •The minister of Health, Labour and Welfare also changes frequently according to the governments. The current one was appointed at August 2017.	**Wider political windows of opportunity for policy change:** • 8 terms of office of an average length of 4.1 years between May 1997 – December 2017 (range 1.2- 10.1 years). • 5 governments have been majority with 1 as coalition, shifting from Labour (Centre Left) with 2 different prime ministers to Conservative-Liberal Democratic, and to Conservative with 2 different prime ministers. • Secretary of State for Health was more stable under Coalition and Conservative governments rather than Labour governments (Centre Left & Left) in earlier periods, accounting for 1 and 4 turnovers respectively. The current one serving over 6 years (name changed to Secretary of State for Health and Social Care in January 2018).
	HEALTH		
	Life expectancy at birth (years)[106]	81 (2000) → 84 (2016)	78 (2000) → 81 (2016) [UK]
	Top five causes of death (age-standardised rate per 100 000 population by cause) between 2000 and 2016 [107]	1) Stroke 50.5 (2000); 2) Ischaemic heart disease 43.8 (2000); 3) Lower respiratory infections 32.7 (2000); 4) Trachea, bronchus, lung cancer 21.9 (2000); 5) Stomach cancer 21.6 (2000) 1) Ischaemic heart disease 31.5 (2016); 2) Stroke 25.8 (2016); 3) Lower respiratory infections 24.3 (2016); 4) Trachea, bronchus, lung cancer 19.6 (2016) 5) Self-harm 14.3 (2016)	1) Ischaemic heart disease 114.7 (2000); 2) Stroke 47.3 (2000); 3) Lower respiratory infections 46.0 (2000); 4) Trachea, bronchus, lung cancer 32.7 (2000) 5) Chronic obstructive pulmonary disease 26.9 (2000) 1) Ischaemic heart disease 47.6 (2016); 2) Alzheimer disease and other dementias 37.6 (2016); 3) Trachea, bronchus, lung cancer 26.7 (2016); 4) Chronic obstructive pulmonary disease 23.1 (2016) 5) Stroke 21.6 (2016) [UK]
	HEALTH CARE UTILISATION		
	Doctors consultations (in all settings) – Number per capita [108]	14.4 (2000) →12.7 (2014)	5 (2009) [UK]
	Occupancy rate of curative (acute) care beds [109]	81.8% (2000) → 74.5% (2015)	83.4% (2001) → 84.3% (2010) [UK]
	Average length of stay in hospital (days)[109]	24.8 (2000) → 16.5 (2015)	10.7 (2000) → 7.0 (2015) [UK]
STRUCTURAL	**POPULATION**		
	Population structure by age group (% of total) [106]	Aged 0-14: 15% (2000) → 14% (2008) → 13% (2016) Aged 15-64: 68% (2000) → 65% (2008) → 60% (2016) Aged 65 and above: 17% (2000) → 21% (2008) → 27% (2016) **NB - Japan population, thousands: 127,534 (2000) → 127,749 (2016)** [107]**.**	Aged 0-14: 19% (2000) → 18% (2008) → 18% (2016) Aged 15-64: 65% (2000) → 66% (2008) → 64% (2016) Aged 65 and above: 16% (2000) → 16% (2008) → 18% (2016) **NB - UK population, thousands: 58,951 (2000) → 65,789 (2016)** [107]**.**

Factor	Component	Japan	England (/UK)
	Density of population (people per sq. km of land area) [106]	348 (2000) → 348 (2016)	243 (2000) → 271 (2016) [UK]
	SOCIO-ECONOMIC		
	GDP per capita (current US$, thousands)[106]	38.53 (2000) → 40.86 (2009) → 38.97 (2016)	27.98 (2000) → 38.26 (2009) → 40.41 (2016) [UK]
	Unemployment, total (% of total labour force)(modelled ILO estimate)[106]	4.7 (2000) → 5.1 (2009) → 2.8 (2017)	5.6 (2000) → 7.5 (2009) → 4.3 (2017) [UK]
	Poverty rate (% below poverty line of 60%) [110]	22%	18% [UK]
	HEALTHCARE MODELS		
	Healthcare models [111]	Bismarck Model. Statutory health insurance system with a mixture of state regulation, social insurance financing, and private care provision [112]. The medical payment is calculated based on medical fee points. Patients pay part of this amount, and the public health insurance pays the remainder. The revision of the medical fee points is decided by the cabinet, the committee on health insurance, and the central social insurance medical council. These medical fee points are revised every two years.	Beveridge Model. NHS being publicly funded through taxation, and characterised by state regulation and control in the provision of services [112].
	Public system financing [113]	General tax revenue; insurance contributions.	General tax revenue (includes employment-related insurance contributions). [England]
	Provider ownership – hospitals [113]	Mainly private non-profit (~70% of beds), some public (~30%).	Mostly public, some private. [England]
	Hospital payment [113]	Case-based per diem payments and fee-for-service or fee-for-service only (includes physician costs).	Mainly case-based payments (60%) plus budgets for mental health, education, and research and training. All include physician costs, drug costs, etc. [England]
	HEALTH EXPENDITURE		
	Total expenditure on health (% of GDP) (2016) [109]	Total: 10.9	Total: 9.7 [UK]
	Health expenditure by type of financing (2015) [109]	Government schemes: 9% Compulsory health insurance: 75% Out-of-pocket: 13% Voluntary health insurance: 2% Other: 1%	Government schemes: 80% Compulsory health insurance: 0% Out-of-pocket: 15% Voluntary health insurance: 3% Other: 2% [UK]
	Health expenditure by provider (2015)[109]	Hospitals: 41% Long-term care facilities:9% Ambulatory providers: 28% Retailers: 17% Other: 5%	Hospitals: 42% Long-term care facilities: 12% Ambulatory providers: 23% Retailers: 11% Other: 12% [UK]
	HEALTH WORKFORCE		
	Practising doctors per 1000 pop.[109]	1.9 (2000) → 2.4 (2014)	2.0 (2000) → 2.8 (2015) [UK]

Factor	Component	Japan	England (/UK)
	Practising nurses per 1000 pop.[109]	8.4 (2002) → 11.0 (2014)	7.9 (2015) [UK]
	Ratio of nurses to doctors [109]	4.6 (2015)	2.8 (2015) [UK]
	Practising pharmacist per 100 000 pop. [109]	113 (2000) → 170 (2015)	59 (2002) → 83 (2015) [UK]
	HEALTH INFRASTRUCTUTRE		
	Hospital beds per 1000 pop. [109]	14.7 (2000) → 13.2 (2015)	4.1 (2000) → 2.6 (2015) [UK]
Cultural	***National culture score (Hofstede country scores based on 6 dimensions)**[114]	1) Power distance: 54 2) Individualism: 46 3) Masculinity: 95 4) Uncertainty avoidance: 92 5) Long-term orientation: 88 6) Indulgence: 42	1) Power distance: 35 2) Individualism: 89 3) Masculinity: 66 4) Uncertainty avoidance: 35 5) Long-term orientation: 51 6) Indulgence: 69 [UK]
Exogenous	**Influence of international institutions**	International alignment and influences apparent, especially US influence. e.g. 12% of interventions identified 2000-17, including MRSA related guidelines based on the Centers for Disease Control (CDC) guidelines and literature reviews, and regularly updated.	Nationally-based initiatives ahead of aspects of global initiatives.
Approaches to MRSA reduction / quality improvement	**Requirement of surveillance**	Voluntary: JANIS voluntary surveillance scheme since 2000 (but more comprehensively since 2007).	Mandatory: National MRSA mandatory surveillance since 2001. Zero tolerance approach to MRSA bloodstream infections and mandatory Post Infection Review (replacing previous root cause analysis) since April 2013.
	Mode of reporting / accountability	Closed information – confidential reporting: Hospital names are anonymised in JANIS open data sources, not intending to promote competitions between hospitals, but to encourage them to improve against their own historical performance trajectories (as bench-marking).	Open information – public reporting: Detailed information disclosure to the public done in an early period (e.g. public reporting of MRSA bloodstream infections at trust level began in 2002).
	Mode of motivation	Mainly intrinsic but with long-term objectives based largely on principles of *Kaizen* (continuous quality improvement).	Both extrinsic & intrinsic.
	Examples of incentive / sanction	Financial incentive: Many AMR interventions use financial incentives such as medical reimbursement system. Process-oriented sanction: Monetary sanctions were held at one time, and the sanctions targeted the infection control measure at hospitals. Process indicators considered as useful in Japan because immediate changes can be implemented.	Financial incentive: Commissioning for Quality and Innovation (CQUIN); quality premium. Outcomes-oriented sanction: Monetary sanctions were held for hospitals that cannot fulfil target reduction rates.

Abbreviations: AMR, antimicrobial resistance; GDP, Growth Domestic Product; JANIS, Japan Nosocomial Infections Surveillance; MRSA, methicillin-resistant *Staphylococcus aureus;* NHS, National Health Service.
NB: The UK comprises England, Scotland, Wales, and Northern Ireland. The data that are only available for the UK are specified in the table.
*1) Power distance: the degree to which the less powerful members of a society accept and expect that power is distributed unequally; 2) Individualism (versus Collectivism): preference for a loosely-knit social framework in which individuals are expected to take care of only themselves and their immediate families; 3) Masculinity (versus Femininity): a preference in society for achievement, heroism, assertiveness, and material rewards for success; 4) Uncertainty avoidance: the degree to which the members of a society feel uncomfortable with uncertainty and ambiguity; 5) Long-term orientation (versus short-term normative orientation): Long-term orientation takes a more pragmatic approach, encouraging thrift and efforts in modern education as a way to prepare for the future; 6) Indulgence (versus Restraint): Indulgence stands for a society that allows relatively free gratification of basic and natural human drives related to enjoying life and having fun. [115]

FIGURES

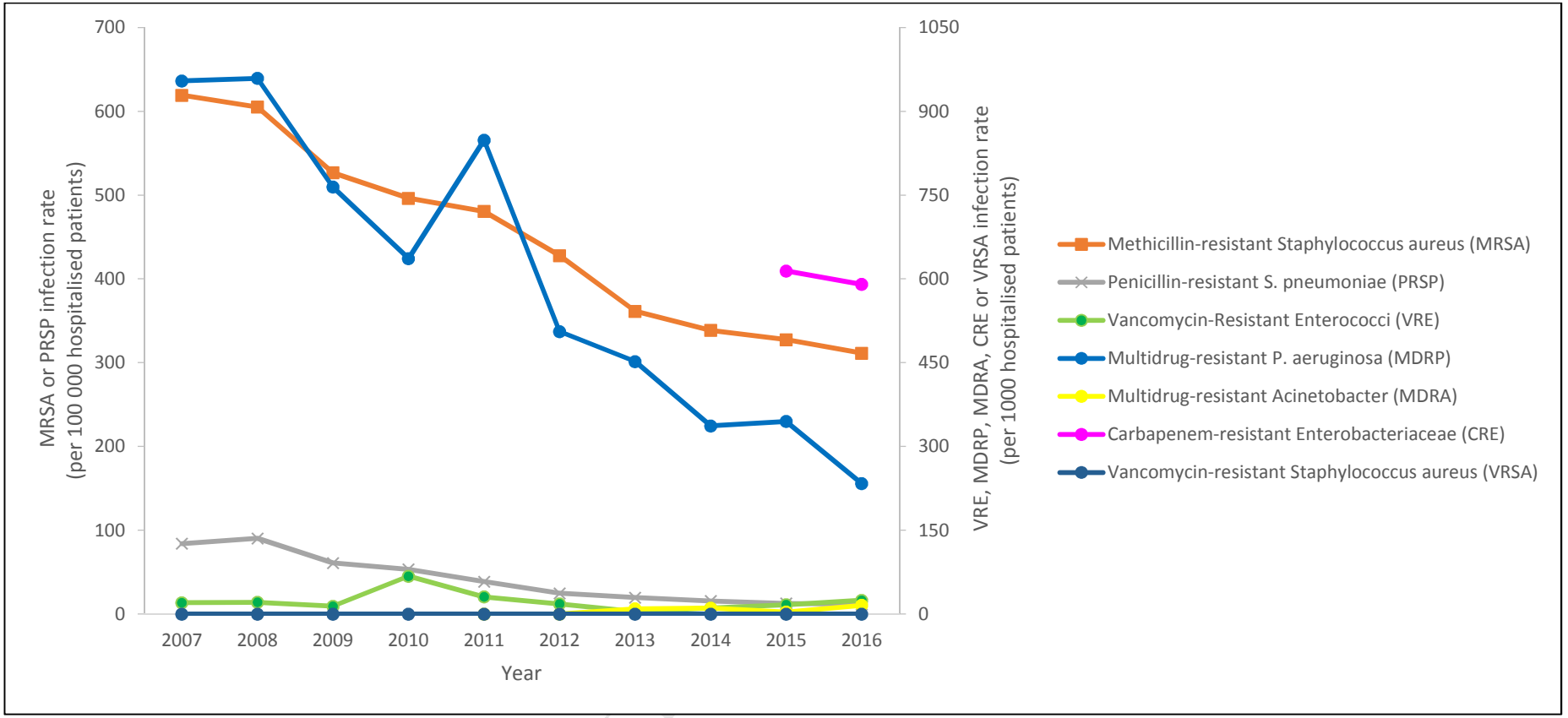

Figure 1. Trends in rates of seven (multi)drug-resistant bacterial infections in Japan based on Antimicrobial-Resistant Bacterial Infection (ARBI) data (Average hospital participation rates ranged between 3% and 10% in 2007 and 2016 respectively); the 2007 data represent the average of July-December 2017 data) [15].

Abbreviations: MDRP, Multidrug-resistant *Pseudomonas aeruginosa*; PRSP, Penicillin-resistant *Streptococcus pneumoniae*. Note: Value of vancomycin-resistant *Staphylococcus aureus* (VRSA) indicates nil during the above period.

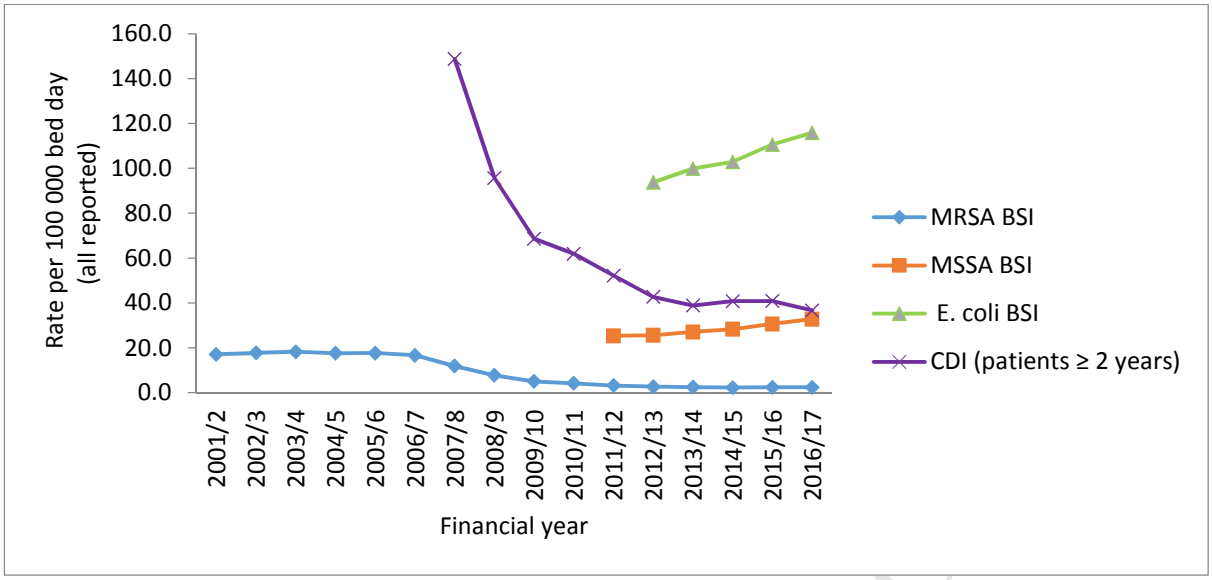

Figure 2. Trends in rates of MRSA, MSSA and *E. coli* bloodstream infections, and *C. difficile* infection (patients aged 2 years and over) for NHS acute trusts – All reported cases (England average)[8]–[12]

Abbreviations: MRSA, meticillin-resistant *Staphylococcus aureus*; BSI, blood stream infection; MSSA, meticillin-sensitive *S. aureus*; CDI, *Clostridium difficile* infection.

NB: 1) April 2001: Mandatory surveillance for MRSA BSIs; 2) January 2004: Mandatory surveillance of *C. difficile*-associated diarrhoea (CDAD) in patients aged 65 years and over began in NHS trusts; 3) April 2007: Mandatory surveillance of CDIs extended to all cases in patients aged 2 years and over for acute NHS trusts; 4) January 2011: Mandatory surveillance extended to meticillin-sensitive *S. aureus* BSIs; 5) June 2011: Mandatory surveillance extended to *Escherichia coli* BSIs.

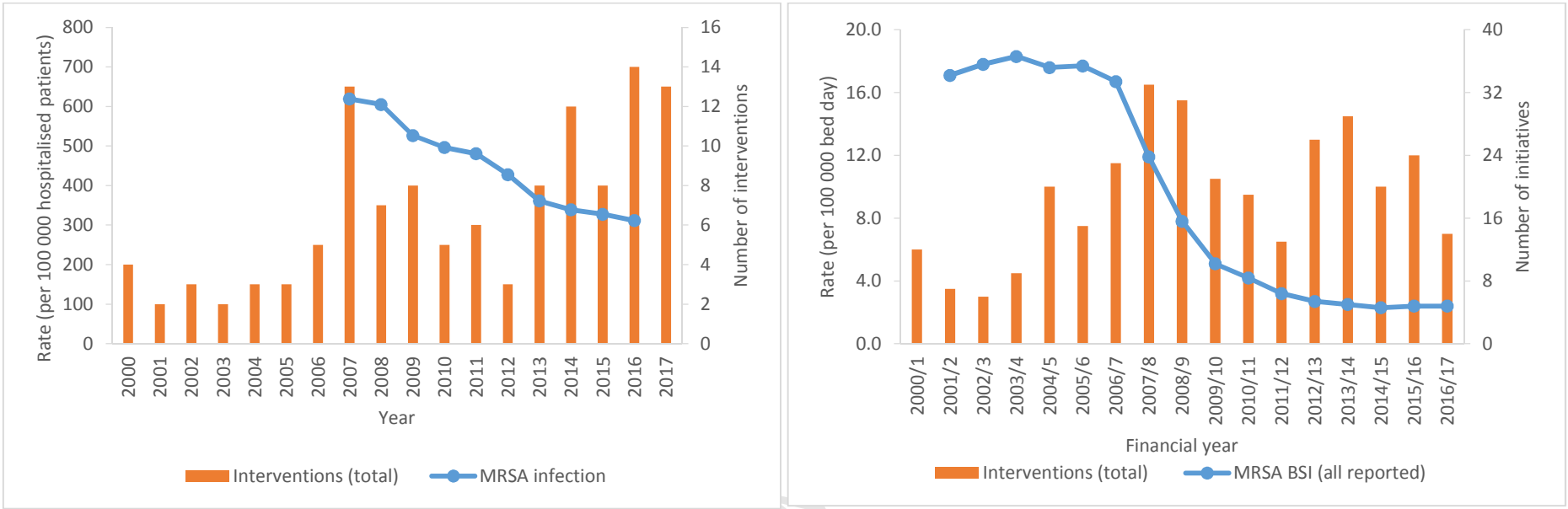

Figure 3. Trends in MRSA and total number of relevant interventions: Japan (left) and England (right)

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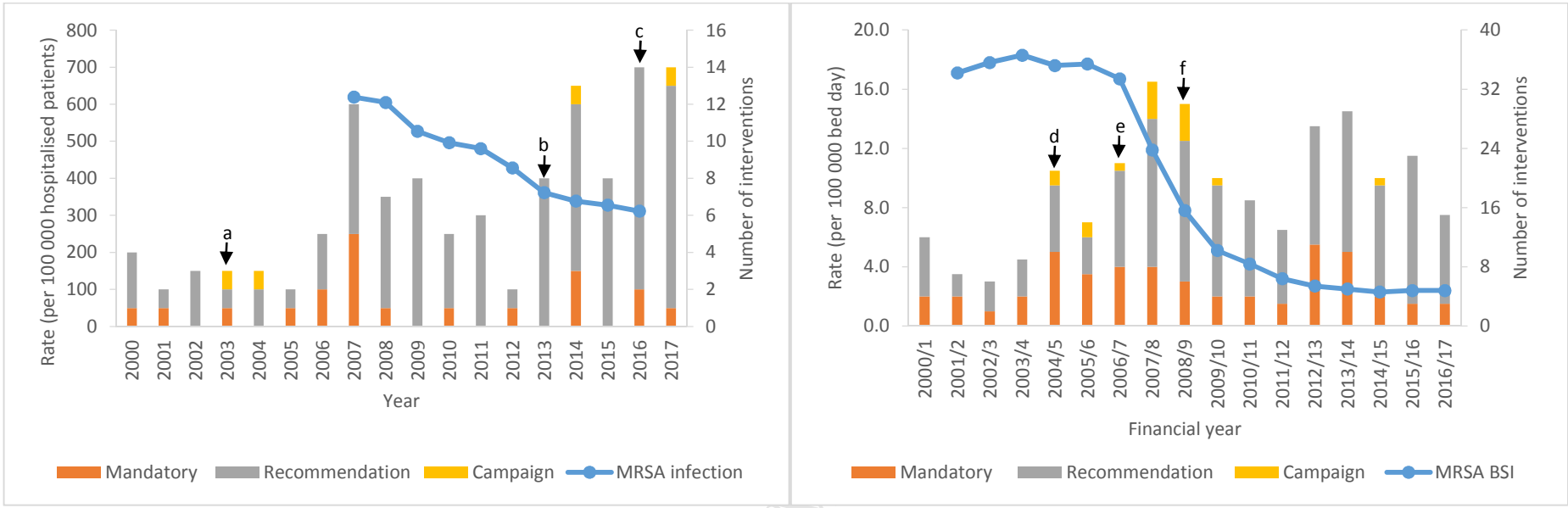

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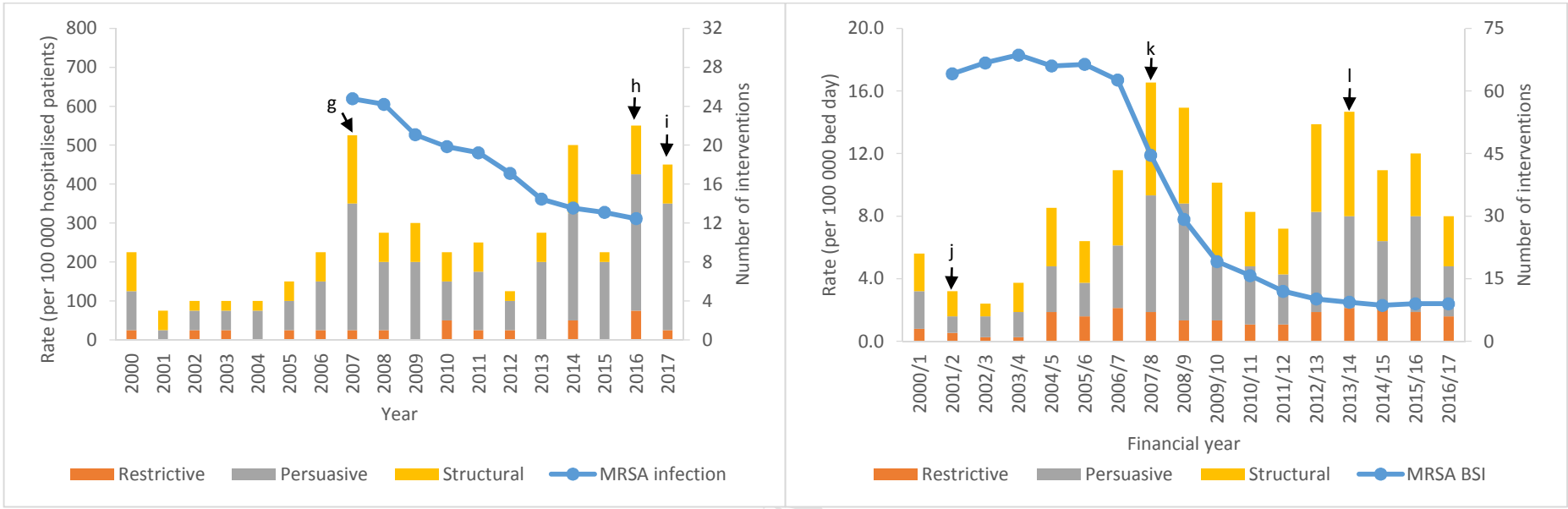

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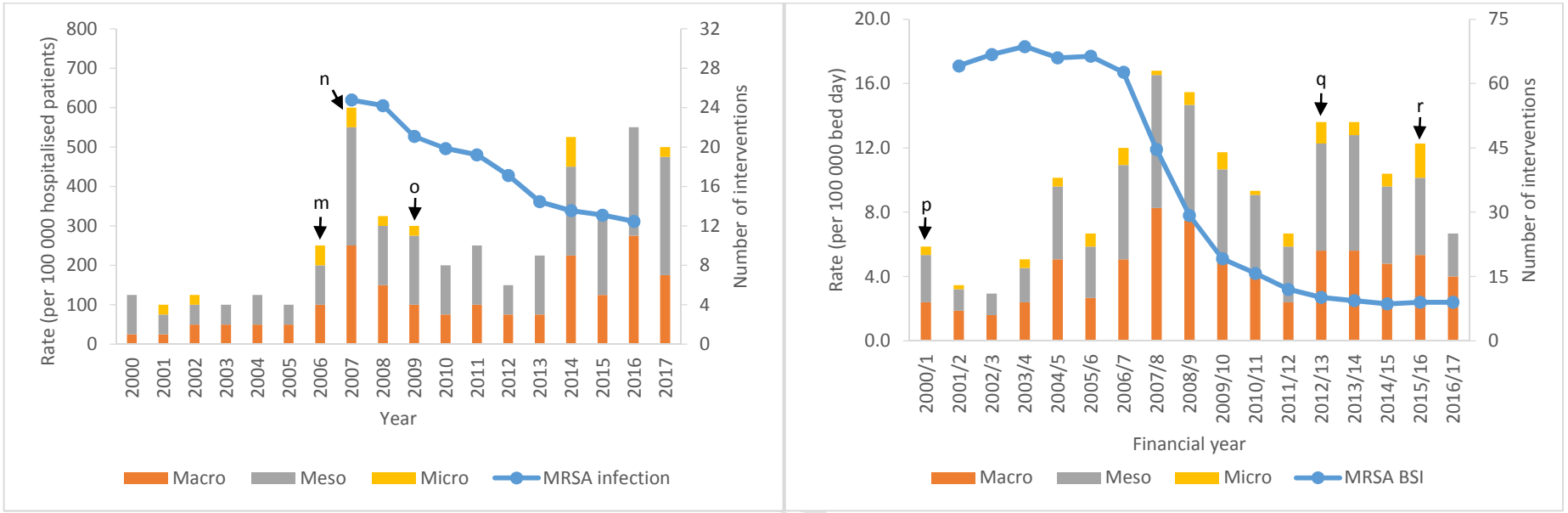

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LEGENDS:

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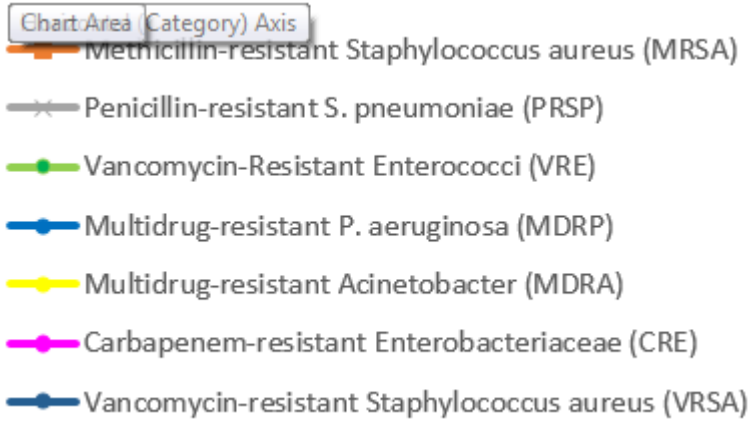

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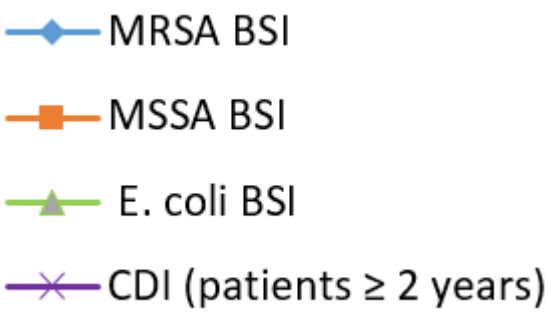

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