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Catheter-related infections: Does the spectrum of microbial causes change over time? A nationwide surveillance study

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Keywords:	CRBSI, catheter infection, bloodstream infection, CLABSI, catheter tip, trends

Catheter-related infections: Does the spectrum of microbial causes change over time? A nationwide surveillance study

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Key words: CRBSI, catheter infections, bloodstream infections, CLABSI, catheter tip, trends

Running title: Epidemiology of catheter-related bloodstream infections

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Abstract:

Objectives: To estimate the incidence and epidemiology of catheter-related bloodstream infections (CRBSI) on a national scale by using prospective epidemiological data from the Swiss *Antibiotic Resistance Surveillance System* (ANRESIS).

Design: Observational study

Setting: National surveillance from 2008 to 2015 for acute hospitals in Switzerland.

Participants: We included acute Swiss hospitals that sent blood cultures and catheter tip culture results on a regular basis during the entire study period to the ANRESIS database.

Outcome measure: A catheter-related bloodstream infection (termed "modified CRBSI", mCRBSI), was defined as isolating the same microorganism with identical antibiogram from ≥1 blood cultures (performed ±7 days around the catheter removal) as the one recovered from the catheter tip. Incidence rates of mCRBSI were calculated per 1000 admissions.

Results: From 2008 to 2015 the mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions (-6% per year, p<0.001). Coagulase-negative staphylococci, *S. aureus* and fungi all exhibited decreasing trends, while rates of Enterococci and Gram-negative bacteria remained stable.

Conclusions: The overall incidence of mCRBSI in Switzerland is decreasing; however, the incidence of mCRBSI due to Enterococci and Gram-negative microorganisms did not change over time. These pathogens may grow in importance in catheter-related infections, which would have clinical implications for the choice of empiric treatment.

Article Summary:

Strengths and limitations of this study

- Provides an estimation of CRBSI on a national scale, an aspect rarely investigated in European countries
- No clinical data were available (patient and catheter data)
- Only those CRBSI episodes, for which the catheter was removed and submitted to the laboratory were included
- The same criteria for identifying CRBSI were used throughout the study period and, therefore, the observed trends should have not been affected by selection bias.
- While surveillance studies on CLABSI or CRBSI mostly focused on overall incidence rates, we also determinated the pathogen distribution.

Introduction:

Catheter-related (CRBSI) or central line-associated bloodstream infections (CLABSI) are associated with increased morbidity, mortality, and healthcare costs [1]. The epidemiology of CLABSI has occasionally been evaluated on a national scale, however, studies focused for the most part on the intensive care unit (ICU) setting [2 3]. In contrast, very few studies investigated CLABSI outside the ICU [4-7]. Of note, the term CLABSI is used for surveillance (where the definition neither requires quantitative criteria nor a microbiological diagnosis of the removed catheter tip), whereas the source of infection in CRBSI is based on a positive culture of the catheter tip. CLABSI surveillance can therefore easily lead to an overestimation of the incidence of CRBSI [8]. More specific surveillance definitions based on single-institution surveillance have previously been proposed, including studies using admissions [9 10] or bed-days [11] as denominator. Such a definition permits the identification of the catheter as source of infection, considering both catheter tip culture results and blood cultures (i.e., a “modified” CRBSI). Moreover, the incidence of CRBSI has rarely been investigated on a national scale in European countries, given the difficulty in obtaining clinical information. Here, we wanted to perform a first exploration of the epidemiology of “modified“ CRBSI in Switzerland, using a national surveillance database.

Methods:

We conducted a nationwide, observational study on CRBSI using ANRESIS data from 2008-2015. The ANRESIS program summarizes all positive blood and catheter tip cultures from twenty Swiss laboratories, each of them collecting data from several hospitals distributed across the country. Accordingly, we analyzed data of patients from 36 Swiss hospitals, including only those centers that sent catheter tip information on a regular basis during the entire study period. All five Swiss university hospital and main regional hospitals were

included, representing the majority of hospitalized patient in the country during the study period.

A catheter tip was included in the analysis if at least one microorganism could be cultivated from it, irrespective of the cut-off of the roll-plate method [12]. If more than one pathogen was isolated from the same catheter tip, each individual pathogen was considered as a separate episode. Information about the microbiological method (quantitative sonication vs semi-quantitative roll-plate culture) was not routinely made available by the participating laboratories. However, in a previous analysis using a similar dataset, 83% of the participating laboratories used the semiquantitive roll-plate culture method [13]. Additional culture tip reports of another catheter tip with the same microorganism in the same patient within 7 days were excluded.

A catheter-related bloodstream infection, here termed "modified CRBSI" (mCRBSI), was defined as isolating the same microorganism with identical antibiogram from ≥1 blood cultures (performed ±7 days around the catheter removal) as the one recovered from the catheter tip. CRBSI episodes diagnosed by differential time-to-positivity or quantitative blood cultures could not be included because this information was not available from the participating laboratories. Incidence rates of mCRBSI were calculated per 1000 admissions using national data on hospital statistics [14]. With this definition, a satisfactory correlation between mCRBSI and CLABSI was previously documented, especially in ICU departments [9]. From 2008 to 2015, an increase of hospital admissions was observed [14]; therefore, a supplementary analysis using hospital-days as denominator (which remained stable) was performed [14]. We then performed trend analyses for the following microorganism groups: *S. aureus*, coagulase-negative Staphylococci (CoNS), *Enterococci*, Enterobacteriaceae, Gram-negative non-fermenters, anaerobes, and fungi. A sub-analysis of the following categories was conducted: age (<65 vs ≥65 years), gender (male vs female), department (ICU vs non-ICU) and type of hospital (community vs university hospital).

Group comparisons were performed using Student's t-test for normally distributed continuous variables, with the Mann-Whitney-Wilcoxon test for non-normally distributed continuous variables, or with Pearson's $\chi 2$ test for dichotomous variables. Models for the overall rate increase per year, adjusted for each of gender, age, type of hospital, department and pathogen (7 groups) were fitted in turn using a Poisson regression model including an offset for the estimated admissions/bed-days in the respective year.

Since the analysis was performed from anonymized non-genetic surveillance data, ethical consent was not required according to the Swiss law for research on human beings (Art. 33 al. 2 LRH). No patients were involved for the purpose of the planning of this study.

Results:

A total of 2'741 mCRBSI episodes were reported between 2008 and 2015, with a mean incidence rate of 342 episodes per year. Twenty-six percent of the episodes (n=714) occurred in ICU departments and 43% (1177) were detected in university hospitals.

The mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions during the study period (-6% per year, p<0.001, Figure 1). The total number of admissions increased from 469'816 in 2008 to 533'017 in 2015. A supplementary analysis using patient-days as denominator showed similar trends (cf. supplementary material). The most notable trends were observed in individuals aged ≥65 years (-3% per year, p=0.04), in university hospitals (-4% per year, p=0.009), and in ICU departments (-4% per year, p=0.04).

CoNS (-7% per year, p<0.001), *S. aureus* (-10% per year, p<0.001) and fungi (-20% per year, p<0.001) all exhibited decreasing trends (Figure 2). On the other hand, enterococci (+3%, p=0.39), Enterobacteriaceae (-2% per year, p=0.25), and Gram-negative non-fermenters (-5%, p=0.1) remained stable over the study period without statistically significant trends. No pathogen group had an upward rate trend over the study period.

Discussion:

Catheter-related infections can either be identified for surveillance purpose (CLABSI) or in clinical terms (CRBSI). Here, we present data from a large surveillance study in 36 hospitals across Switzerland, corresponding to approximately 38% of all national hospital admissions in 2015[14]. Our study appears to mirror a trend of decreasing incidence of CLABSI seen elsewhere, using the more precise and clinically-oriented definition of modified CRBSI. Our report could be of particular interest to other countries where a nationwide surveillance of CLABSI has not been established yet. Indeed, the main finding of this analysis is that, overall, mCRBSI decreased both in ICU and non-ICU patients. A comparison with other surveillance studies is difficult, since few studies relied on this (or a similar) case definition [10] [11] [15]. Our definition was in fact closely linked to one used by Rodriguez-Créixems et al.[9]. Possible reasons for the observed decrease of the mCRBSI rate may include: i) implementation of national initiatives aimed at improving standards in hospital infection prevention [16], ii) a decreasing average duration of hospitalization with early discharge of patients potentially prone to develop CRBSI [17]; iii) changing policies in recommending tip cultures to be taken if a catheter is removed; possibly, catheter tip cultures were less and less frequently recommended by local clinicians over the course of the study period; and iv) an increasing number of admissions from 2008 to 2015 could have led to an apparent decrease in the incidence of mCRBSI. However, a supplementary analysis using patient-days as denominator revealed similar trends as the main analysis.

Interestingly, the incidence of CoNS, *S. aureus*, and fungi decreased significantly over time, while Gram-negative microorganisms and Enterococci remained stable over the study period. These stable trends are of particular concern, since both Enterococci and Gram-negative infections may be associated with high resistance and mortality rates [18] [19]. While surveillance studies on CLABSI or CRBSI mostly focused on overall incidence rates, comparatively little attention has been drawn to the pathogen distribution of catheter-related infections. Recently published data showed that enterococcal catheter infections either predominated in terms of pathogen distribution [6] [20], or showed increasing trends in two reports [2] [21]. Similar trends or patterns were observed for Gram-negative CRBSI [11] [22] [23]. It is

conceivable that the improved standards in hospital infection prevention have had less impact on these particular microorganism groups [22]. An increase in multidrug-resistant strains or the rise in the medical complexity of hospital patients might be further reasons for these trends [23]. Most epidemiological studies so far have neglected to focus on Gram-negative bacteria and Enterococci as causes of catheter infections. We are convinced that further research should focus on these two subsets of CRBSI.

Our study has several limitations. First, our definition of mCRBSI is highly specific and some cases of catheter-related infections might have been missed. In particular, only those CRBSI in which the catheter was removed and submitted to the laboratory were included, which may have led to an underestimation of the total burden of catheter-related infections. However, the same criteria for identifying CRBSI were used throughout the study period and, therefore, the observed *trends* should not be affected. By including episodes up to seven days after the catheter removal, non-catheter related infections may have been included. However, a satisfactory correlation between mCRBSI and CLABSI has previously been documented in ICU patients [9]. Second, neither information on the catheter type was available nor pertinent clinical data. Finally, using admission as denominator, possible changes in device-days were not considered. However, we believe that this drawback is outweighed by the advantage of obtaining reliable mCRBSI trends where clinical surveillance was not feasible. We were unable to correlate the CLABSI rates with our results of mCRBSI, since there is no national CLABSI surveillance in Switzerland yet; to assess the gap between rates of CLABSI and mCRBSI on a national scale would be an interesting next step.

Our data suggest that the overall incidence of mCRBSI in Switzerland is decreasing; however, mCRBSI due to Enterococci and Gram-negative microorganisms did not change over time. These pathogens may grow in importance in catheter-related infections, which would have clinical implications for the choice of empiric treatment.

Figures:

Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups

Footnote: ICU, intensive care unit. All trends were significant

Figure 2: Incidence of mCRBSI caused by CoNS, S. aureus, Enterococci, Enterobacteriaceae, Gram-negative non fermenters, and Fungi

Footnote: ICU, intensive care unit. CoNS, Coagulase-negative Staphylococci. CoNS, *S. aureus* and fungi showed a significant decrease (solid line).

Declarations:

Funding: The ANRESIS database is funded by the Federal Office of Public Health and the University of Bern, Switzerland.

Competing interest statement: There are no financial and non-financial competing interests.

Author contributions: Niccolò Buetti (NB), Jonas Marschall (JM), Elia Lo Priore (ELP) conceived and designed the study. NB, Andrew Atkinson, ELP analyzed the data. NB, JM, Andreas Kronenberg, ELP, Andreas Widmer wrote the manuscript. All authors contributed to the discussion and reviewed the manuscript. All authors commented and approved the final version of the paper. The ANRESIS program summarizes all positive blood and catheter tip cultures from twenty Swiss laboratories, each of them collecting data from several hospitals distributed across Switzerland.

Consent form: As the analysis was performed on anonymized non-genetic surveillance data, ethical consent was not required according to the Swiss law for research on humans (Art. 33 al. 2 LRH).

Data sharing statement: The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Patient involvement: No patients were involved for the purpose of the planning of this study.

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We thank all microbiology laboratories participating in the ANRESIS network: Institute for Laboratory Medicine, Cantonal Hospital Aarau; Central Laboratory, Microbiology Section, Cantonal Hospital Baden; Clinical Microbiology, University Hospital Basel; Viollier AG, Basel; Laboratory Medicine EOLAB, Department of Microbiology, Bellinzona; Institute for Infectious Diseases, University Bern; Microbiology Laboratory, Unilabs, Coppet ; Central Laboratory, Cantonal Hospital Graubünden; Microbiology Laboratory, Hospital Thurgau; Microbiology Laboratory Hôpital Fribourgeois, Fribourg; Bacteriology Laboratory, Geneva University Hospitals, Geneva; ADMED Microbiology, La Chaux-de-Fonds; Institute for Microbiology, Université de Lausanne; Centre for Laboratory Medicine, Cantonal Hospital Luzern; Centre for Laboratory Medicine, Cantonal Hospital Schaffhausen; Centre for Laboratory Medicine Dr. Risch, Schaan; Central Institute, Hôpitaux Valaisans (ICHV), Sitten; Centre of Laboratory Medicine St. Gallen; Institute for Medical Microbiology, University Hospital Zürich; Laboratory for Infectious Diseases, University Children's Hospital Zürich

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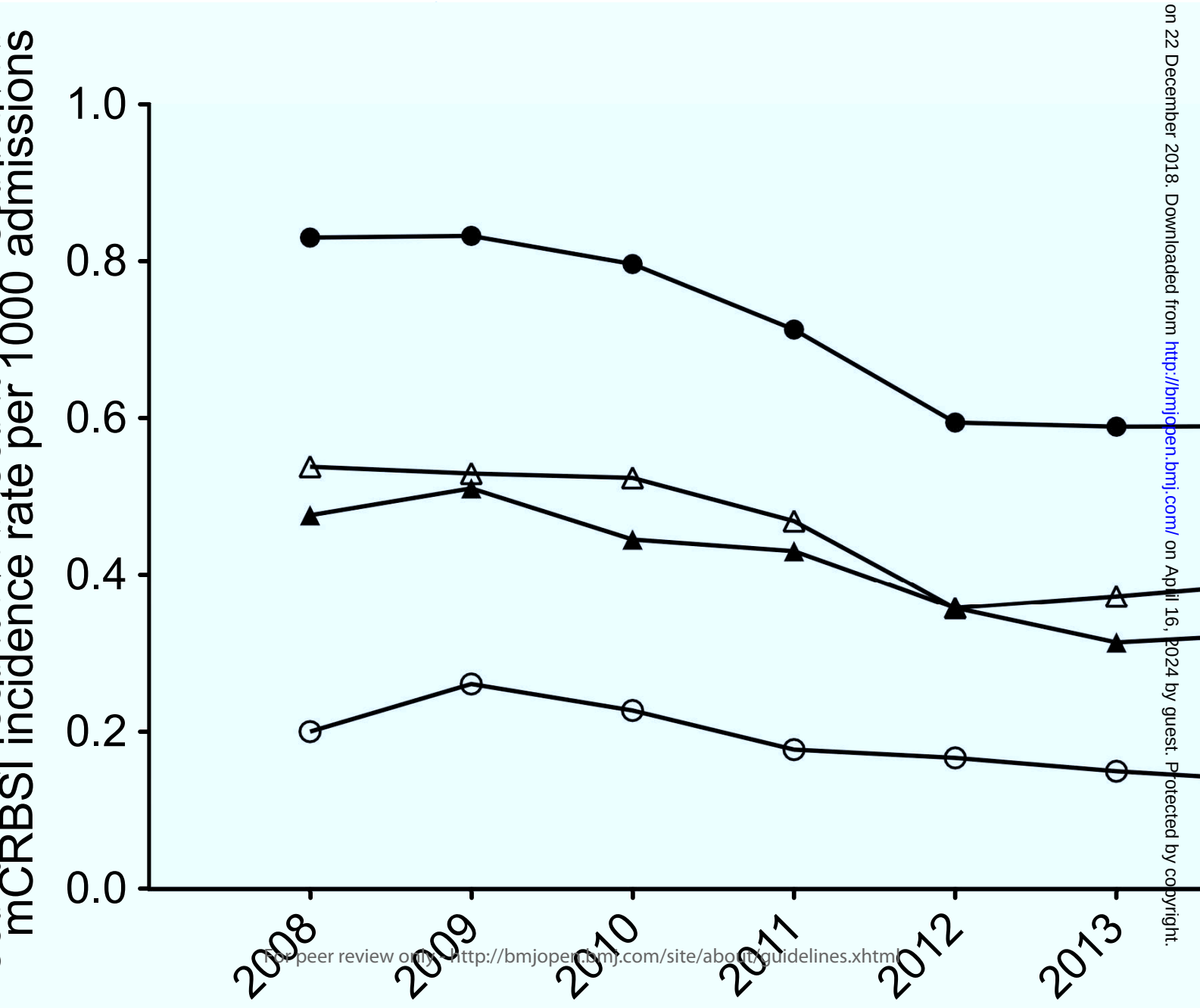
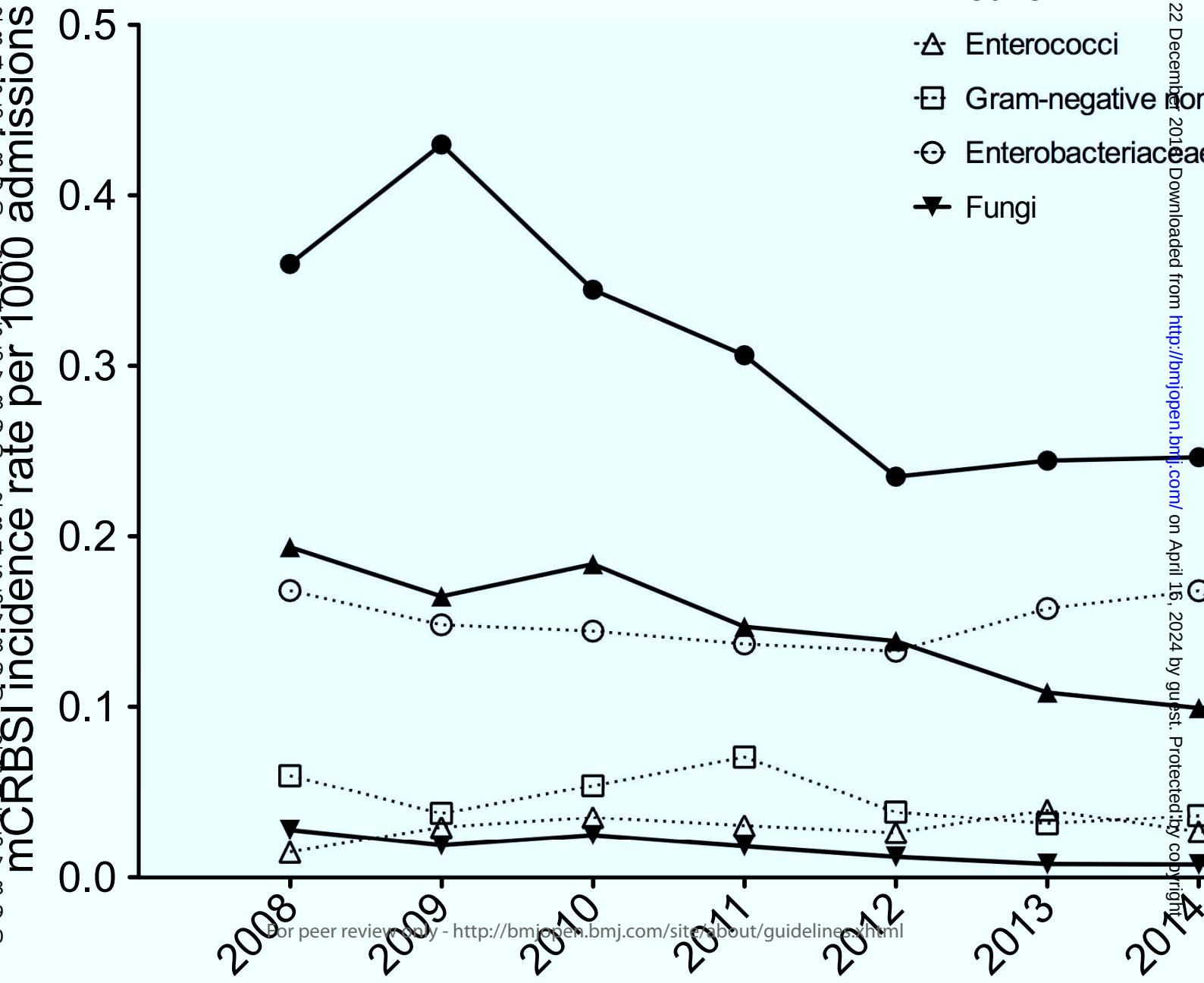




Supplementary material:

Figure A: Incidence of CRBSI per 1000 patient-days:

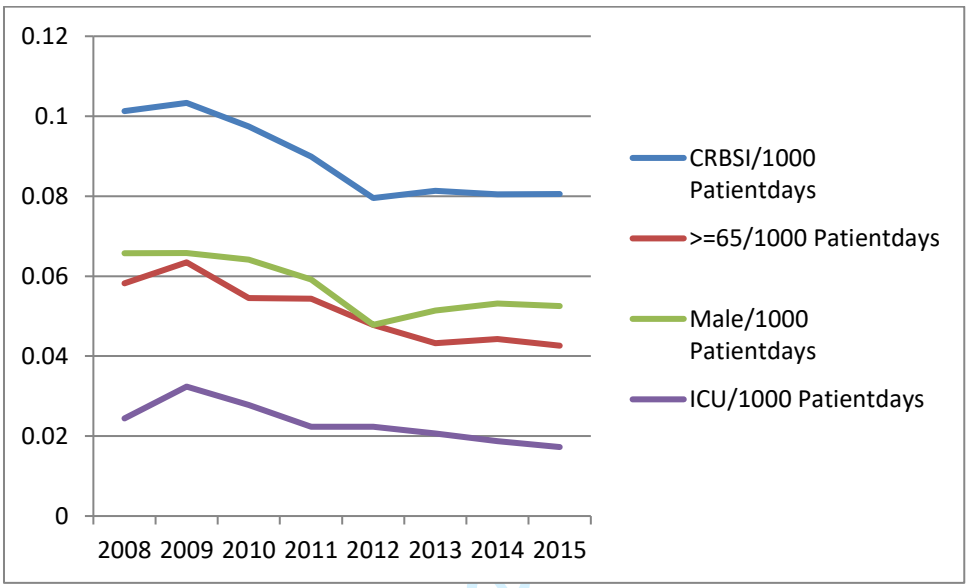
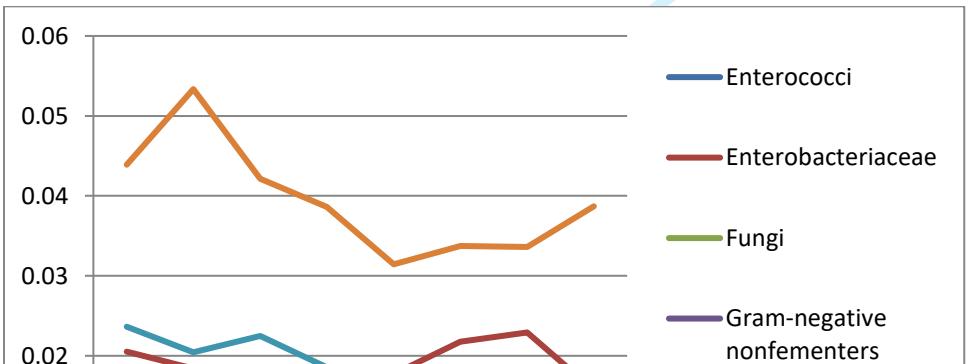


Figure B Incidence of CRBSI by CoNS, S. aureus, Enterococci, Enterobacteriaceae, Gram-negative non fermenters, and Fungi per 1000 patient-days:



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Abstract:

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Setting: National surveillance from 2008 to 2015 for acute hospitals in Switzerland.

Participants: We included acute Swiss hospitals that sent blood cultures and catheter tip culture results on a regular basis during the entire study period to the ANRESIS database.

Outcome measure: A catheter-related bloodstream infection (termed "modified CRBSI", mCRBSI), was defined as isolating the same microorganism with identical antibiogram from ≥1 blood cultures (performed ±7 days around the catheter removal) as the one recovered from the catheter tip. Incidence rates of mCRBSI were calculated per 1000 admissions.

Results: From 2008 to 2015 the mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions (-6% per year, p<0.001). Coagulase-negative staphylococci, *S. aureus* and fungi all exhibited decreasing trends, while rates of Enterococci and Gram-negative bacteria remained stable.

Conclusions: The overall incidence of mCRBSI in Switzerland is decreasing; however, the incidence of mCRBSI due to Enterococci and Gram-negative microorganisms did not change over time. These pathogens may grow in importance in catheter-related infections, which would have clinical implications for the choice of empiric treatment.

Article Summary:

Strengths and limitations of this study

- Provides an estimation of CRBSI on a national scale, an aspect rarely investigated in European countries
- The observed trends should have not been affected by selection bias given the use of the same CRBSI definition throughout the study period.
- While surveillance studies on CLABSI or CRBSI mostly focused on overall incidence rates, we also determinate the pathogen distribution
- No clinical data were available (patient and catheter data)
- Only those CRBSI episodes, for which the catheter was removed and submitted to the laboratory were included

Introduction:

Catheter-related (CRBSI) or central line-associated bloodstream infections (CLABSI) are associated with increased morbidity, mortality, and healthcare costs [1]. The epidemiology of CLABSI has occasionally been evaluated on a national scale, however, studies focused for the most part on the intensive care unit (ICU) setting [2, 3]. In contrast, very few studies investigated CLABSI outside the ICU [4-7]. Of note, the term CLABSI is used for surveillance purposes (where the definition neither requires quantitative criteria nor a microbiological diagnosis of the removed catheter tip), whereas the source of infection in CRBSI is based on a positive culture of the catheter tip. CLABSI surveillance can therefore easily lead to an overestimation of the incidence of CRBSI [8]. More specific definitions based on single-institution surveillance studies have previously been proposed, including the use of admissions [9 10] or bed-days [11] as denominator. Such a definition permits the identification of the catheter as source of infection, considering both catheter tip culture results and blood cultures (i.e., a "modified" CRBSI). Moreover, the incidence of CRBSI has rarely been investigated on a national scale in European countries, given the difficulty in obtaining clinical information. Here, we wanted to perform a first estimation of changes in the epidemiology of CRBSI in Switzerland according to the "modified" CRBSI definition, using a national microbiological surveillance database.

Methods:

We conducted a nationwide, observational study on CRBSI using ANRESIS data from 2008-2015. The ANRESIS program summarizes all positive blood and catheter tip cultures from twenty Swiss laboratories, each of them collecting data from several hospitals distributed across the country. Accordingly, we analysed data of patients from 36 Swiss hospitals,

including only those centres that sent catheter tip information on a regular basis during the entire study period. All five Swiss university hospitals and main regional hospitals were included, representing the majority of hospitalized patients in the country during the study period.

A catheter tip was included in the analysis if at least one microorganism could be cultivated, irrespective of the cut-off of the roll-plate method [12]. In case of a polymicrobial CBRSI, each microorganism isolated was considered as a single event. Information about the microbiological method (quantitative sonication vs semi-quantitative roll-plate culture) was not routinely made available by the participating laboratories. However, in a previous analysis using a similar dataset, 83% of the participating laboratories used the semiquantitive roll-plate culture method [13]. Additional culture tip reports of another catheter tip with the same microorganism in the same patient within 7 days were excluded.

A catheter-related bloodstream infection, here termed “modified CRBSI” (mCRBSI), was defined as isolating the same microorganism with identical antibiogram from ≥1 blood culture (performed ±7 days around the catheter removal) as the one recovered from the catheter tip. CRBSI episodes diagnosed by differential time-to-positivity or quantitative blood cultures could not be included because this information was not available from the participating laboratories. Incidence rates of mCRBSI were calculated per 1000 admissions using national data on hospital statistics [14]. With this definition, a satisfactory correlation between mCRBSI and CLABSI was previously documented [9]. From 2008 to 2015, an increase of hospital admissions was observed [14]; therefore, a supplementary analysis using hospital-days as denominator was performed [14]. Moreover, a supplementary analysis using a stricter definition of mCRBSI (isolation of the same microorganism in blood cultures performed -7 days to +2 days around the catheter removal and in the catheter tip cultures) was performed. We then performed trend analyses for the following microorganism groups: *S. aureus*, coagulase-negative Staphylococci (CoNS), *Enterococci*, Enterobacteriaceae, Gram-negative non-fermenters, anaerobes, and fungi. For Enterobacteriaceae, Gram negative non-fermenters

and enterococci we performed a trend analysis of resistance to ceftriaxone, cefepime and vancomycin, respectively. A sub-analysis of the following categories was conducted: age (<65 vs ≥65 years), gender (male vs female), department (ICU vs non-ICU) and type of hospital (community vs university hospital).

Group comparisons were performed using Student's t-test for normally distributed continuous variables, with the Mann-Whitney-Wilcoxon test for non-normally distributed continuous variables, or with Pearson's $\chi 2$ test for dichotomous variables. Models for the overall rate increase per year, adjusted for each of gender, age, type of hospital, department and pathogen (7 groups) were fitted in turn using a Poisson regression model including an offset for the estimated admissions/bed-days in the respective year.

Since the analysis was performed from anonymized non-genetic surveillance data, neither approval from an ethics committee nor patient consent were required according to the Swiss law for research on human beings (Art. 33 al. 2 LRH).

Patient and Public involvement:

No patients were involved in the design, recruitment or conduct of this study.

Results:

A total of 2'741 mCRBSI episodes were reported between 2008 and 2015, with a mean incidence rate of 342 episodes per year. Twenty-six percent of the episodes (n=714) occurred in ICU departments and 43% (1177) were detected in university hospitals.

The mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions during the study period (-6% per year, p<0.001, Figure 1). The total number of admissions increased from 469'816 in 2008 to 533'017 in 2015. A supplementary analysis using patient-days (which remained constant during the study period) as denominator showed similar trends (cf. supplementary material, Figures A and B). Moreover, comparable trends were observed when limiting the analysis to bloodstream infection episodes -7 days to +2 days

around the catheter removal (cf. supplementary material, Figure C). The most notable trends were observed in individuals aged ≥65 years (-3% per year, p=0.04), in university hospitals (-4% per year, p=0.009), and in ICU departments (-4% per year, p=0.04).

CoNS (-7% per year, p<0.001), *S. aureus* (-10% per year, p<0.001) and fungi (-20% per year, p<0.001) all exhibited decreasing trends (Figure 2). On the other hand, enterococci (+3%, p=0.39), Enterobacteriaceae (-2% per year, p=0.25), and Gram-negative non-fermenters (-5%, p=0.1) remained stable over the study period without statistically significant trends. No pathogen group had an upward rate trend over the study period.

Among Enterobacteriaceae (n=681) a slightly non-significant increase in ceftriaxone resistance was observed during the study period. A significant upward trend in vancomycin resistance was noted in enterococci (n=116). No significant trend was found in cefepime resistance in Gram-negative non-fermenters (n=182), (cf. supplementary material, Figure D1-3).

Discussion:

Catheter-related infections can either be identified for surveillance purpose (CLABSI) or in clinical terms (CRBSI). Here, we present data from a large surveillance study in 36 hospitals across Switzerland, corresponding to approximately 38% of all national hospital admissions in 2015[14]. Our study appears to mirror a trend of decreasing incidence of CLABSI seen elsewhere, using the more precise and clinically-oriented definition of modified CRBSI. Our report could be of particular interest to other countries where no nationwide surveillance of CLABSI has been established yet. Indeed, the main finding of this analysis is that, overall, mCRBSI decreased both in ICU and non-ICU patients. A comparison with other surveillance studies is difficult, since few studies relied on this (or a similar) case definition [10 11 15]. Our definition was in fact closely linked to one used by Rodriguez-Créixems et al.[9]. Possible reasons for the observed decrease of the mCRBSI rate may include: i) implementation of national initiatives aimed at improving standards in hospital infection prevention [16], ii) a

decreasing average duration of hospitalization with early discharge of patients potentially prone to develop CRBSI [17]; iii) changing policies in recommending tip cultures to be taken if a catheter is removed; possibly, catheter tip cultures were less and less frequently recommended by local clinicians over the course of the study period; and iv) an increasing number of admissions from 2008 to 2015 could have led to an apparent decrease in the incidence of mCRBSI. However, a supplementary analysis using patient-days as denominator revealed similar trends as the main analysis.

Interestingly, the incidence of CoNS, *S. aureus*, and fungi decreased significantly over time, while Gram-negative microorganisms and Enterococci remained stable over the study period. These stable trends are of particular concern, since both Enterococci and Gram-negative infections may be associated with high resistance and mortality rates [18 19]. A rise in vancomycin resistance in Enterococci was noted, but given that only four samples showed vancomycin resistance this finding remains difficult to interpret. No significant increase in resistance Gram negative bacteria could be detected. While surveillance studies on CLABSI or CRBSI mostly focused on overall incidence rates, comparatively little attention has been drawn to the pathogen distribution of catheter-related infections. Recently published data showed that enterococcal catheter infections either predominated in terms of pathogen distribution [6 20], or showed increasing trends in two reports [2 21]. Similar trends or patterns were observed for Gram-negative CRBSI [11 22 23]. It is conceivable that the improved standards in hospital infection prevention have had less impact on these particular microorganism groups [22]. An increase in multidrug-resistant strains or the rise in the medical complexity of hospital patients might be further reasons for these trends [23]. Most epidemiological studies so far have neglected to focus on Gram-negative bacteria and Enterococci as causes of catheter infections. We are convinced that further research should focus on these two subsets of CRBSI.

Our study has several limitations. First, our definition of mCRBSI is highly specific and some cases of catheter-related infections might have been missed. In particular, only those CRBSI

in which the catheter was removed and submitted to the laboratory were included, which may have led to an underestimation of the total burden of catheter-related infections. However, the same criteria for identifying CRBSI were used throughout the study period and, therefore, the observed trends should have not be affected. The inclusion of cases with only 1 positive blood culture for commensals could have led to an overestimation of the CRBSI rate (e.g., in case of colonisation or contamination). However, by requiring a positive catheter tip we think that this effect has been mitigated. By including episodes up to seven days after the catheter removal, non-catheter related infections may have been included. However, a satisfactory correlation between mCRBSI and CLABSI has previously been documented in ICU patients [9]. Second, neither information on the catheter type nor pertinent clinical data was available, which may have led to the inclusion of peripheral venous/arterial catheters or catheter tips sent without clinical indication. Finally, using admission as denominator, possible changes in device-days were not considered. However, we believe that this drawback is outweighed by the advantage of obtaining reliable mCRBSI trends where clinical surveillance was not feasible. We were unable to correlate the CLABSI rates with our results of mCRBSI, since there is no national CLABSI surveillance in Switzerland yet; to assess the gap between rates of CLABSI and mCRBSI on a national scale would be an interesting next step.

Our data suggest that the overall incidence of mCRBSI in Switzerland is decreasing; however, mCRBSI due to Enterococci and Gram-negative microorganisms did not change over time. These pathogens may grow in importance in catheter-related infections, which would have clinical implications for the choice of empiric treatment.

Figures:

Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups

Footnote: ICU, intensive care unit. All trends were significant

Figure 2: Incidence of mCRBSI caused by CoNS, S. aureus, Enterococci, Enterobacteriaceae, Gram-negative non-fermenters, and Fungi

Footnote: ICU, intensive care unit.

Declarations:

Funding: No funding was required for this study

Competing interest statement: There are no financial and non-financial competing interests.

Author contributions: Niccolò Buetti (NB), Jonas Marschall (JM), Elia Lo Priore (ELP) conceived and designed the study. NB, Andrew Atkinson, ELP analyzed the data. NB, JM, Andreas Kronenberg, ELP and Andreas Widmer wrote the manuscript. All authors contributed to the discussion and reviewed the manuscript. All authors commented and approved the final version of the paper. The ANRESIS program summarizes all positive blood and catheter tip cultures from twenty Swiss laboratories, each of them collecting data from several hospitals distributed across Switzerland.

Consent form: As the analysis was performed on anonymized non-genetic surveillance data, ethical consent was not required according to the Swiss law for research on humans (Art. 33 al. 2 LRH).

Data sharing statement: The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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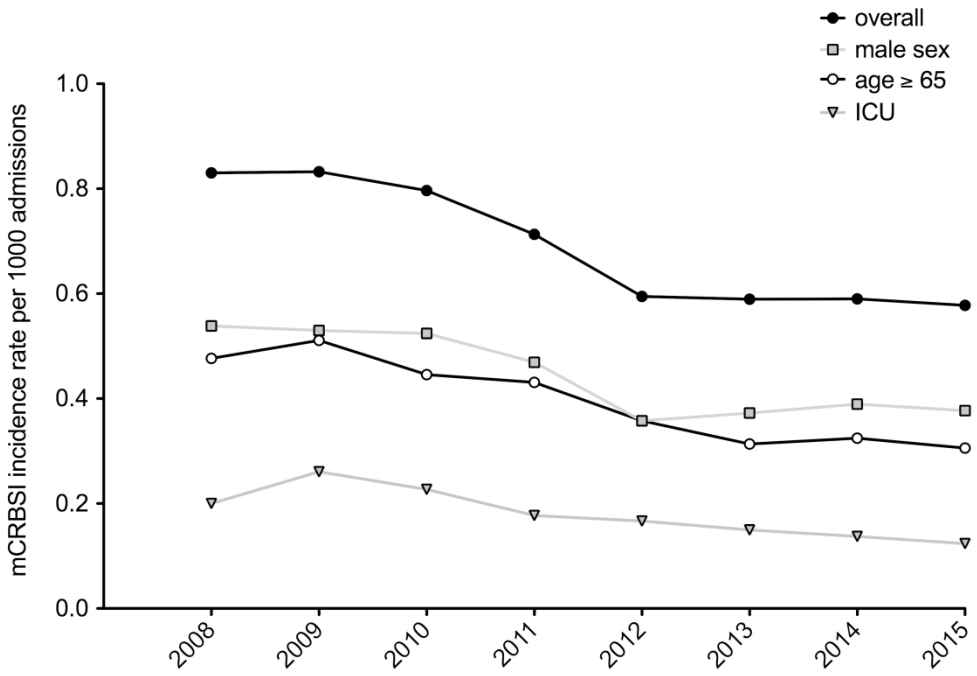

Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups
Footnote: ICU, intensive care unit. All trends were significant

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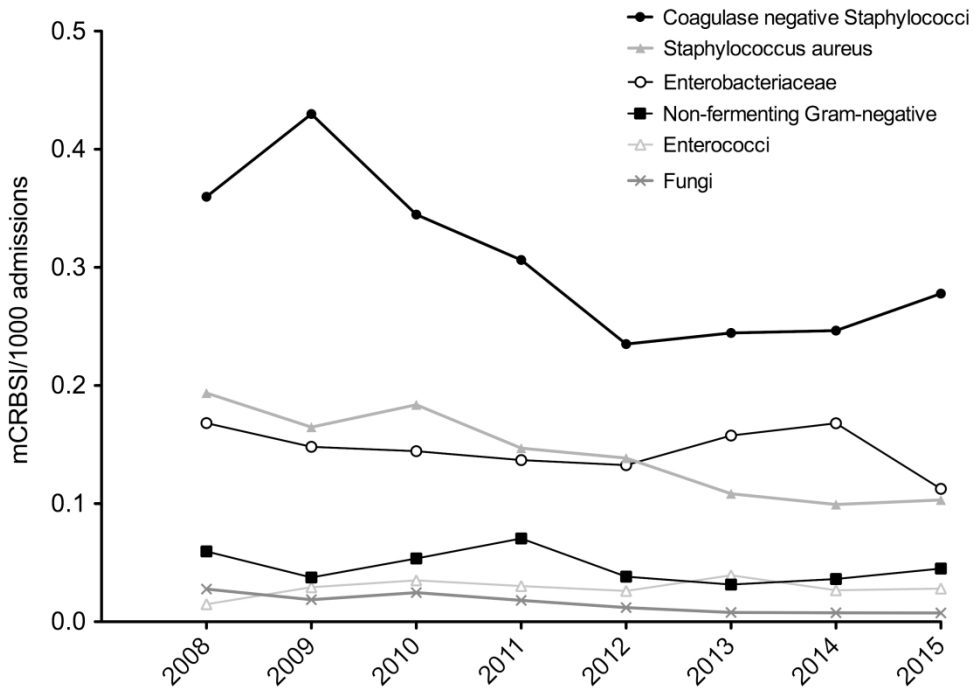


Figure 2: Incidence of mCRBSI caused by CoNS, S. aureus, Enterococci, Enterobacteriaceae, Gram-negative non-fermenters, and Fungi
Footnote: ICU, intensive care unit.

251x180mm (300 x 300 DPI)

Supplementary Material

Figure A:
mCRBSI incidence rate per 1000 patient-days: Overall and subgourps

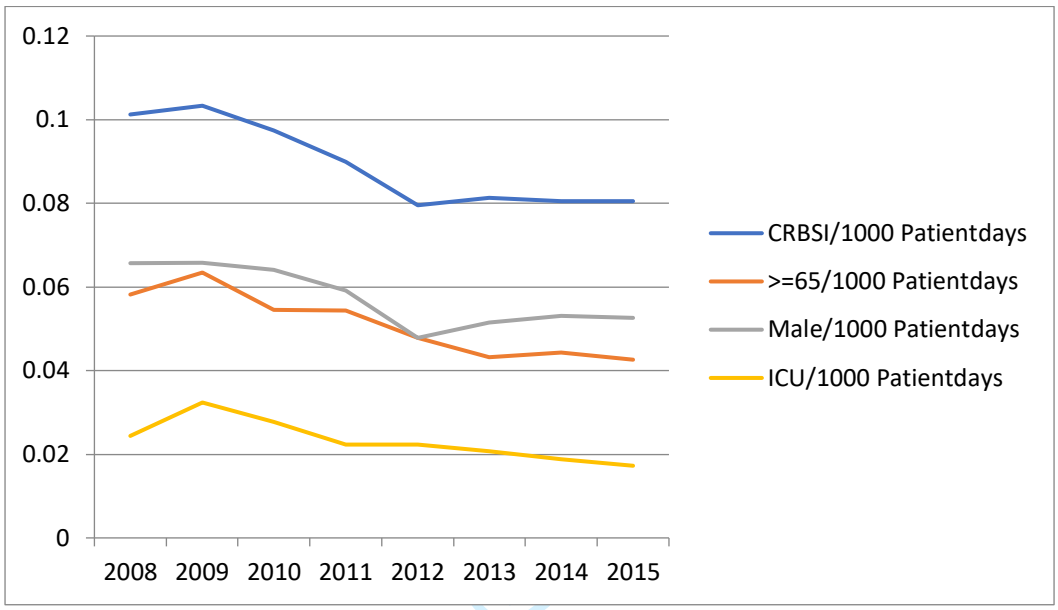


Figure B:
mCRBSI incidence rate per 1000 patient-days by causative organism

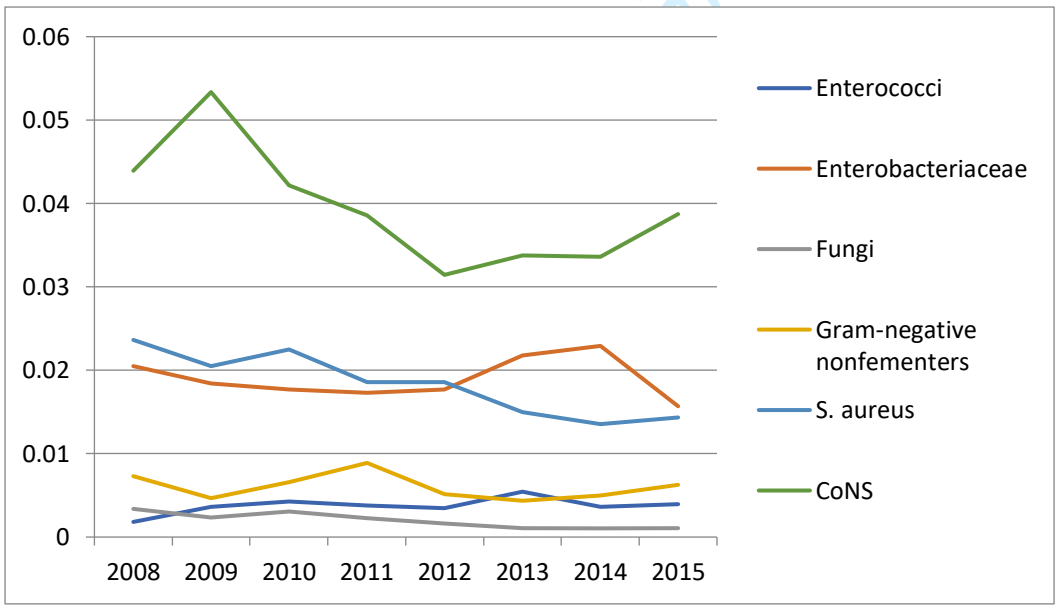
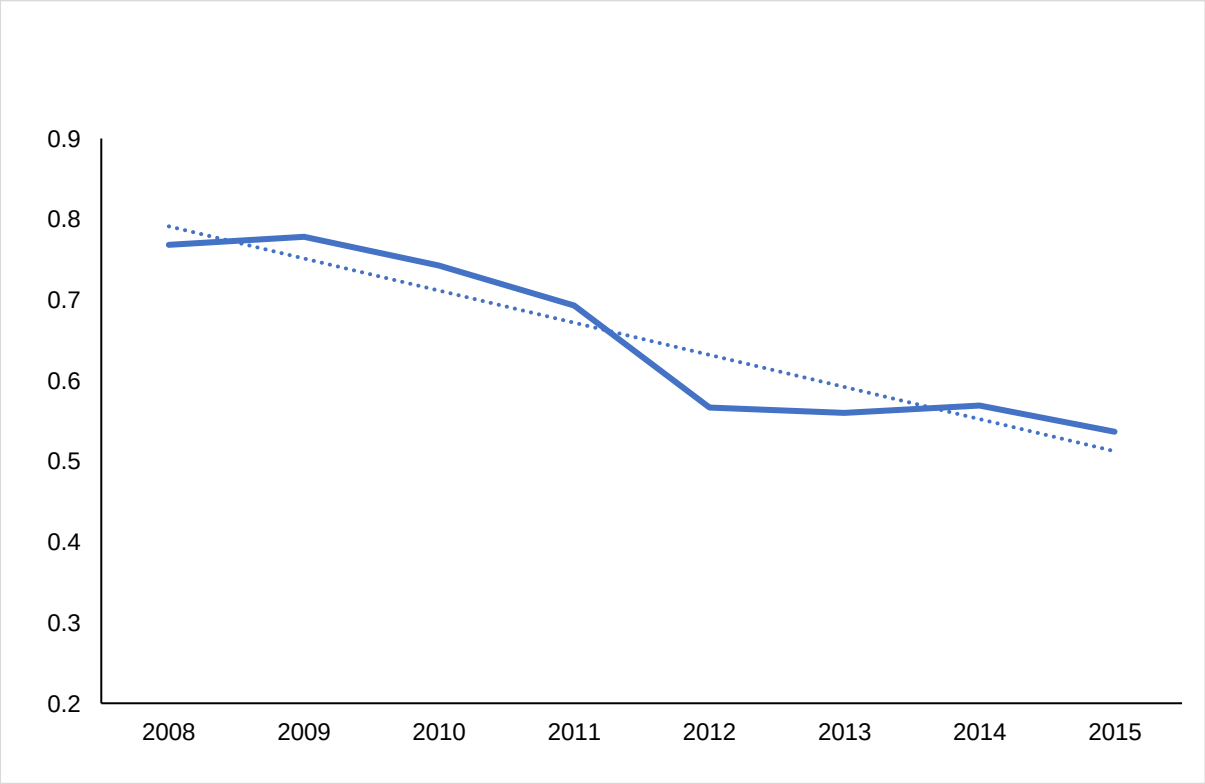


Figure C
Overall mCRBSI incidence rate per 1000 admissions



Footnote: *mCRBSI was defined as isolating the same microorganism with identical antibiogram from ≥1 blood cultures (performed -7 days to +2 days around the catheter removal) as the one recovered from the catheter tip.

Figure D (1-3)

Figure D1
Evolution of ceftriaxone resistance in Enterobacteriaceae

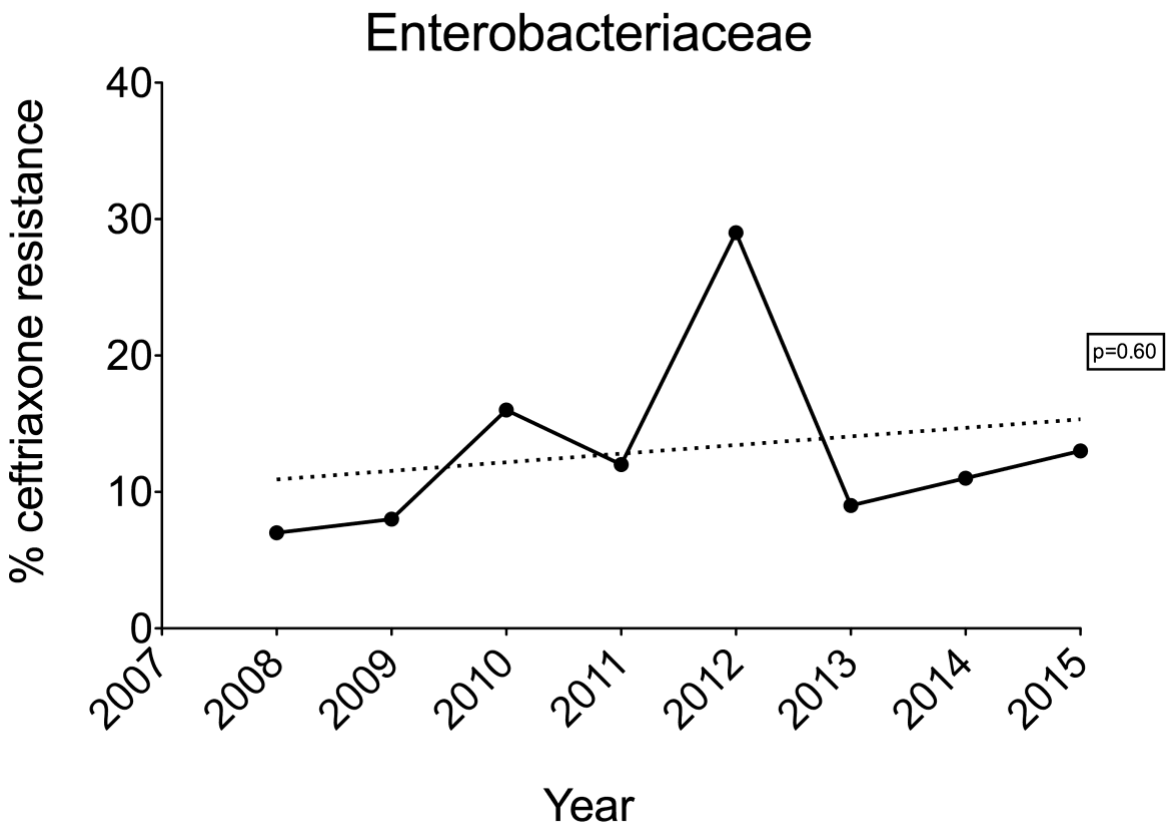


Figure D2
Evolution of vancomycin resistance in Enterococci

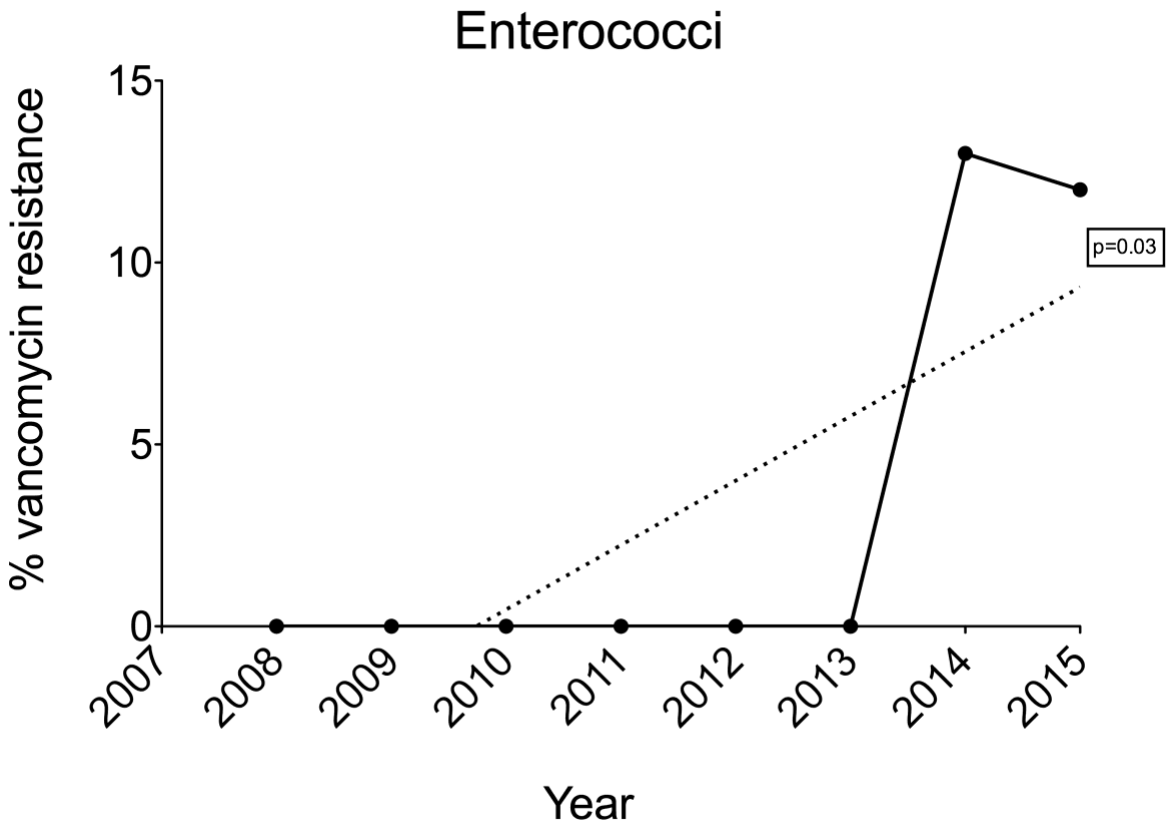
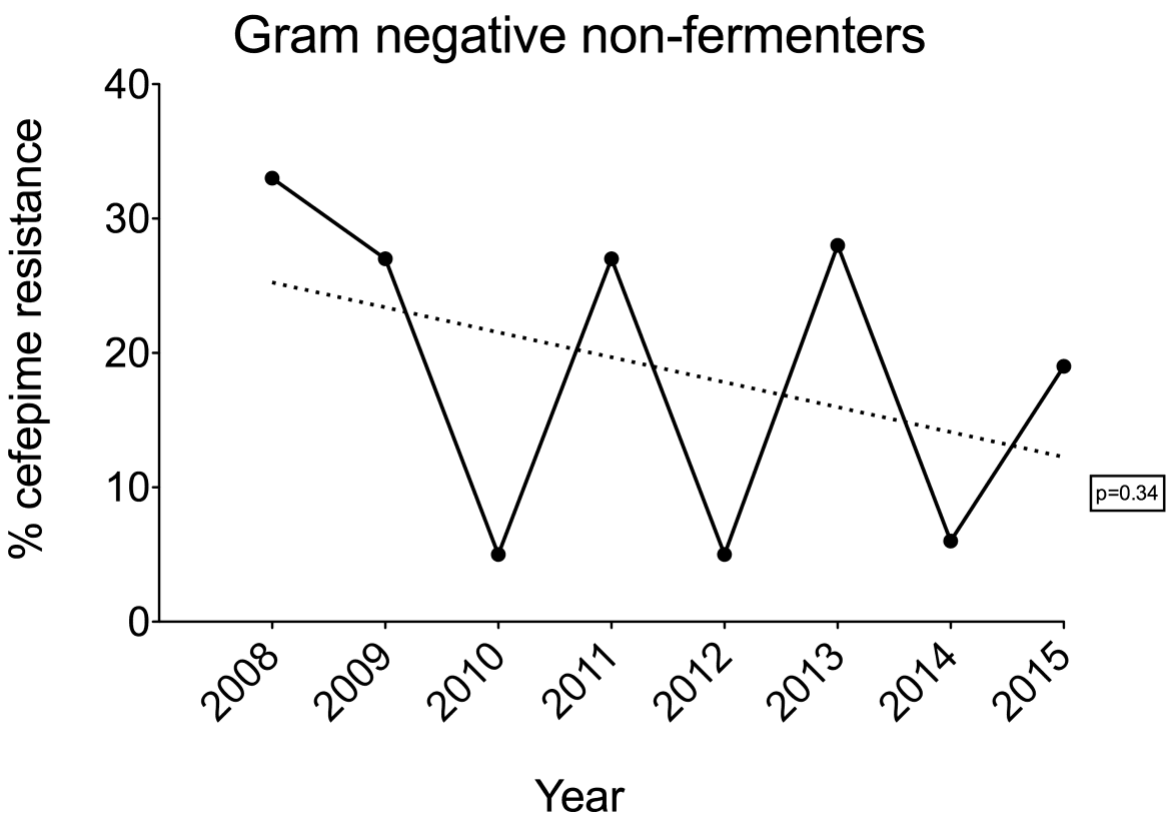


Figure D3
Evolution of cefepime resistance in Gram negative non-fermenters



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. See p. 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. See p. 1
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. See p. 3
Objectives	3	State specific objectives, including any prespecified hypotheses. See p. 3
Methods		
Study design	4	Present key elements of study design early in the paper. See p. 3, 4, 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. See p. 3, 4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. See p. 4, 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. See p. 4, 5, 6, 7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. See p. 4, 5
Bias	9	Describe any efforts to address potential sources of bias. See p. 5, 6, 7, 8
Study size	10	Explain how the study size was arrived at. Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. See p. 5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses See p. 5.

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Not applicable
		(b) Give reasons for non-participation at each stage. Not applicable
		(c) Consider use of a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders See p. 1, 2
		(b) Indicate number of participants with missing data for each variable of interest. Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) See p. 5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time See p. 5, 6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Not applicable
		(*b*) Report category boundaries when continuous variables were categorized Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses See p. 5, 6
Discussion		
Key results	18	Summarise key results with reference to study objectives. See p. 6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. See p. 6, 7, 8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. See p. 6, 7, 8
Generalisability	21	Discuss the generalisability (external validity) of the study results. See p. 6, 7, 8
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. See p. 10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.