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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

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3 1 **Catheter-related infections: Does the spectrum of microbial causes change over**
4 2 **time? A nationwide surveillance study**
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33 28 **Key words:** CRBSI, catheter infections, bloodstream infections, CLABSI, catheter tip, trends

34 29 **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.

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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 determined the pathogen distribution.

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45 78 **Introduction:**
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8 79 Catheter-related (CRBSI) or central line-associated bloodstream infections (CLABSI) are
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10 80 associated with increased morbidity, mortality, and healthcare costs ¹. The epidemiology of
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12 81 CLABSI has occasionally been evaluated on a national scale, however, studies focused for
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14 82 the most part on the intensive care unit (ICU) setting ^{2 3}. In contrast, very few studies
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16 83 investigated CLABSI outside the ICU ⁴⁻⁷. Of note, the term CLABSI is used for surveillance
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18 84 (where the definition neither requires quantitative criteria nor a microbiological diagnosis of
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20 85 the removed catheter tip), whereas the source of infection in CRBSI is based on a positive
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22 86 culture of the catheter tip. CLABSI surveillance can therefore easily lead to an overestimation
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24 87 of the incidence of CRBSI ⁸. More specific surveillance definitions based on single-institution
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26 88 surveillance have previously been proposed, including studies using admissions ^{9 10} or bed-
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28 89 days ¹¹ as denominator. Such a definition permits the identification of the catheter as source
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30 90 of infection, considering both catheter tip culture results and blood cultures (i.e., a “modified”
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32 91 CRBSI). Moreover, the incidence of CRBSI has rarely been investigated on a national scale
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34 92 in European countries, given the difficulty in obtaining clinical information. Here, we wanted
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36 93 to perform a first exploration of the epidemiology of “modified” CRBSI in Switzerland, using a
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38 94 national surveillance database.

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4243 96 **Methods:**
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46 97 We conducted a nationwide, observational study on CRBSI using ANRESIS data from 2008-
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48 98 2015. The ANRESIS program summarizes all positive blood and catheter tip cultures from
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50 99 twenty Swiss laboratories, each of them collecting data from several hospitals distributed
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52 100 across the country. Accordingly, we analyzed data of patients from 36 Swiss hospitals,
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54 101 including only those centers that sent catheter tip information on a regular basis during the
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56 102 entire study period. All five Swiss university hospital and main regional hospitals were

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3 103 included, representing the majority of hospitalized patient in the country during the study
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5 104 period.

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7 105 A catheter tip was included in the analysis if at least one microorganism could be cultivated
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9 106 from it, irrespective of the cut-off of the roll-plate method ¹². If more than one pathogen was
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11 107 isolated from the same catheter tip, each individual pathogen was considered as a separate
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13 108 episode. Information about the microbiological method (quantitative sonication vs semi-
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15 109 quantitative roll-plate culture) was not routinely made available by the participating
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17 110 laboratories. However, in a previous analysis using a similar dataset, 83% of the participating
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19 111 laboratories used the semiquantitative roll-plate culture method ¹³. Additional culture tip reports
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21 112 of another catheter tip with the same microorganism in the same patient within 7 days were
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23 113 excluded.

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26 114 A catheter-related bloodstream infection, here termed “modified CRBSI” (mCRBSI), was
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28 115 defined as isolating the same microorganism with identical antibiogram from ≥ 1 blood
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30 116 cultures (performed ± 7 days around the catheter removal) as the one recovered from the
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32 117 catheter tip. CRBSI episodes diagnosed by differential time-to-positivity or quantitative blood
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34 118 cultures could not be included because this information was not available from the
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36 119 participating laboratories. Incidence rates of mCRBSI were calculated per 1000 admissions
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38 120 using national data on hospital statistics ¹⁴. With this definition, a satisfactory correlation
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40 121 between mCRBSI and CLABSI was previously documented, especially in ICU departments ⁹.
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42 122 From 2008 to 2015, an increase of hospital admissions was observed ¹⁴; therefore, a
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44 123 supplementary analysis using hospital-days as denominator (which remained stable) was
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46 124 performed ¹⁴. We then performed trend analyses for the following microorganism groups: *S.*
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48 125 *aureus*, coagulase-negative Staphylococci (CoNS), *Enterococci*, Enterobacteriaceae, Gram-
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50 126 negative non-fermenters, anaerobes, and fungi. A sub-analysis of the following categories
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52 127 was conducted: age (<65 vs ≥ 65 years), gender (male vs female), department (ICU vs non-
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54 128 ICU) and type of hospital (community vs university hospital).

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3 129 Group comparisons were performed using Student's t-test for normally distributed continuous
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5 130 variables, with the Mann-Whitney-Wilcoxon test for non-normally distributed continuous
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7 131 variables, or with Pearson's χ^2 test for dichotomous variables. Models for the overall rate
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9 132 increase per year, adjusted for each of gender, age, type of hospital, department and
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11 133 pathogen (7 groups) were fitted in turn using a Poisson regression model including an offset
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13 134 for the estimated admissions/bed-days in the respective year.

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15 135 Since the analysis was performed from anonymized non-genetic surveillance data, ethical
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17 136 consent was not required according to the Swiss law for research on human beings (Art. 33
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19 137 al. 2 LRH). No patients were involved for the purpose of the planning of this study.

138 **Results:**

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25 139 A total of 2'741 mCRBSI episodes were reported between 2008 and 2015, with a mean
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27 140 incidence rate of 342 episodes per year. Twenty-six percent of the episodes (n=714)
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29 141 occurred in ICU departments and 43% (1177) were detected in university hospitals.

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31 142 The mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions during
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33 143 the study period (-6% per year, $p < 0.001$, Figure 1). The total number of admissions
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35 144 increased from 469'816 in 2008 to 533'017 in 2015. A supplementary analysis using patient-
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37 145 days as denominator showed similar trends (cf. supplementary material). The most notable
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39 146 trends were observed in individuals aged ≥ 65 years (-3% per year, $p = 0.04$), in university
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41 147 hospitals (-4% per year, $p = 0.009$), and in ICU departments (-4% per year, $p = 0.04$).

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44 148 CoNS (-7% per year, $p < 0.001$), *S. aureus* (-10% per year, $p < 0.001$) and fungi (-20% per
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46 149 year, $p < 0.001$) all exhibited decreasing trends (Figure 2). On the other hand, enterococci
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48 150 (+3%, $p = 0.39$), Enterobacteriaceae (-2% per year, $p = 0.25$), and Gram-negative non-
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50 151 fermenters (-5%, $p = 0.1$) remained stable over the study period without statistically significant
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52 152 trends. No pathogen group had an upward rate trend over the study period.

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56 154 **Discussion:**

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3 155 Catheter-related infections can either be identified for surveillance purpose (CLABSI) or in
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5 156 clinical terms (CRBSI). Here, we present data from a large surveillance study in 36 hospitals
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7 157 across Switzerland, corresponding to approximately 38% of all national hospital admissions
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9 158 in 2015¹⁴. Our study appears to mirror a trend of decreasing incidence of CLABSI seen
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11 159 elsewhere, using the more precise and clinically-oriented definition of modified CRBSI. Our
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13 160 report could be of particular interest to other countries where a nationwide surveillance of
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15 161 CLABSI has not been established yet. Indeed, the main finding of this analysis is that,
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17 162 overall, mCRBSI decreased both in ICU and non-ICU patients. A comparison with other
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19 163 surveillance studies is difficult, since few studies relied on this (or a similar) case definition ¹⁰
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21 164 ^{11 15}. Our definition was in fact closely linked to one used by Rodriguez-Créixems et al.⁹.
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23 165 Possible reasons for the observed decrease of the mCRBSI rate may include: i)
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25 166 implementation of national initiatives aimed at improving standards in hospital infection
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27 167 prevention ¹⁶, ii) a decreasing average duration of hospitalization with early discharge of
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29 168 patients potentially prone to develop CRBSI ¹⁷; iii) changing policies in recommending tip
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31 169 cultures to be taken if a catheter is removed; possibly, catheter tip cultures were less and
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33 170 less frequently recommended by local clinicians over the course of the study period; and iv)
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35 171 an increasing number of admissions from 2008 to 2015 could have led to an apparent
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37 172 decrease in the incidence of mCRBSI. However, a supplementary analysis using patient-
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39 173 days as denominator revealed similar trends as the main analysis.

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41 174 Interestingly, the incidence of CoNS, *S. aureus*, and fungi decreased significantly over time,
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43 175 while Gram-negative microorganisms and Enterococci remained stable over the study
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45 176 period. These stable trends are of particular concern, since both Enterococci and Gram-
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47 177 negative infections may be associated with high resistance and mortality rates ^{18 19}. While
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49 178 surveillance studies on CLABSI or CRBSI mostly focused on overall incidence rates,
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51 179 comparatively little attention has been drawn to the pathogen distribution of catheter-related
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53 180 infections. Recently published data showed that enterococcal catheter infections either
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55 181 predominated in terms of pathogen distribution ^{6 20}, or showed increasing trends in two
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57 182 reports ^{2 21}. Similar trends or patterns were observed for Gram-negative CRBSI ^{11 22 23}. It is

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3 183 conceivable that the improved standards in hospital infection prevention have had less
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5 184 impact on these particular microorganism groups²². An increase in multidrug-resistant strains
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7 185 or the rise in the medical complexity of hospital patients might be further reasons for these
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9 186 trends²³. Most epidemiological studies so far have neglected to focus on Gram-negative
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11 187 bacteria and Enterococci as causes of catheter infections. We are convinced that further
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13 188 research should focus on these two subsets of CRBSI.

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15 189 Our study has several limitations. First, our definition of mCRBSI is highly specific and some
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17 190 cases of catheter-related infections might have been missed. In particular, only those CRBSI
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19 191 in which the catheter was removed and submitted to the laboratory were included, which may
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21 192 have led to an underestimation of the total burden of catheter-related infections. However,
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23 193 the same criteria for identifying CRBSI were used throughout the study period and, therefore,
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25 194 the observed *trends* should not be affected. By including episodes up to seven days after the
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27 195 catheter removal, non-catheter related infections may have been included. However, a
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29 196 satisfactory correlation between mCRBSI and CLABSI has previously been documented in
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31 197 ICU patients⁹. Second, neither information on the catheter type was available nor pertinent
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33 198 clinical data. Finally, using admission as denominator, possible changes in device-days were
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35 199 not considered. However, we believe that this drawback is outweighed by the advantage of
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37 200 obtaining reliable mCRBSI trends where clinical surveillance was not feasible. We were
38
39 201 unable to correlate the CLABSI rates with our results of mCRBSI, since there is no national
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41 202 CLABSI surveillance in Switzerland yet; to assess the gap between rates of CLABSI and
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43 203 mCRBSI on a national scale would be an interesting next step.

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46 204 Our data suggest that the overall incidence of mCRBSI in Switzerland is decreasing;
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48 205 however, mCRBSI due to Enterococci and Gram-negative microorganisms did not change
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50 206 over time. These pathogens may grow in importance in catheter-related infections, which
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52 207 would have clinical implications for the choice of empiric treatment.

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11 212 **Figures:**
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14 213 Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups
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19 215 Footnote: ICU, intensive care unit. All trends were significant
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24 217 Figure 2: Incidence of mCRBSI caused by CoNS, *S. aureus*, Enterococci,
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26 218 Enterobacteriaceae, Gram-negative non fermenters, and Fungi
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32 220 Footnote: ICU, intensive care unit. CoNS, Coagulase-negative Staphylococci. CoNS, *S.*
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34 221 *aureus* and fungi showed a significant decrease (solid line).
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3 223 **Declarations:**

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11
12 227 interests.

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16
17 229 conceived and designed the study. NB, Andrew Atkinson, ELP analyzed the data. NB, JM,
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19 230 Andreas Kronenberg, ELP, Andreas Widmer wrote the manuscript. All authors contributed to
20
21 231 the discussion and reviewed the manuscript. All authors commented and approved the final
22
23 232 version of the paper. The ANRESIS program summarizes all positive blood and catheter tip
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25 233 cultures from twenty Swiss laboratories, each of them collecting data from several hospitals
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27 234 distributed across Switzerland.

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30 235 **Consent form:** As the analysis was performed on anonymized non-genetic surveillance
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32 236 data, ethical consent was not required according to the Swiss law for research on humans
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34 237 (Art. 33 al. 2 LRH).

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36 238 **Data sharing statement:** The datasets generated and/or analyzed during the current study
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38 239 are not publicly available but are available from the corresponding author on reasonable
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40 240 request.

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43 241 **Patient involvement:** No patients were involved for the purpose of the planning of this study.
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11 248 Laboratory Medicine EOLAB, Department of Microbiology, Bellinzona; Institute for Infectious
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13 249 Diseases, University Bern; Microbiology Laboratory, Unilabs, Coppet ; Central Laboratory,
14
15 250 Cantonal Hospital Graubünden; Microbiology Laboratory, Hospital Thurgau; Microbiology
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17 251 Laboratory Hôpital Fribourgeois, Fribourg; Bacteriology Laboratory, Geneva University
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19 252 Hospitals, Geneva; ADMED Microbiology, La Chaux-de-Fonds; Institute for Microbiology,
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21 253 Université de Lausanne; Centre for Laboratory Medicine, Cantonal Hospital Luzern; Centre
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23 254 for Laboratory Medicine, Cantonal Hospital Schaffhausen; Centre for Laboratory Medicine
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25 255 Dr. Risch, Schaan; Central Institute, Hôpitaux Valaisans (ICHV), Sitten; Centre of Laboratory
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27 256 Medicine St. Gallen; Institute for Medical Microbiology, University Hospital Zürich; Laboratory
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29 257 for Infectious Diseases, University Children's Hospital Zürich
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31
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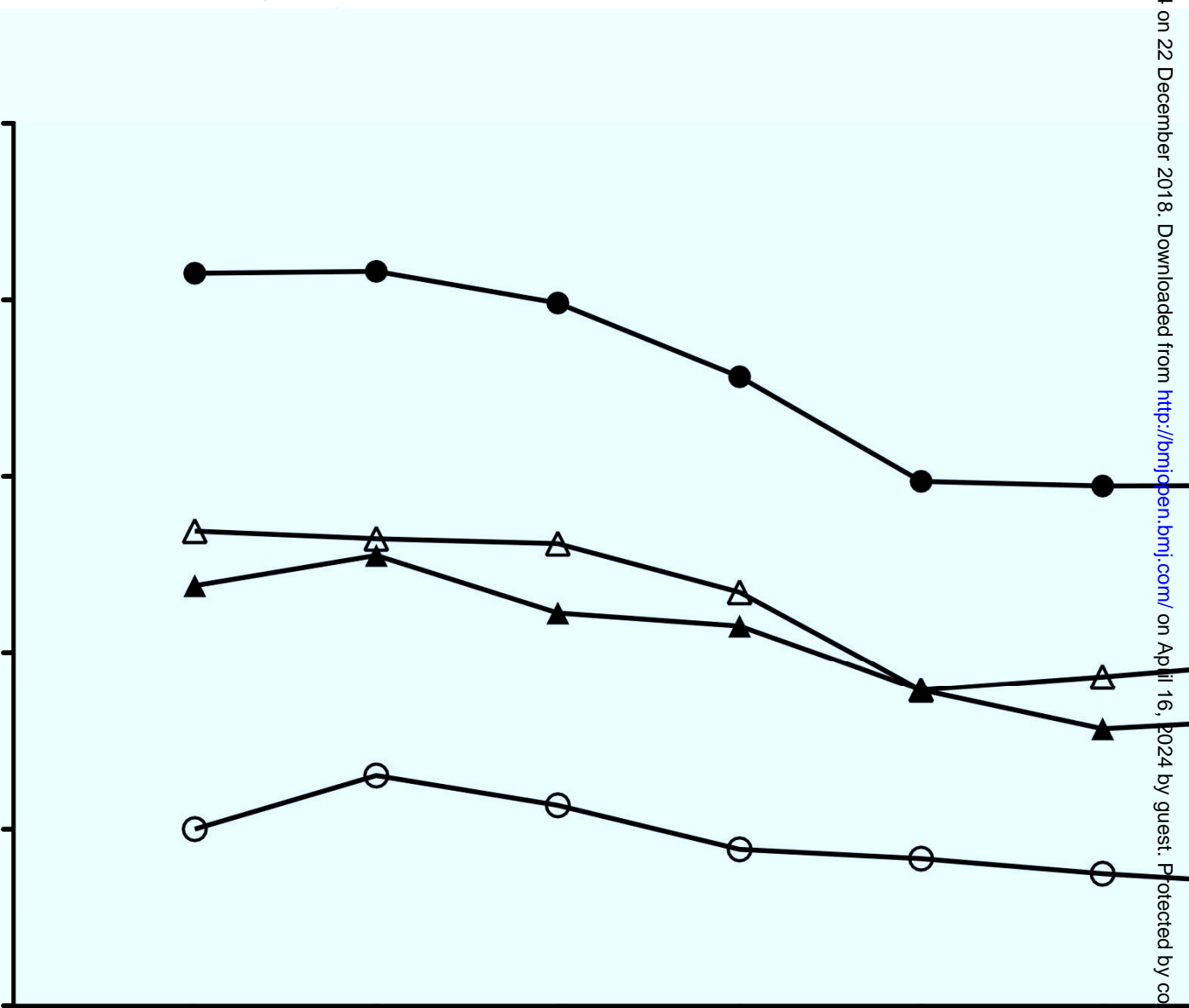
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mCRBSI incidence rate per 1000 admissions

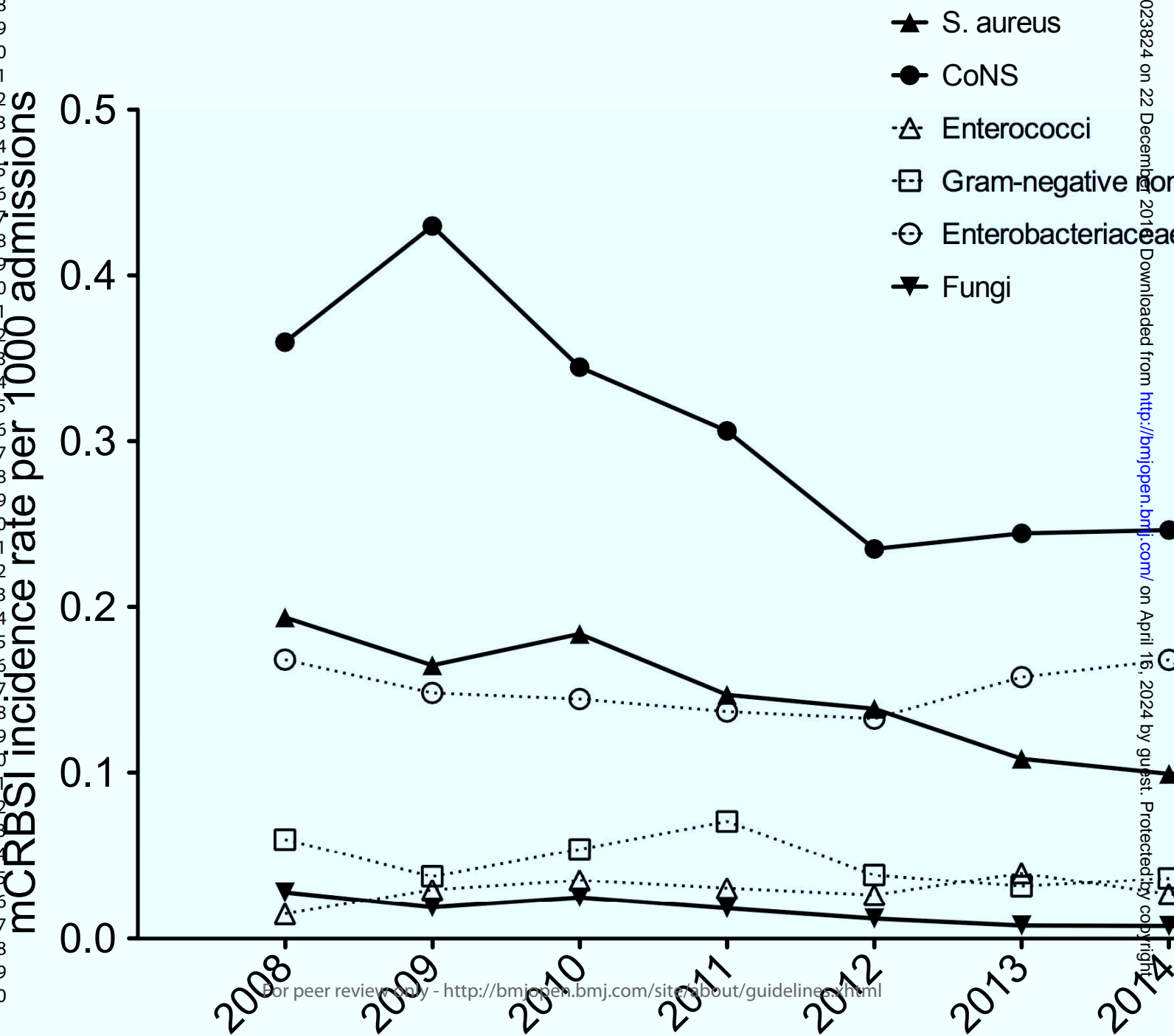
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Supplementary material:

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

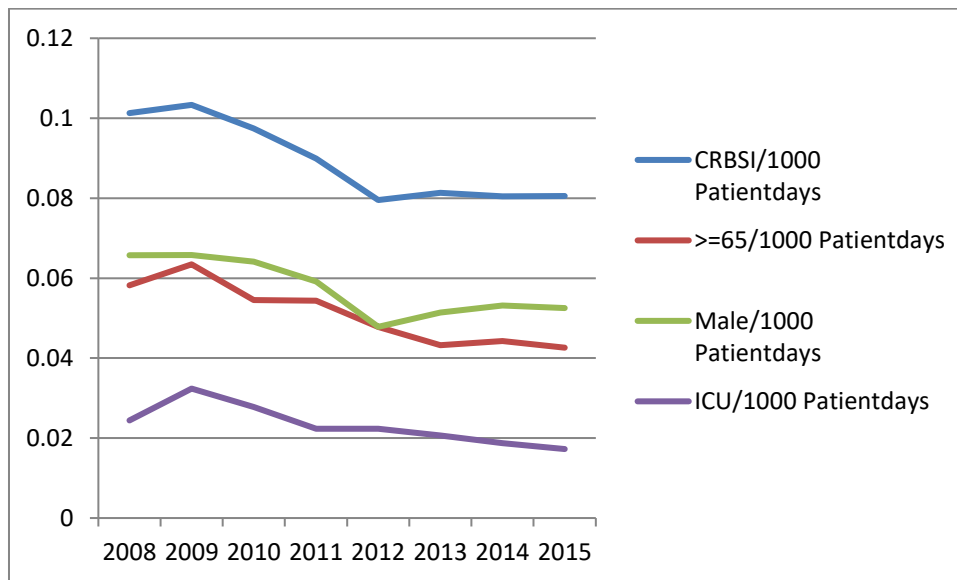
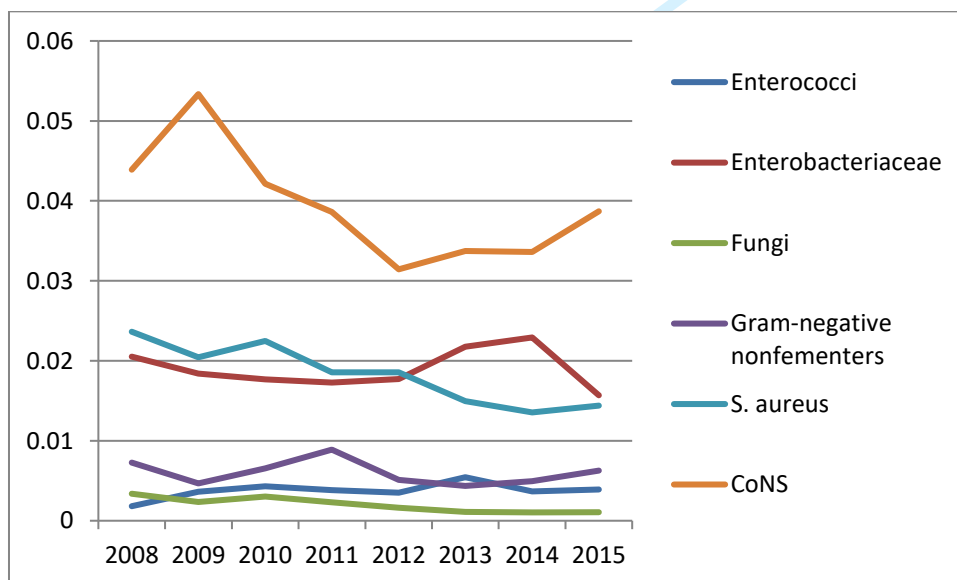


Figure B Incidence of CRBSI by CoNS, S. aureus, Enterococci, Enterobacteriaceae, Gram-negative non fermenters, and Fungi per 1000 patient-days:



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

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Primary Subject Heading:	Infectious diseases
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Keywords:	CRBSI, catheter infection, bloodstream infection, CLABSI, catheter tip, trends

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Manuscripts

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3 1 **Catheter-related infections: Does the spectrum of microbial causes change over**
4 2 **time? A nationwide surveillance study**
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6 3

7
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17 12
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23 18 *University of Bern, Switzerland; S. Luyet, Swiss Conference of the Cantonal Ministers of*
24 19 *Public Health, Switzerland; P. Nordmann, Molecular and Medical Microbiology, Department*
25 20 *of Medicine, University Fribourg, Switzerland; V. Perreten, Institute of Veterinary*
26 21 *Bacteriology, University of Bern, Switzerland; J.-C. Piffaretti, Interlifescience, Massagno,*
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33 28 **Key words:** CRBSI, catheter infections, bloodstream infections, CLABSI, catheter tip, trends

34 29 **Running title:** Epidemiology of catheter-related bloodstream infections

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41 33 **Word count:**

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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.

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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

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77 Introduction:

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

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96 Methods:

97 We conducted a nationwide, observational study on CRBSI using ANRESIS data from 2008-
98 2015. The ANRESIS program summarizes all positive blood and catheter tip cultures from
99 twenty Swiss laboratories, each of them collecting data from several hospitals distributed
100 across the country. Accordingly, we analysed data of patients from 36 Swiss hospitals,

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3 101 including only those centres that sent catheter tip information on a regular basis during the
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5 102 entire study period. All five Swiss university hospitals and main regional hospitals were
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7 103 included, representing the majority of hospitalized patients in the country during the study
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9 104 period.

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11 105 A catheter tip was included in the analysis if at least one microorganism could be cultivated,
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13 106 irrespective of the cut-off of the roll-plate method ¹². In case of a polymicrobial CBRSI, each
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15 107 microorganism isolated was considered as a single event. Information about the
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17 108 microbiological method (quantitative sonication vs semi-quantitative roll-plate culture) was
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19 109 not routinely made available by the participating laboratories. However, in a previous
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21 110 analysis using a similar dataset, 83% of the participating laboratories used the semiquantitative
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23 111 roll-plate culture method ¹³. Additional culture tip reports of another catheter tip with the same
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25 112 microorganism in the same patient within 7 days were excluded.

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28 113 A catheter-related bloodstream infection, here termed “modified CRBSI” (mCRBSI), was
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30 114 defined as isolating the same microorganism with identical antibiogram from ≥ 1 blood culture
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32 115 (performed ± 7 days around the catheter removal) as the one recovered from the catheter tip.
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34 116 CRBSI episodes diagnosed by differential time-to-positivity or quantitative blood cultures
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36 117 could not be included because this information was not available from the participating
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38 118 laboratories. Incidence rates of mCRBSI were calculated per 1000 admissions using national
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40 119 data on hospital statistics ¹⁴. With this definition, a satisfactory correlation between mCRBSI
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42 120 and CLABSI was previously documented ⁹. From 2008 to 2015, an increase of hospital
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44 121 admissions was observed ¹⁴; therefore, a supplementary analysis using hospital-days as
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46 122 denominator was performed ¹⁴. Moreover, a supplementary analysis using a stricter definition
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48 123 of mCRBSI (isolation of the same microorganism in blood cultures performed -7 days to +2
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50 124 days around the catheter removal and in the catheter tip cultures) was performed. We then
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52 125 performed trend analyses for the following microorganism groups: *S. aureus*, coagulase-
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54 126 negative Staphylococci (CoNS), *Enterococci*, Enterobacteriaceae, Gram-negative non-
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56 127 fermenters, anaerobes, and fungi. For Enterobacteriaceae, Gram negative non-fermenters

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3 128 and enterococci we performed a trend analysis of resistance to ceftriaxone, cefepime and
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5 129 vancomycin, respectively. A sub-analysis of the following categories was conducted: age
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7 130 (<65 vs ≥65 years), gender (male vs female), department (ICU vs non-ICU) and type of
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9 131 hospital (community vs university hospital).

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11 132 Group comparisons were performed using Student's t-test for normally distributed continuous
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13 133 variables, with the Mann-Whitney-Wilcoxon test for non-normally distributed continuous
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15 134 variables, or with Pearson's χ^2 test for dichotomous variables. Models for the overall rate
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17 135 increase per year, adjusted for each of gender, age, type of hospital, department and
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19 136 pathogen (7 groups) were fitted in turn using a Poisson regression model including an offset
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21 137 for the estimated admissions/bed-days in the respective year.

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24 138 Since the analysis was performed from anonymized non-genetic surveillance data, neither
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26 139 approval from an ethics committee nor patient consent were required according to the Swiss
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28 140 law for research on human beings (Art. 33 al. 2 LRH).

30 31 141 **Patient and Public involvement:**

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34 142 No patients were involved in the design, recruitment or conduct of this study.

35 36 143 **Results:**

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39 144 A total of 2'741 mCRBSI episodes were reported between 2008 and 2015, with a mean
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41 145 incidence rate of 342 episodes per year. Twenty-six percent of the episodes (n=714)
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43 146 occurred in ICU departments and 43% (1177) were detected in university hospitals.

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46 147 The mCRBSI incidence rate decreased from 0.83 to 0.58 episodes/1000 admissions during
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48 148 the study period (-6% per year, $p < 0.001$, Figure 1). The total number of admissions
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50 149 increased from 469'816 in 2008 to 533'017 in 2015. A supplementary analysis using patient-
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52 150 days (which remained constant during the study period) as denominator showed similar
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54 151 trends (cf. supplementary material, Figures A and B). Moreover, comparable trends were
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56 152 observed when limiting the analysis to bloodstream infection episodes -7 days to +2 days

153 around the catheter removal (cf. supplementary material, Figure C). The most notable trends
154 were observed in individuals aged ≥ 65 years (-3% per year, $p=0.04$), in university hospitals (-
155 4% per year, $p=0.009$), and in ICU departments (-4% per year, $p=0.04$).

156 CoNS (-7% per year, $p<0.001$), *S. aureus* (-10% per year, $p<0.001$) and fungi (-20% per
157 year, $p<0.001$) all exhibited decreasing trends (Figure 2). On the other hand, enterococci
158 (+3%, $p=0.39$), Enterobacteriaceae (-2% per year, $p=0.25$), and Gram-negative non-
159 fermenters (-5%, $p=0.1$) remained stable over the study period without statistically significant
160 trends. No pathogen group had an upward rate trend over the study period.

161 Among Enterobacteriaceae ($n=681$) a slightly non-significant increase in ceftriaxone
162 resistance was observed during the study period. A significant upward trend in vancomycin
163 resistance was noted in enterococci ($n=116$). No significant trend was found in cefepime
164 resistance in Gram-negative non-fermenters ($n=182$), (cf. supplementary material, Figure D1-
165 3).

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167 Discussion:

168 Catheter-related infections can either be identified for surveillance purpose (CLABSI) or in
169 clinical terms (CRBSI). Here, we present data from a large surveillance study in 36 hospitals
170 across Switzerland, corresponding to approximately 38% of all national hospital admissions
171 in 2015¹⁴. Our study appears to mirror a trend of decreasing incidence of CLABSI seen
172 elsewhere, using the more precise and clinically-oriented definition of modified CRBSI. Our
173 report could be of particular interest to other countries where no nationwide surveillance of
174 CLABSI has been established yet. Indeed, the main finding of this analysis is that, overall,
175 mCRBSI decreased both in ICU and non-ICU patients. A comparison with other surveillance
176 studies is difficult, since few studies relied on this (or a similar) case definition^{10 11 15}. Our
177 definition was in fact closely linked to one used by Rodriguez-Créixems et al.⁹. Possible
178 reasons for the observed decrease of the mCRBSI rate may include: i) implementation of
179 national initiatives aimed at improving standards in hospital infection prevention¹⁶, ii) a

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3 180 decreasing average duration of hospitalization with early discharge of patients potentially
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5 181 prone to develop CRBSI ¹⁷; iii) changing policies in recommending tip cultures to be taken if a
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7 182 catheter is removed; possibly, catheter tip cultures were less and less frequently
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9 183 recommended by local clinicians over the course of the study period; and iv) an increasing
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11 184 number of admissions from 2008 to 2015 could have led to an apparent decrease in the
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13 185 incidence of mCRBSI. However, a supplementary analysis using patient-days as
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15 186 denominator revealed similar trends as the main analysis.

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17 187 Interestingly, the incidence of CoNS, *S. aureus*, and fungi decreased significantly over time,
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19 188 while Gram-negative microorganisms and Enterococci remained stable over the study
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21 189 period. These stable trends are of particular concern, since both Enterococci and Gram-
22
23 190 negative infections may be associated with high resistance and mortality rates ^{18 19}. A rise in
24
25 191 vancomycin resistance in Enterococci was noted, but given that only four samples showed
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27 192 vancomycin resistance this finding remains difficult to interpret. No significant increase in
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29 193 resistance Gram negative bacteria could be detected. While surveillance studies on CLABSI
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31 194 or CRBSI mostly focused on overall incidence rates, comparatively little attention has been
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33 195 drawn to the pathogen distribution of catheter-related infections. Recently published data
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35 196 showed that enterococcal catheter infections either predominated in terms of pathogen
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37 197 distribution ^{6 20}, or showed increasing trends in two reports ^{2 21}. Similar trends or patterns
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39 198 were observed for Gram-negative CRBSI ^{11 22 23}. It is conceivable that the improved
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41 199 standards in hospital infection prevention have had less impact on these particular
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43 200 microorganism groups ²². An increase in multidrug-resistant strains or the rise in the medical
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45 201 complexity of hospital patients might be further reasons for these trends ²³. Most
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47 202 epidemiological studies so far have neglected to focus on Gram-negative bacteria and
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49 203 Enterococci as causes of catheter infections. We are convinced that further research should
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51 204 focus on these two subsets of CRBSI.

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54 205 Our study has several limitations. First, our definition of mCRBSI is highly specific and some
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56 206 cases of catheter-related infections might have been missed. In particular, only those CRBSI

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3 207 in which the catheter was removed and submitted to the laboratory were included, which may
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5 208 have led to an underestimation of the total burden of catheter-related infections. However,
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7 209 the same criteria for identifying CRBSI were used throughout the study period and, therefore,
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9 210 the observed trends should have not be affected. The inclusion of cases with only 1 positive
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11 211 blood culture for commensals could have led to an overestimation of the CRBSI rate (e.g., in
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13 212 case of colonisation or contamination). However, by requiring a positive catheter tip we think
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15 213 that this effect has been mitigated. By including episodes up to seven days after the catheter
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17 214 removal, non-catheter related infections may have been included. However, a satisfactory
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19 215 correlation between mCRBSI and CLABSI has previously been documented in ICU patients
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21 216 ⁹. Second, neither information on the catheter type nor pertinent clinical data was available,
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23 217 which may have led to the inclusion of peripheral venous/arterial catheters or catheter tips
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25 218 sent without clinical indication. Finally, using admission as denominator, possible changes in
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27 219 device-days were not considered. However, we believe that this drawback is outweighed by
28
29 220 the advantage of obtaining reliable mCRBSI trends where clinical surveillance was not
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31 221 feasible. We were unable to correlate the CLABSI rates with our results of mCRBSI, since
32
33 222 there is no national CLABSI surveillance in Switzerland yet; to assess the gap between rates
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35 223 of CLABSI and mCRBSI on a national scale would be an interesting next step.

36
37 224 Our data suggest that the overall incidence of mCRBSI in Switzerland is decreasing;
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39 225 however, mCRBSI due to Enterococci and Gram-negative microorganisms did not change
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41 226 over time. These pathogens may grow in importance in catheter-related infections, which
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43 227 would have clinical implications for the choice of empiric treatment.

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3 233 **Figures:**
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5 234 Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups
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8 235 Footnote: ICU, intensive care unit. All trends were significant
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14 237 Figure 2: Incidence of mCRBSI caused by CoNS, *S. aureus*, Enterococci,
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16 238 Enterobacteriaceae, Gram-negative non-fermenters, and Fungi
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18 239 Footnote: ICU, intensive care unit.
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3 240 **Declarations:**

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5 241 **Funding:** No funding was required for this study

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7
8 242 **Competing interest statement:** There are no financial and non-financial competing
9 interests.

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11
12 244 **Author contributions:** Niccolò Buetti (NB), Jonas Marschall (JM), Elia Lo Priore (ELP)
13 conceived and designed the study. NB, Andrew Atkinson, ELP analyzed the data. NB, JM,
14 Andreas Kronenberg, ELP and Andreas Widmer wrote the manuscript. All authors
15 contributed to the discussion and reviewed the manuscript. All authors commented and
16 approved the final version of the paper. The ANRESIS program summarizes all positive
17 blood and catheter tip cultures from twenty Swiss laboratories, each of them collecting data
18 from several hospitals distributed across Switzerland.
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28 251 **Consent form:** As the analysis was performed on anonymized non-genetic surveillance
29 data, ethical consent was not required according to the Swiss law for research on humans
30 (Art. 33 al. 2 LRH).
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34 254 **Data sharing statement:** The datasets generated and/or analyzed during the current study
35 are not publicly available but are available from the corresponding author on reasonable
36 request.
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3 259 **Acknowledgments:**
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7 261 Laboratory Medicine, Cantonal Hospital Aarau; Central Laboratory, Microbiology Section,
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9 262 Cantonal Hospital Baden; Clinical Microbiology, University Hospital Basel; Viollier AG, Basel;
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11 263 Laboratory Medicine EOLAB, Department of Microbiology, Bellinzona; Institute for Infectious
12
13 264 Diseases, University Bern; Microbiology Laboratory, Unilabs, Coppet ; Central Laboratory,
14
15 265 Cantonal Hospital Graubünden; Microbiology Laboratory, Hospital Thurgau; Microbiology
16
17 266 Laboratory Hôpital Fribourgeois, Fribourg; Bacteriology Laboratory, Geneva University
18
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20
21 268 Université de Lausanne; Centre for Laboratory Medicine, Cantonal Hospital Luzern; Centre
22
23 269 for Laboratory Medicine, Cantonal Hospital Schaffhausen; Centre for Laboratory Medicine
24
25 270 Dr. Risch, Schaan; Central Institute, Hôpitaux Valaisans (ICHV), Sitten; Centre of Laboratory
26
27 271 Medicine St. Gallen; Institute for Medical Microbiology, University Hospital Zürich; Laboratory
28
29 272 for Infectious Diseases, University Children's Hospital Zürich
30
31
32 273 In addition, we appreciate the steering committee of ANRESIS for supporting this analysis.
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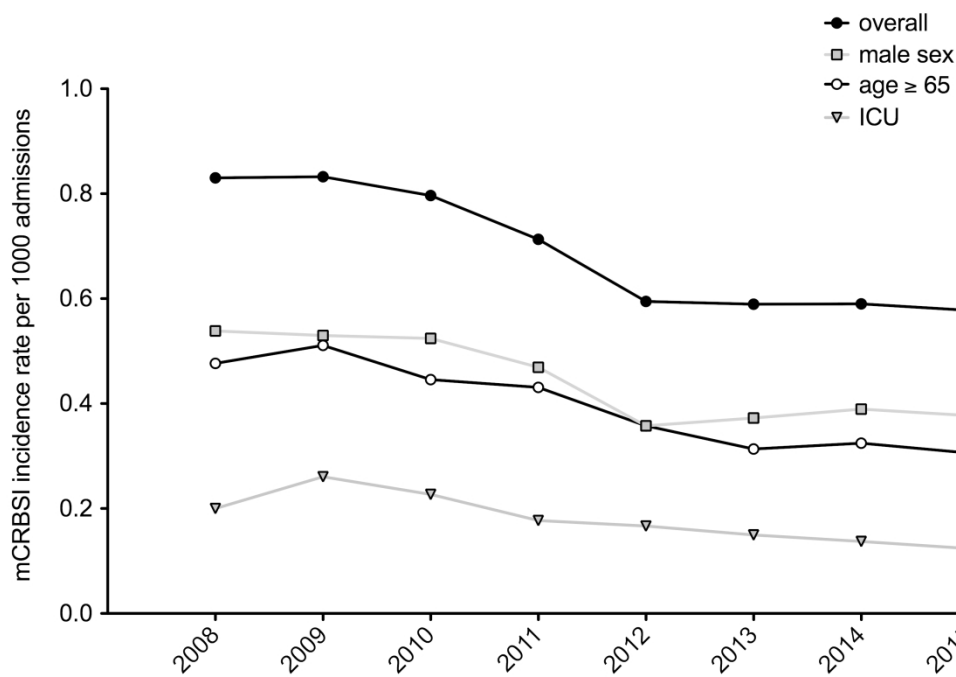


Figure 1: Incidence of mCRBSI per 1000 hospital admissions: overall trends and subgroups
Footnote: ICU, intensive care unit. All trends were significant

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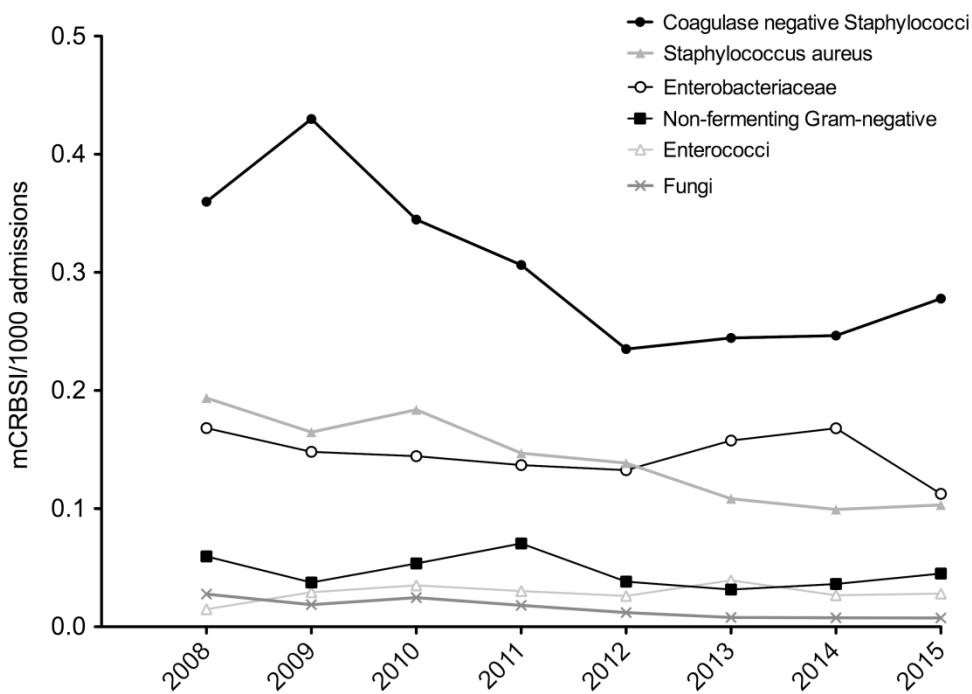


Figure 2: Incidence of mCRBSI caused by CoNS, *S. aureus*, Enterococci, Enterobacteriaceae, Gram-negative non-fermenters, and Fungi
Footnote: ICU, intensive care unit.

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Supplementary Material

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

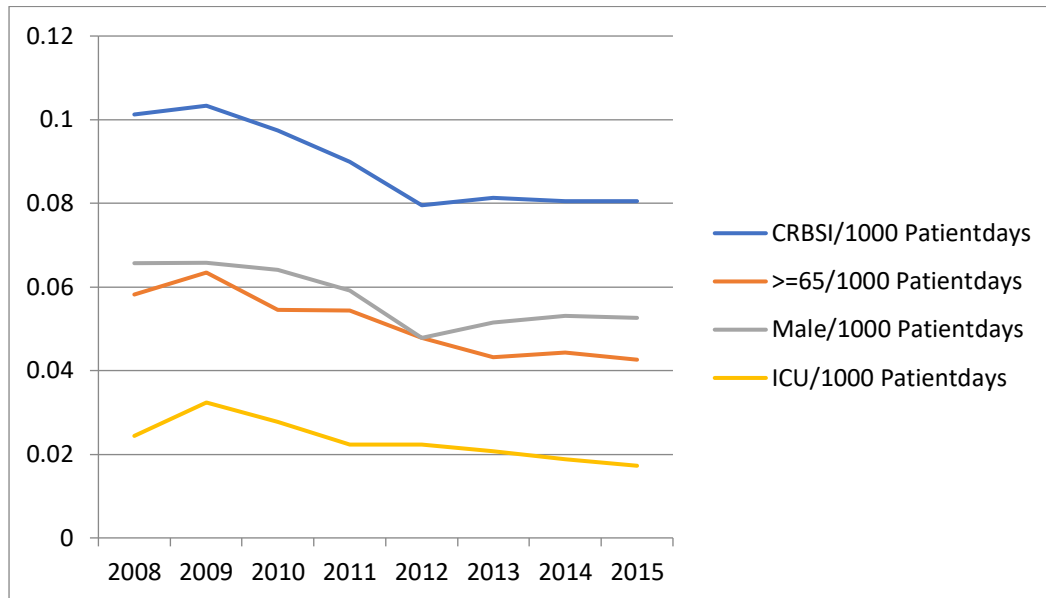


Figure B:
mCRBSI incidence rate per 1000 patient-days by causative organism

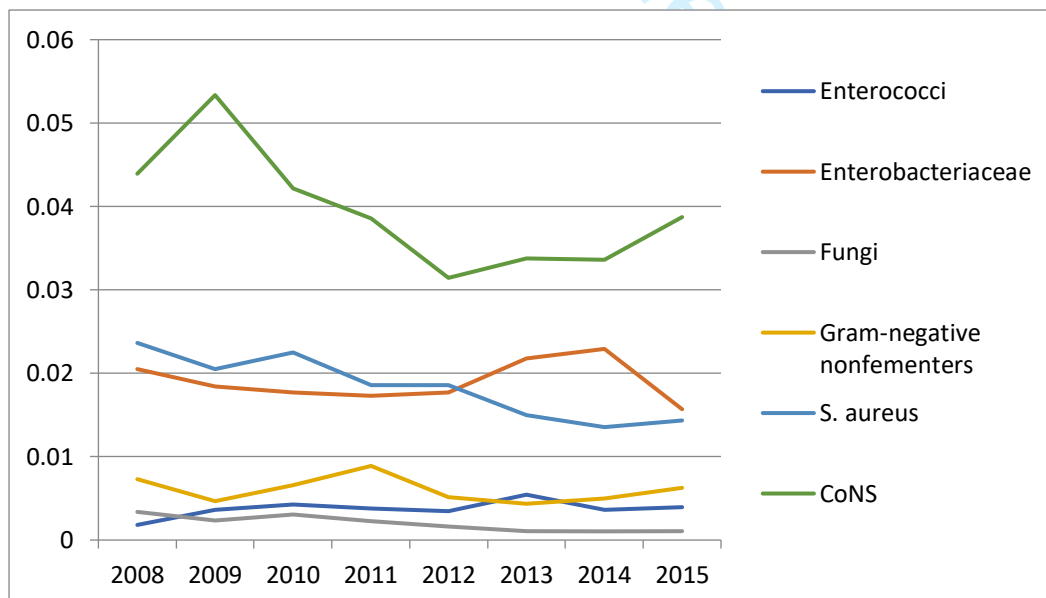
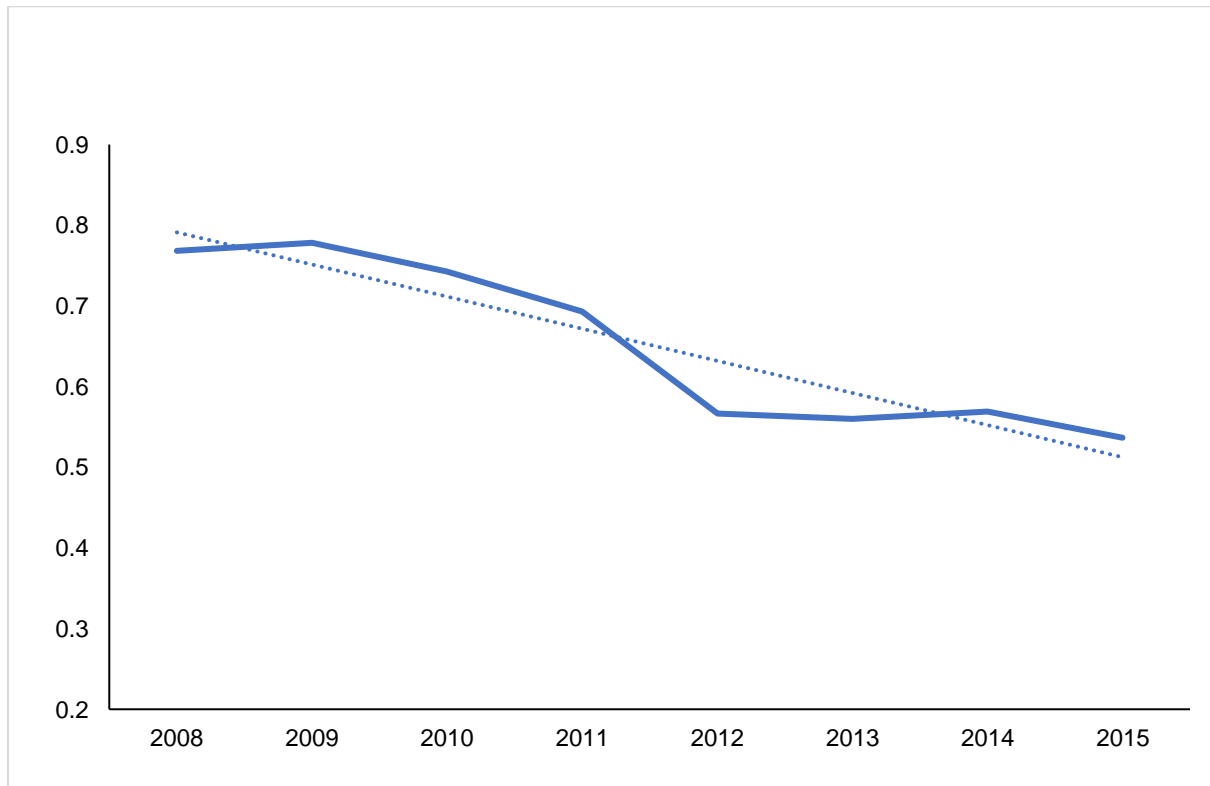


Figure C
Overall mCRBSI incidence rate per 1000 admissions



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

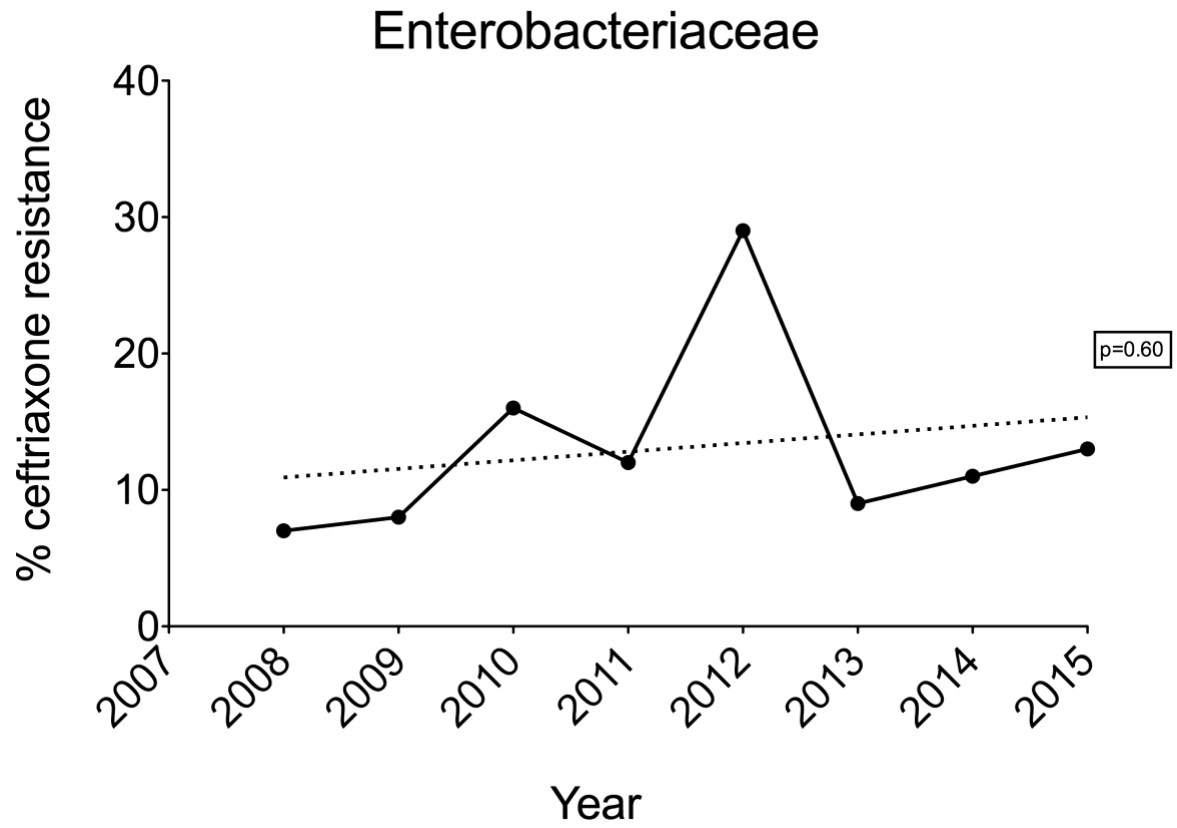
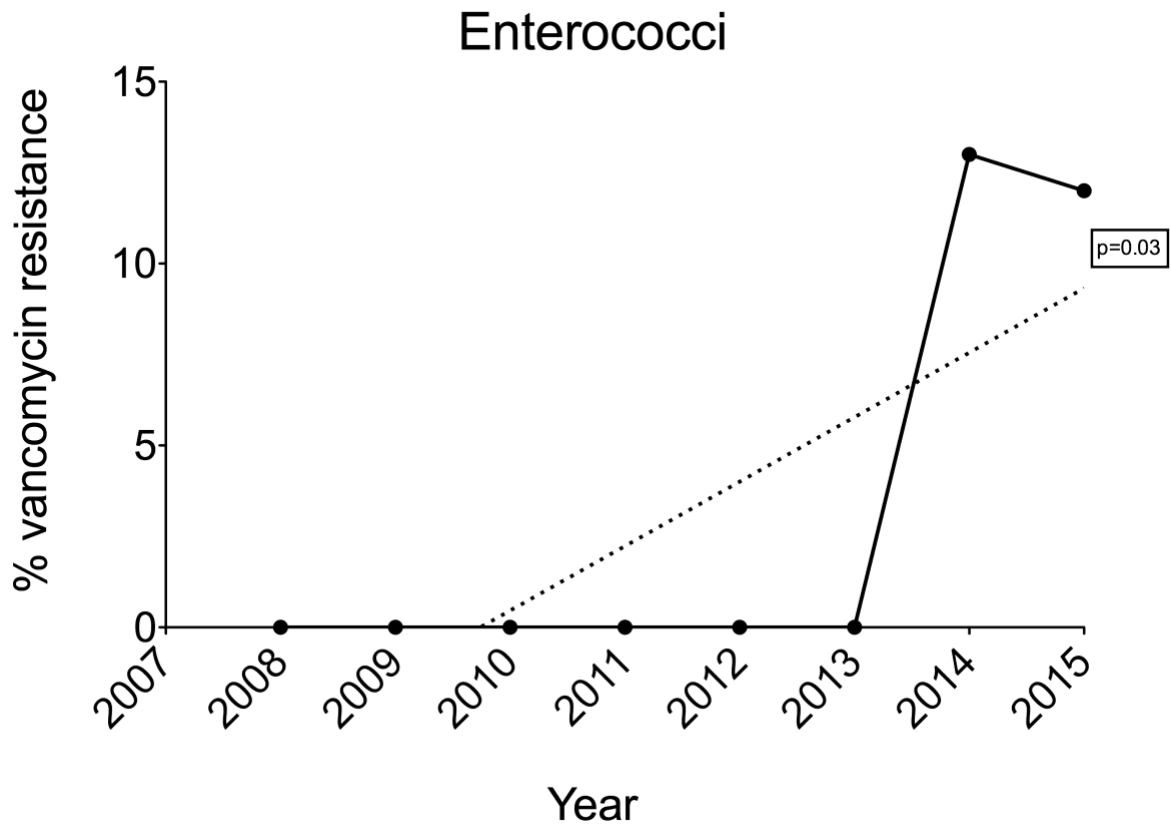
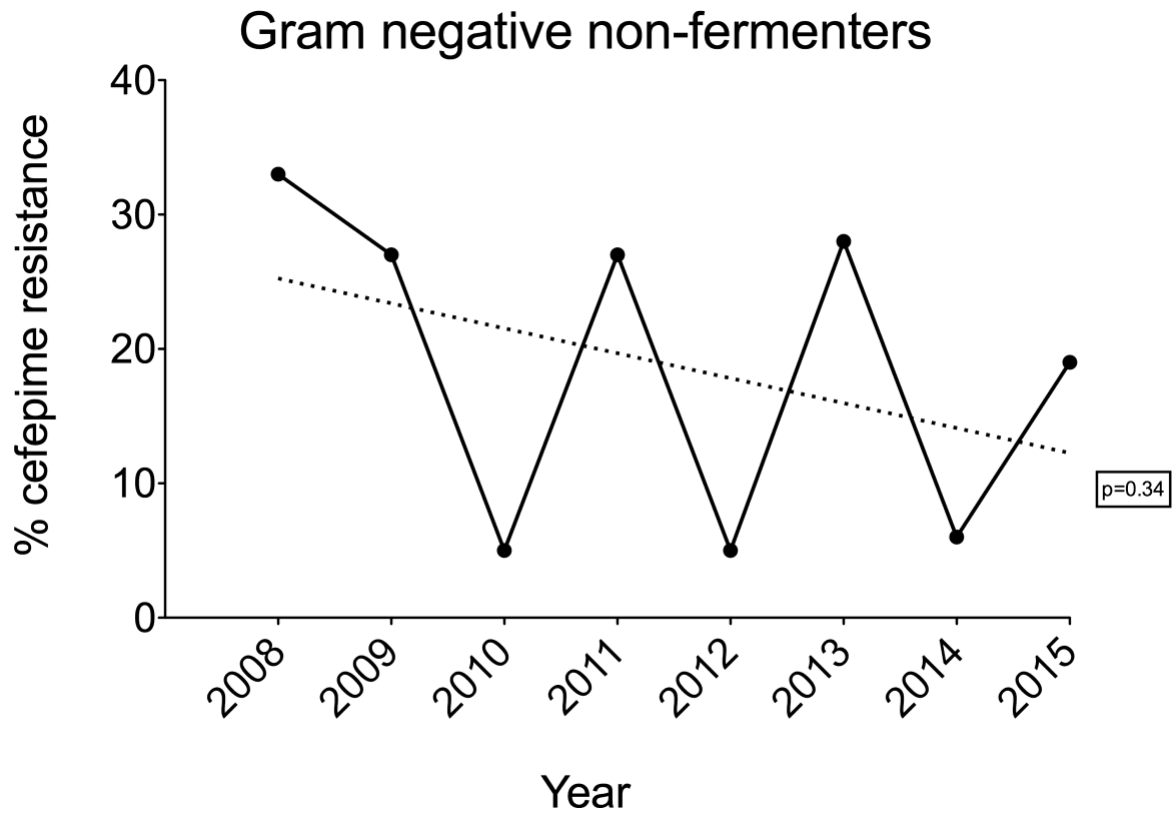


Figure D2
Evolution of vancomycin resistance in Enterococci



Peer Review Only

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



view only

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) <i>Cohort study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses See p. 5.

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60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) See p. 5
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time See p. 5, 6 <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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
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*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

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