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Emergence of Vancomycin-Resistant Enterococci in Switzerland: a Nation-Wide Survey.

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EXECUTIVE SUMMARY:

- Between May 1st and June 19th 2018, a nationwide 33-item questionnaire asking for VRE incidence, occurrence of VRE outbreaks and associated infection control measures was sent to 205 healthcare institutions providing inpatient care.

- 144 institutions answered (70% response rate); 142 institutions were included in the final analysis (representing approximately 23'000 beds included).

- 65% institutions were in the German-speaking part of Switzerland; 73% were public hospitals.

- The questionnaire inquired about VRE cases from 1st January 2015 to 31st March 2018, a 39-months period.

- VRE were detected in one third of hospitals over this time period (46/142, 32%).

- The total number of VRE cases increased from 96 in 2015 to 146 in the first 3 months of 2018. The incidence rate increased from 0.26 cases/day in 2015 to 1.58 in 2018.

- 23 VRE outbreaks were observed with different resistance types (vanA, vanB and mixed vanA and vanB).

- From 1st January 2018 to the beginning of April 2018 five outbreaks were observed, of which four were ongoing at the time the database was closed (all four located in the German part of Switzerland; two with vanB clones and two with vanA clones). Of note, 70% (102/146) of new VRE cases in 2018 were outbreak-related (i.e., hospital-acquired).

- A heterogeneity regarding the management of VRE outbreaks appears to characterize current infection prevention and control practices in Switzerland.

ZUSAMMENFASSUNG:

- In der Zeit von 1.5. bis 19.6.2018 wurde ein Fragebogen mit 33 Fragen über die VRE-Inzidenz, VRE-Ausbrüchen und Infektionspräventionsmassnahmen schweizweit an 205 akutmedizinische Einrichtungen mit stationärem Angebot verschickt.

- 144 Institutionen antworteten (einer Rate von 70% entsprechend); 142 Institutionen (mit rund 23'000 Spitalbetten) wurden in die endgültige Analyse eingeschlossen.

- 65% Institutionen befanden sich in deutschsprachigen Regionen der Schweiz; 73% der Einrichtungen waren öffentliche Spitäler.

- Der Fragebogen erhob VRE-Fälle, die zwischen dem 1.1.2015 und dem 31.3.2018 aufgetreten waren, einer Periode von 39 Monaten.

- VRE-Fälle wurden über diese Zeitperiode in 46 Spitälern detektiert (46/142, 32%).

- Die Inzidenz nahm von 96 VRE-Fällen (im gesamten 2015) auf 146 Fälle im ersten Quartal 2018 zu. Die Inzidenzrate stieg von 0.26 Fällen pro Tag im 2015 auf 1.58 Fälle pro Tag im 2018.

- Es wurden 23 VRE-Ausbrüche mit jeweils unterschiedlichen Resistenztypen beobachtet (vanA, vanB bzw. gemischt vanA & vanB).

- Vom 1.1.2018 bis Anfang April 2018 wurden fünf Ausbrüche erkannt, von denen bei Abschluss der Datensammlung vier noch andauerten (alle vier wurden aus deutschsprachigen Regionen berichtet; zwei davon mit vanB- und zwei mit vanA-Klonen). Bemerkenswerterweise waren 70% (102/146) der neuen VRE-Fälle im 2018 mit einem Ausbruch assoziiert (d.h., nosokomial erworben).

- Das gegenwärtige Management von VRE-Ausbrüchen in der Schweiz ist gemäss dieser Umfrage durch eine Heterogenität der Präventions- und Kontrollmassnahmen gekennzeichnet.

RÉSUMÉ:

- Entre le 1er mai et le 19 juin 2018, un questionnaire comprenant 33 items a été adressé à 250 institutions de soins aigus de Suisse, abordant l'incidence des cas VRE, la survenue d'épidémies et les mesures de prévention et contrôle prises

- 144 institutions ont répondu (taux de réponse de 70%); 142 institutions ont été incluses dans l'analyse finale (environ 23'000 lits inclus).

- 65% des institutions étaient localisées en Suisse allemande; 73% étaient des hôpitaux publics.

- Le questionnaire relevait les cas VRE du 1er janvier 2015 au 31 mars 2018, sur une période de 39 mois.

- Durant la période de l'étude, des VRE ont été détectés dans un tiers des hôpitaux (46/142, 32%).

- Le nombre global de cas VRE est passé de 96 en 2015 (année entière), à 146 pour les 3 premiers mois de 2018. Le taux d'incidence a augmenté de 0.26 cas par jour en 2015 à 1.58 en 2018.

- 23 épidémies de VRE ont été observées, avec différents types de résistance (vanA, vanB ou vanA + vanB)

- Entre le 1er janvier 2018 et début avril 2018, 5 épidémies VRE ont été observées, parmi lesquelles 4 étaient en cours au moment de l'analyse des données (toutes localisées en Suisse allemande ; 2 avec des clones vanB et 2 avec des clones vanA). On note qu'en 2018 70% (102/146) des nouveaux cas VRE étaient liés à une épidémie (i.e., acquis à l'hôpital).

- Actuellement on relève une hétérogénéité des mesures de prévention et contrôle de l'infection dans la prise en charge des épidémies VRE en Suisse.

RIASSUNTO:

- Tra maggio e Giugno 2018 è stato spedito a 205 istituzioni sanitarie con letti stazionari acuti un questionario con 33 domande sull'incidenza dei VRE, sulla comparsa di epidemie con VRE e sui metodi di prevenzione adottati.

- 144 istituzioni hanno risposto (70% delle istituzioni) al questionario ; 142 istituzioni sono state incluse nell'analisi finale (corrispondente all'incirca a 23'000 letti stazionari inclusi).

- Il 65% dei questionari ritornati provenivano dalla Svizzera tedesca; nel 73% si trattava di ospedali pubblici.

- Con l'inchiesta raccoglievano informazioni sui casi di enterococchi resistenti alla vancomicina (VRE) dal 1 gennaio 2015 sino al 31 marzo 2018 (39 mesi).

- Durante lo studio sono stati osservati VRE in 46 ospedali (46/142, 32%).

- L'incidenza è aumentata da 96 casi di VRE (considerando l'intero 2015) fino a 146 casi nei soli primi 3 mesi del 2018. L'incidenza è aumentata da 0.26 casi di VRE per giorno nel 2015 a 1.58 casi di VRE per giorno nel 2018.

- In totale sono state evidenziate 23 epidemie con differenti tipi di resistenza (vanA, vanB o epidemie "miste" con vanA e vanB).

- Dal primo di gennaio 2018 sino all'inizio di aprile 2018 sono state osservate 5 epidemie, quattro delle quali erano ancora attive alla chiusura dell'inchiesta (tutte e quattro nella Svizzera tedesca, due con vanB e due con vanA). Il 70% (102/146) dei casi di VRE nel 2018 era associato ad epidemie (quindi da ritenere nosocomiali).

- Un'importante eterogeneità caratterizza le pratiche correnti di prevenzione e controllo dell'infezioni per quanto riguarda la presa a carico delle epidemie con VRE in Svizzera.

INTRODUCTION:

Vancomycin-resistant enterococci (VRE) are multi-drug resistant microorganisms that can cause healthcare-associated infections and increase both length of stay and in-hospital mortality (1, 2). The WHO listed VRE as a pathogen of high priority in its global list of important antibiotic-resistant bacteria (3). In Europe, several countries reported an increasing prevalence proportion of vancomycin resistance among invasive isolates of *Enterococcus faecium* (4). In Switzerland, VRE incidence is currently not being monitored at a national level for infection control purposes. Moreover, in recent years nosocomial VRE outbreaks have been reported from several hospitals in Switzerland (5-7), revealing that VRE is of concern to our healthcare system. Therefore, an update addressing all Swiss acute-care hospitals was deemed necessary to evaluate the current VRE epidemiology and identify possible gaps in the outbreak detection and management strategies.

OBJECTIVES:

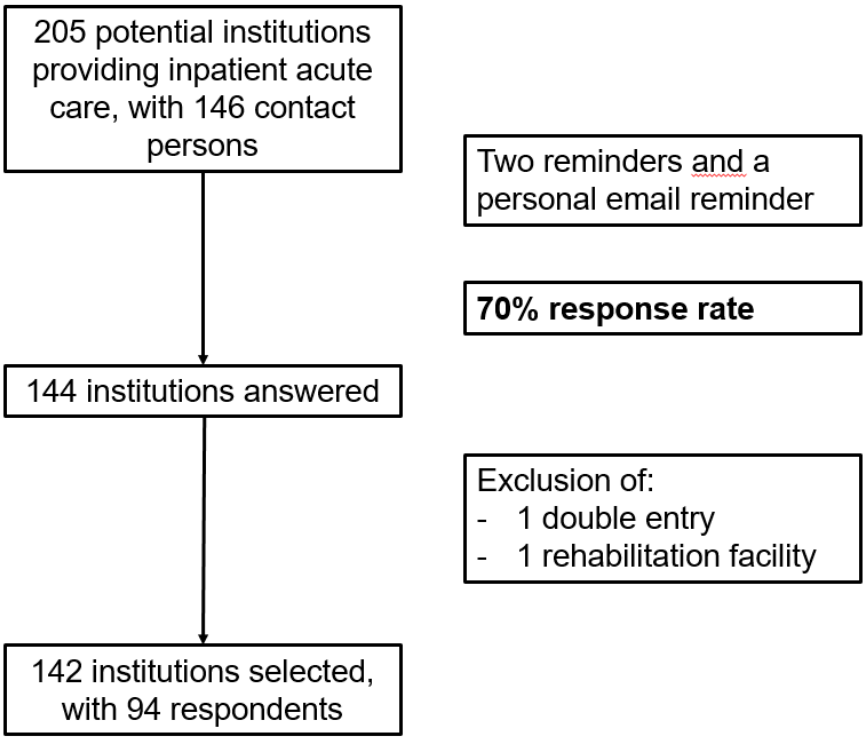
- To describe the epidemiology of VRE in Switzerland
- To identify unrecognized ongoing VRE outbreaks in Switzerland
- To identify weaknesses in the current management strategies.

METHODS:

This survey included 205 public or private institutions providing inpatient care in Switzerland. The list of hospitals consisted of acute-care hospitals and was created in 2016 based on the official hospital list of the Federal Office of Public Health (www.bag.admin.ch) with inputs from the Swiss Hospital Society (www.hplus.ch). This list has been updated regularly since its first use in 2016 (last update in March 2018). Psychiatric institutions, palliative care, long-term care facilities, rehabilitation facilities and pain therapy centers were excluded. Between May 1st and June 19th 2018, a 33-item questionnaire was sent via email to 146 contact

persons at 205 acute-care institutions providing inpatient care. Each email was sent in the respective local language (German, French or Italian). Two reminders as well as a personalized email were addressed to each non-responding institution. Overall, 144 institutions answered, corresponding to a 70% response rate. Most of the 61 institutions that did not complete the survey were small hospitals (i.e., only three non-responding hospitals had >200 beds). After the exclusion of one double entry and one rehabilitation facility, 142 institutions were included in the final analysis (Figure 1).

Figure 1: Survey institutions and respondents



The survey was created, pre-tested locally and shared through the online platform SurveyMonkey®. We collected epidemiological data of VRE cases. Moreover, details on VRE outbreaks as well as information on VRE outbreak management strategies was inquired. An outbreak was defined as an unusual or unexpected increase in VRE colonizations and/or infections (i.e., ≥ 2 in the same time period in an individual hospital) with

or without molecular analysis of strains. Only two major outbreaks per institution were analyzed in more detail.

All epidemiological information on both VRE in general and whether an institution had witnessed VRE outbreaks was institution-based (n= 142) and not respondent-based (n=94) as certain contacts were responsible for multiple institutions.

Information about VRE outbreak management strategy was obtained from physicians or specialized nurses who were involved in the management of a VRE outbreak and were therefore respondent-based (n=14).

Data were extracted from the online platform to an Excel® spread-sheet, checked for accuracy and exported for descriptive analysis using SPSS (Version 25). The incidence rate was expressed in VRE cases per day.

RESULTS

Responding institutions:

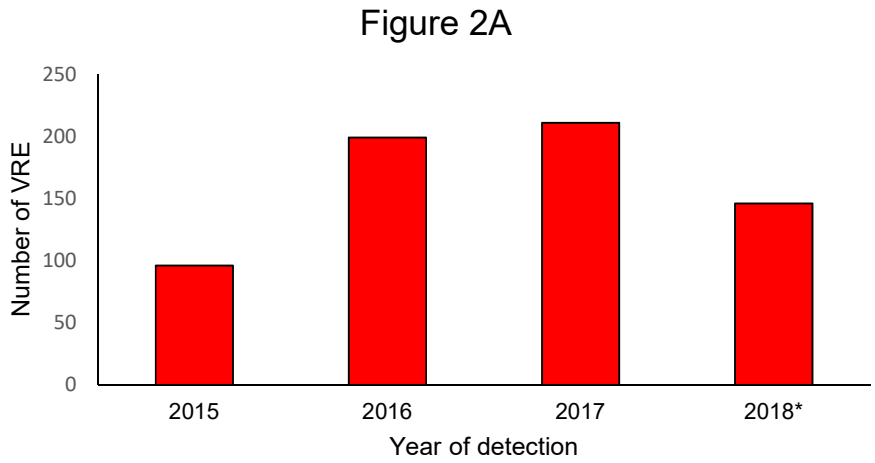
Overall, 94 respondents answered for 142 institutions, accounting for 23'803 beds. Seventy-five percent (107) were small-size (<200 beds), 18% (26) medium size (200-500 beds), and 6% (9) large-size institutions (>500 beds). Ninety-two (65%) hospitals were located in the German-speaking part of Switzerland. There were 104 (73%) public hospitals among the 142 institutions.

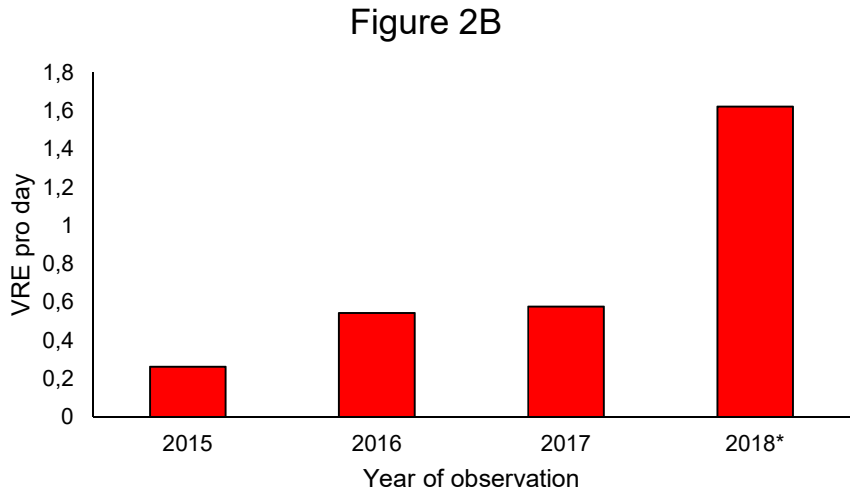
VRE epidemiology:

From 1st January 2015 to 31st March 2018, VRE cases were observed in one third of hospitals (46/142, 32%). Overall, 652 VRE patients (colonized or infected) were detected, of which 67 (10%) represented invasive infections.

The total number of VRE cases increased from 96 in the year 2015 to 146 in the first three months of 2018 (Figure 2A). Of note, the incidence rate increased from 0.26 cases/day in 2015 to 1.58 cases/day in 2018 in the approximately >23'000 beds observed (Figure 2B), with an increase of more than 270% between 2017 and 2018.

Figure 2: Number of VRE cases detected (A) and VRE incidence per day (B) from 2015 to 2018 in 142 Swiss institutions





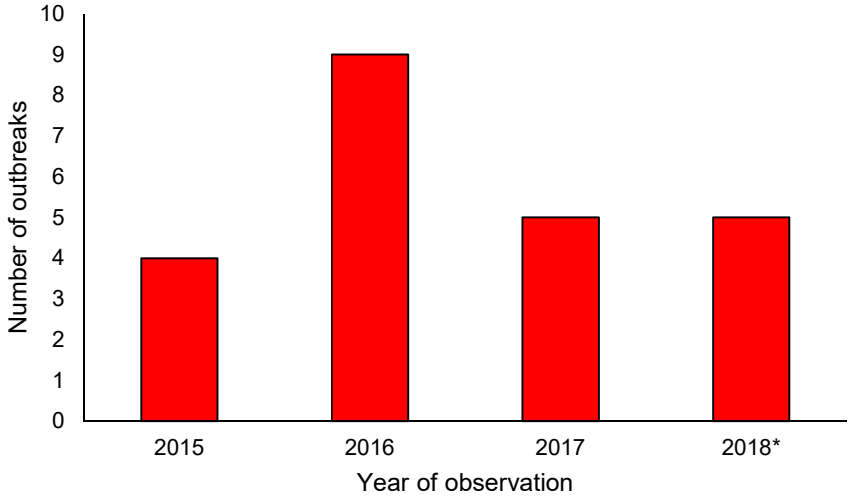
Note: Figure B with trend line (dotted). VRE: vancomycin resistant enterococci. *in 2018 only data for the first quarter were included.

VRE outbreaks in Switzerland:

Twenty-three outbreaks were reported during the study period. Among the 20 major outbreaks analyzed, 250 VRE cases including 10 bacteremias (4%) were observed. Eight outbreaks took place on internal medicine floors, five in a surgical unit and four in an intensive care unit. Nine, five and two outbreaks showed a *vanB*, *vanA* and mixed *vanA* and *vanB* resistance type, respectively.

The mean number of outbreaks per year was seven; in 2016 nine outbreaks were observed (Figure 3).

Figure 3: VRE Outbreaks in Switzerland per year from 1st January 2015 to early April 2018



Note:* in 2018 only data until the beginning of April were included.

From 1st January 2018 to the beginning of April 2018 five outbreaks were observed, four of which were ongoing (all of them located in the German-speaking part of Switzerland) when

the data collection ended. Of note, 70% (102/146) of new VRE cases in 2018 were outbreak-related (i.e., hospital-acquired).

VRE outbreak management strategies:

Frequently used VRE outbreak management strategies were contact precautions for VRE colonized or infected patients (14 of 14 respondents, 100%), contact tracing (13/14, 93%) and pre-emptive contact precautions for high-risk contact patients (12/14, 86%) until negative screening samples were collected, reinforcement of hand hygiene compliance (14/14, 100%), and implementation of disinfectant based environmental cleaning (12/14, 86%). Screening samples of healthcare workers (2/14, 14%) as well decolonization of VRE patients (1/14, 7%) were infrequently used measures. Heterogeneity was noted regarding the following measures: temporary ward closure (implemented in 8/14, 57%) or temporary re-organization of wards into sectors (7/14, 50%), cohorting of contact patients (5/14, 36%), staff cohorting (7/14, 50%), active screening cultures irrespective of exposition (performed in 10/14, 71%), and environmental screening cultures (only performed in 5/14, 36%). Only two hospitals implemented antimicrobial stewardship measures during an outbreak.

DISCUSSION:

This nationwide survey on the VRE epidemiology is representative of Switzerland by including 144 institutions and characterized by an excellent response rate of 70%. The survey revealed an increasing number of VRE cases detected in 2018, which correlates with an increased number of outbreaks observed in the German-speaking part of Switzerland during the first three months of 2018. This upward trend is likely due to the nosocomial spread of these resistant microorganisms.

Outbreaks that occurred in the French-speaking part of Switzerland in 2015-2017 were mainly due to clones ST 17, ST 80 and ST 117 (7). Recently, the efficient dissemination of a new clone (ST796) was described in two hospitals that participated in this survey (8). This clone has been characterized by a rapid intra- and inter-hospital spread with a propensity to adapt, probably in response to specific hospital environments (9, 10).

A recent Swiss survey of screening practices for detecting carriers of multi-drug resistant organisms illustrated a lack of awareness of the potential spread of VRE by means of unidentified carriers, including patients transferred within Switzerland: Among hospitals with on-admission screening, only 44% of institutions systematically performed VRE screening. Overall, only 19% of hospitals currently screen intra-Switzerland transfers for VRE (manuscript in preparation, personal communication, S. Harbarth, Geneva). The benefit and downsides of expanding inter-hospital VRE screening are currently being discussed by national expert organizations. The marked upward trend in incidence is of particular concern, as several outbreaks were still ongoing in early April 2018. Moreover, a heterogeneity regarding the management of VRE outbreaks appears to characterize current infection prevention and control practices in Switzerland. National recommendations should therefore quickly be implemented in order to provide a uniform standard of practice.

This study has several limitations. First, mean incidence rates were calculated using days as a denominator, leading to possible overestimation of the total incidence in 2018 (e.g., temporary increase of VRE cases during a short period of observation). Second, an external validation of the respondents' answers was not performed (this could potentially be provided by a future comparison with ANRESIS data). Third, bacteremia and invasive infection rates should be interpreted with caution as these data were not available in all interviewed institutions. Fourth, we excluded long-term care facilities and rehabilitation centers, which may represent an underestimated reservoir of multi-drug resistant organisms (11). Fifth, our outbreak definition included both small clusters and large outbreaks; however, only 30% of outbreaks observed included <5 VRE detections. Finally, we cannot rule out the possibility

that a patient with VRE carriage was recorded by more than one institution due to multiple presentations, leading to a possible overestimation of the total burden of VRE.

In conclusion, these findings highlight the emergence of VRE in parts of Switzerland not affected before, probably for the most part in the nosocomial setting. A harmonized nationwide strategy for VRE containment that includes active screening surveillance, uniform standards of detection and outbreak management, reporting at a national level with a central surveillance as well as guidance for patient transfers should therefore be implemented.

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