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MAJOR ARTICLE

Long-term Risk of Infection Among Patients Colonized With Antimicrobial-Resistant Pathogens: A Population-wide Cohort Study

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Background. Antimicrobial-resistant (AMR) pathogens represent an ongoing global health burden. Colonization is often a prerequisite for infection, but the risk of infection after AMR colonization is not well understood. Using population-level health administrative data, we sought to investigate the risk of infection with the same AMR organism after detection of colonization.

Methods. We conducted a retrospective population-wide cohort study among residents of Ontario, Canada, over a 5-year period to determine the risk of infection after detection of colonization with the following AMR pathogens: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, extended-spectrum β-lactamase–producing Enterobacterales, and carbapenemase-producing Enterobacterales. We also examined the effects of age, sex, and health care setting of colonization detection on subsequent infection risk.

Results. There were 69 998 individuals with a positive AMR pathogen surveillance test result during the study period, 15.6% of which subsequently developed a sterile or nonsterile site infection within a median 57 days (IQR, 11–228). Infection rates varied among organisms: 18.3% for methicillin-resistant *S aureus* within a median 57 days (IQR, 10–239), 2.8% for vancomycin-resistant *Enterococcus* within a median 37 days (IQR, 11–119), 21.5% for extended-spectrum β-lactamase–producing Enterobacterales within a median 71 days (IQR, 18–231), and 20.3% for carbapenemase-producing Enterobacterales within a median 10 days (IQR, 3–42). A positive surveillance test result detected in a hospital was associated with increased infection risk after colonization as compared with the community setting.

Conclusions. The overall infection rate after colonization with an AMR pathogen was high for most organisms, highlighting the importance of detecting colonization from both an infection control and empiric antibiotic selection perspective.

Keywords. antimicrobial resistance; CPE; ESBL; MRSA; VRE.

Antimicrobial-resistant (AMR) pathogens represent an ongoing global health burden, associated with an estimated 4.95 million deaths in 2019 [1]. Antimicrobial resistance affects all regions across the globe but disproportionately burdens low- and middle-income countries [1]. Colonization is often a prerequisite for infection, as most cases of infection arise from an individual's endogenous flora [2, 3]. For example, previous studies have shown that in most cases, colonizing strains of methicillin-resistant *Staphylococcus aureus* (MRSA) are those that are detected in and responsible for subsequent infections [2, 4].

The risk of infection after AMR colonization is not well understood due to methodologic challenges in existing studies. Previous studies are often limited by small sample sizes [5–7], single-care settings (eg, 1 institution or hospital system) [5, 6, 8–10], an exclusive focus on high-risk settings such as intensive care units (ICUs) [11, 12] or high-risk populations such as patients who are immunocompromised [13], or short follow-up times, usually during hospitalization or up to 1 year after colonization detection [5, 12, 14]. Studies with prolonged follow-up times are typically able to capture only those infections presenting back to the same health care institution [5, 7] or to select

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institutions (eg, publicly funded hospitals) [9]. Existing studies based on population-level data have either focused on homogenous populations (eg, military veterans) [15] or investigated a narrow scope of infection (eg, exclusively bloodstream or urine infections) [16, 17].

Using population-level health administrative data, we sought to investigate the risk of infection with the same AMR organism after detection of colonization, and understand how factors such as age, sex, and setting of colonization detection affect future infection risk after colonization.

METHODS

General Study Design

We conducted a retrospective population-wide cohort study among residents of Ontario, Canada, between 1 January 2017 and 31 December 2021 to determine the risk of infection after detection of colonization with an AMR pathogen.

Data Sources

We used provincial health administrative data sets linked by unique encoded identifiers and analyzed at ICES (formerly, the Institute for Clinical Evaluative Sciences). ICES is an independent nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Information from all 15 million Ontario residents is included at ICES, as the singular provincial health insurance program in Ontario is publicly funded. The primary data set for this study was the Ontario Laboratories Information System, which combines data from 114 hospital, community, and public health laboratories into a single repository (additional linked databases listed in supplementary methods).

AMR Organisms of Interest

The specific AMR organisms of interest in this study included MRSA, vancomycin-resistant *Enterococcus* (VRE), extended-spectrum β-lactamase–producing Enterobacterales (ESBL), and carbapenemase-producing Enterobacterales (CPE; Supplementary Table 1).

Patient Selection Criteria

We examined the Ontario Laboratories Information System for surveillance tests for the AMR organisms of interest. We excluded tests belonging to individuals with invalid identifier numbers in the database, missing demographic information (eg, sex, birth date, postal code), non-Ontario residency status, or cases recorded with a negative age or an age >105 years. Furthermore, we excluded anyone who had clinical infection present at time of colonization detection, based on a clinical culture collected on the same calendar day ±1 day that was positive for the same AMR organism as the surveillance culture.

Outcomes

For individuals colonized with an AMR pathogen (ie, a positive surveillance test result), we examined subsequent clinical cultures yielding the same pathogen, which could be collected anywhere in Ontario. Patients were censored after an AMR outcome detection, death, emigration from Ontario, or end of the observation period (31 December 2021). The primary outcome was detection of the same AMR organism in a culture from any clinical specimen within the follow-up period, whether sterile (blood, tissue, body fluid, any aspirate or abscess, or stone) or nonsterile (primarily urine or wound; Supplementary Table 2). Secondary outcomes included detection of the same AMR organism in a sterile site culture exclusively or detection of infection in a nonsterile site with a corresponding *ICD-10* diagnostic code for infection during an emergency department visit or hospitalization in which the organism was detected.

Statistical Analysis

We described the characteristics of individuals with AMR pathogen colonization overall and separately for each organism of interest. We calculated the incidence of infection detection during the follow-up period in the overall cohort and in a subgroup that excluded all persons who developed infection within 5 days of colonization detection, to further minimize the possibility of initial colonization detection representing infection. We also calculated the incidence of infection detection in the overall cohort at intervals of 30 and 90 days, and 6, 12, and 24 months after colonization detection. Cox proportional hazards modeling was used to calculate unadjusted hazard ratios for covariates affecting risk of infection: age (<65 vs ≥65 years), sex (female vs male), setting of colonization detection (hospital, long-term care [LTC], community), and immunocompromised status (yes vs no; supplementary methods). Community-based samples included few ambulatory samples, in addition to samples from patients discharged home from the emergency department (and never admitted to the hospital) and from patients admitted to rehabilitation or mental health facilities. These are captured outside of acute care and LTC databases and are more representative of the community population than the population that is admitted to acute care hospitals or resides in LTC. We also calculated the proportion of infections that occurred within the same health care setting as colonization detection as well as within the same hospital institution. Cumulative infection risk after colonization was modeled over time with Kaplan-Meier curves.

Table 1. Baseline Characteristics of Individuals Who Were AMR Colonized

Characteristic	MRSA (n = 41 542)	VRE (n = 16 707)	ESBL (n = 14 411)	CPE (n = 1056)	Total: Any AMR (n = 69 998)[a]
Age, y	72 (56–84)	75 (64–85)	73 (58–84)	68 (55–78)	73 (58–84)
Age ≥65 y	26 211 (63.1)	12 267 (73.4)	9549 (66.3)	610 (57.8)	46 034 (65.8)
Female sex	20 002 (48.1)	8238 (49.3)	7946 (55.1)	452 (42.8)	34 870 (49.8)
Setting of detection					
Community[b]	20 412 (49.1)	8151 (48.8)	6996 (48.5)	511 (48.4)	34 478 (49.3)
Long-term care	12 987 (31.3)	4638 (27.8)	4584 (31.8)	508 (48.1)	21 824 (31.2)
Hospital	8143 (19.6)	3918 (23.5)	2831 (19.6)	37 (3.5)	13 696 (19.6)

Data are presented as median (IQR) or No. (%).

Abbreviations: AMR, antimicrobial resistant; CPE, carbapenemase-producing Enterobacterales; ESBL, extended-spectrum β-lactamase–producing Enterobacterales; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

[a]The sum of individual AMR pathogens exceeds 69 998 because some patients were colonized with >1 pathogen.

[b]Colonization in the community also included detection in the emergency department (if patients were discharged home without admission) and rehabilitation or mental health facilities.

Table 2. Risk and Time to Infection Among Individuals Who Were AMR Colonized

Same AMR Infection	MRSA (n = 41 542)	VRE (n = 16 707)	ESBL (n = 14 411)	CPE (n = 1056)	Total: Any AMR (n = 69 998)[a]
Any sterile/nonsterile	7618 (18.3)	472 (2.8)	3095 (21.5)	214 (20.3)	10 893 (15.6)
Days to infection	57 (10–239)	37 (11–119)	71 (18–231)	10 (3–42)	57 (11–228)
Sterile site	1472 (3.5)	151 (0.9)	434 (3.0)	51 (4.8)	2010 (2.9)
Days to infection	43 (5–244)	40 (14–119)	91 (16–364)	15 (5–120)	47 (7–241)
Nonsterile site	6996 (16.8)	354 (2.1)	2916 (20.2)	197 (18.7)	9996 (14.3)
Days to infection	66 (13–258)	40 (11–129)	75 (20–236)	11 (3–51)	65 (14–241)
Nonsterile site plus hospital infection, *ICD-10*	2169 (5.2)	174 (1.0)	965 (6.7)	81 (7.7)	3231 (4.6)
Days to infection	45 (6–244)	31 (11–110)	80 (14–327)	11 (5–61)	47 (7–252)

Data are presented as median (IQR) or No. (%).

Abbreviations: AMR, antimicrobial resistant; CPE, carbapenemase-producing Enterobacterales; ESBL, extended-spectrum β-lactamase–producing Enterobacterales; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

[a]The sum of individual AMR pathogens exceeds 69 998 because some patients were colonized with >1 pathogen.

RESULTS

Cohort With AMR Colonization and Overall Risk of Infection

There were 69 998 individuals in Ontario with positive surveillance test results for at least 1 of the AMR pathogens of interest between 1 January 2017 and 31 December 2021, with MRSA representing the majority. Baseline characteristics of those who were AMR colonized are shown in Table 1. The median (IQR) age of detection of any AMR pathogen was 73 (58–84) years, and AMR pathogens were identified most frequently in the community. Within the follow-up period, 15.6% of all persons colonized with an AMR pathogen developed an infection with that same AMR pathogen in any sterile or nonsterile site, and the median (IQR) time to infection was 57 (11–228) days (Table 2).

Methicillin-Resistant *S aureus*

There were 3 872 562 MRSA surveillance tests completed during the study period, of which 123 109 (3.2%) were positive for MRSA, representing 41 542 unique eligible individuals. The median (IQR) age of the MRSA-colonized cohort was 72 (56–84) years, and the majority were male and had a test collected in the community (Table 1). In total, 7618 (18.3%) people were MRSA colonized and developed an MRSA infection within the follow-up period, with a median (IQR) time to infection of 57 (10–239) days (Table 2). Most MRSA infections occurred within 90 days of initial detection of colonization (Supplementary Table 3). Female sex was associated with lower risk of MRSA infection among those who were colonized (unadjusted hazard ratio [HR], 0.80; 95% CI, .77–.84), which was consistent over the follow-up period (Supplementary Figure 1A), whereas detection of colonization in the hospital (unadjusted HR, 1.70; 95% CI, 1.61–1.79) or LTC (unadjusted HR, 1.41; 95% CI, 1.32–1.51) was associated with increased infection risk as compared with the community (Table 3, Supplementary Figure 1B). There was no association between age and MRSA infection risk (Table 3, Supplementary Figure 1C).

Vancomycin-Resistant *Enterococcus*

There were 1 392 470 VRE surveillance tests completed during the study period, of which 38 577 (2.8%) were positive among 16 707 unique individuals with a median (IQR) age of 75 (64–85) years (Table 1). Most of the cohort was older than 65 years and male, with VRE colonization detected in the community. In total, 472 people were VRE colonized (2.8%) and

Table 3. Association of Age, Sex, and Setting of Colonization Detection on the Hazards of AMR Infection Among Individuals Who Were AMR Colonized

	Unadjusted Hazard Ratio (95% CI)			
Covariate	MRSA	VRE	ESBL	CPE
Age ≥65 vs <65 y	1.03 (0.98–1.08)	0.52 (0.44–0.63)	2.31 (2.12–2.52)	1.17 (0.89–1.54)
Female vs male	0.80 (0.77–0.84)	1.10 (0.92–1.32)	1.42 (1.32–1.53)	0.80 (0.61–1.06)
Hospital vs community	1.70 (1.61–1.79)	2.53 (2.01–3.20)	1.89 (1.72–2.07)	1.63 (1.24–2.16)
Long-term care vs community	1.41 (1.32–1.51)	0.47 (0.31–0.69)	3.06 (2.77–3.39)	1.83 (0.85–3.44)

Abbreviations: AMR, antimicrobial resistant; CPE, carbapenemase-producing Enterobacterales; ESBL, extended-spectrum β-lactamase–producing Enterobacterales; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

developed a VRE infection within the follow-up period, detected at a median (IQR) 37 (11–119) days (Table 2). More than half of all VRE infections occurred within 90 days of initial detection of colonization (Supplementary Table 3). Age >65 years (unadjusted HR, 0.52; 95% CI, .44–.63) and colonization detection in LTC as compared with the community (unadjusted HR, 0.47; 95% CI, .31–.69) were associated with lower risk of VRE infection after colonization (Table 3, Supplementary Figure 1B and 1C). Colonization detection in a hospital vs the community was associated with an increased risk of infection (unadjusted HR, 2.53; 95% CI, 2.01–3.20) (Table 3, Supplementary Figure 1B). There was no association between sex and VRE infection risk (Table 3, Supplementary Figure 1A).

Extended-Spectrum β-Lactamase–Producing Enterobacterales

There were 284 924 ESBL surveillance tests completed during the study period, of which 36 109 (12.7%) were positive, representing 14 411 individuals after exclusions. The median (IQR) age at colonization was 73 (58–84) years, and most of the cohort was older than 65 years and female, with a test collected in the community (Table 1). There were 3095 people (21.5%) colonized with ESBL who developed a subsequent infection with the same organism after a median (IQR) 71 (18–231) days (Table 2). Over half of all ESBL infections occurred within 90 days of colonization detection (Supplementary Table 3). Older age (unadjusted HR, 2.31; 95% CI, 2.12–2.52), female sex (unadjusted HR, 1.42; 95% CI, 1.32–1.53), and test collection in the hospital or LTC as compared with the community (unadjusted HR, 1.89; 95% CI, 1.72–2.07; unadjusted HR, 3.06; 95% CI, 2.77–3.39, respectively) were all associated with an increased risk of infection (Table 3, Supplementary Figure 1).

Carbapenemase-Producing Enterobacterales

There were 265 618 CPE surveillance tests completed during the study period, with 2112 positive test results (0.8%) representing 1056 individuals after exclusions. The median (IQR) age of the cohort at colonization was 68 (55–78) years, and most of the cohort was older than 65 years and male, with a test collected in the community or in LTC (Table 1). There were 214 people (20.3%) who developed a CPE infection within the follow-up period at a median (IQR) 10 (3–42) days after colonization detection (Table 2). Most CPE infections occurred within 30 days of colonization detection (Supplementary Table 3). Colonization detection in the hospital as compared with the community conferred an increased risk of subsequent CPE infection (unadjusted HR, 1.63; 95% CI, 1.24–2.16); there was no effect of sex, age, or test collection in LTC (Table 3, Supplementary Figure 1).

Comparison Across AMR Organisms

Of the different AMR organisms studied, ESBL, followed by CPE, had the highest rate of sterile/nonsterile site infection after colonization detection (Figure 1). The infection rate was similar for all organisms when excluding individuals who developed infection within 5 days of colonization detection (Supplementary Table 4), although slightly lower for CPE (20.3% vs 14.0%). Overall, CPE had the shortest median time to infection at just 10 days, as opposed to ≥30 days for the other organisms (Table 2), although we found ongoing infection risk within the first 2 years after colonization detection for all organisms (Supplementary Table 3). Moreover, CPE had the highest rate of infection after colonization detection for sterile sites exclusively and nonsterile sites with concomitant hospital diagnostic codes. By contrast, VRE had the lowest rates of infection after colonization detection. For all organisms studied, at least half of infections occurred during the first 90 days after colonization detection, and there was generally a quicker time to infection if colonization was detected in a hospital as compared with the community; for CPE specifically, colonization in LTC had the quickest time to infection after colonization detection (Supplementary Table 5). The association of age with infection risk was variable across AMR pathogens, with older age being associated with an increased risk of ESBL infections but decreased risk of VRE infections (Table 3). Similarly, sex had a variable association across AMR organisms, with female sex being associated with a higher risk of ESBL infection but decreased risk of MRSA infection. A positive surveillance test result detected in the hospital was universally associated with an increased infection risk across all organism types as compared with the community. A test collected in LTC, however, was associated with a variable risk of infection, with a higher infection risk for ESBL and MRSA as compared with the community but lower

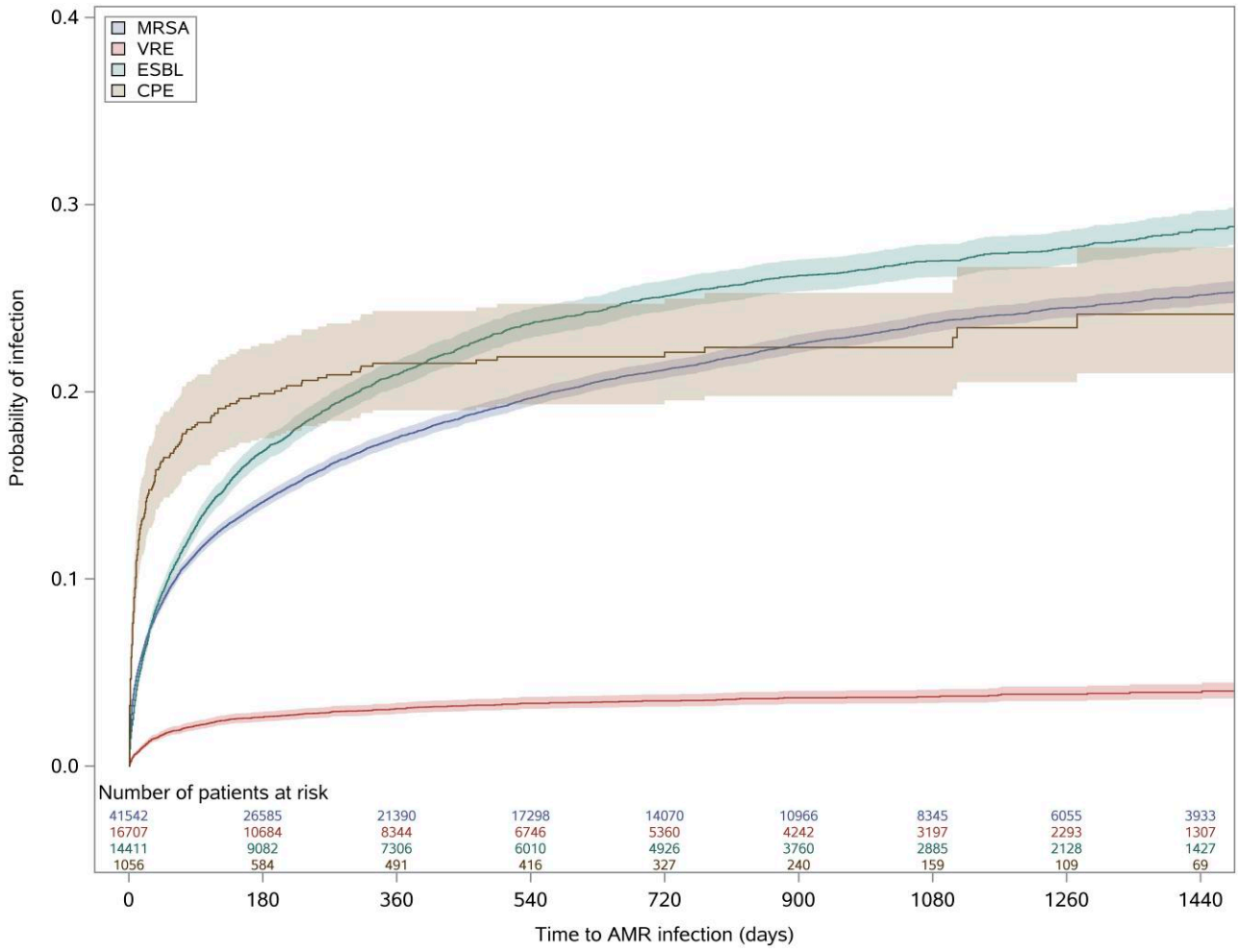

Figure 1. Kaplan-Meier curves demonstrate time to sterile or nonsterile site infection (days) after detection of colonization with different AMR pathogens. The total number of patients at risk of infection (ie, those who remain colonized with the AMR pathogen) is denoted at the bottom of the curves, and the different AMR organisms are differentiated by line color: blue for MRSA, red for VRE, green for ESBL, and brown for CPE. Shaded regions indicate 95% CI. AMR, antimicrobial resistant; CPE, carbapenemase-producing Enterobacterales; ESBL, extended-spectrum β-lactamase–producing Enterobacterales; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

risk of VRE. There were 16 052 people (22.9%) colonized with an AMR pathogen who were immunocompromised, which was associated with a greater infection risk after colonization detection for all organisms except CPE (Supplementary Table 6). Many infections overall were detected in a different health care sector than colonization, including 31.8% of MRSA infections, 30.3% of VRE infections, 30.8% of ESBL infections, and 19.2% of CPE infections (Table 4). Even when colonization and infection were detected within hospitals, a substantial number of infections presented at a different institution: 13.6% of MRSA, 15.5% of VRE, 17.5% of ESBL, and ≤5% of CPE infections.

DISCUSSION

The overall infection rate after colonization detection with any AMR pathogen was high, highlighting the importance of examining infection rates with population-level data. Infection usually occurred relatively quickly after colonization detection, with more than half of infections occurring within 90 days; among the organisms studied, CPE had the shortest time to infection. We found the highest rates of sterile/nonsterile site infection after colonization detection for ESBL, with VRE having the lowest. Depending on the specific AMR pathogen, age, sex, and setting of colonization detection had variable effects on infection risk after colonization, apart from colonization detection in a hospital, which was consistently associated with an increased infection risk as compared with the community. Many infections presented in a different health care setting than initial colonization detection, and many within the acute care hospital setting presented to a different institution.

Previous studies that have examined infection risk after colonization with AMR pathogens have used variable

Table 4. Health Care Setting for Detection of Initial Colonization vs Subsequent Infection

Subsequent Infection	Initial Colonization											
	MRSA			VRE			ESBL			CPE		
	Hospital (n = 4187)	LTC (n = 1481)	Community (n = 1950)	Hospital (n = 348)	LTC (n = 33)	Community (n = 91)	Hospital (n = 1521)	LTC (n = 930)	Community (n = 644)	Hospital (n = 122)	LTC (n = 9)	Community (n = 83)
Hospital	**2406 (57.5)**	151 (10.2)	421 (21.6)	**258 (74.1)**	13 (39.4)	40 (44.0)	**834 (54.8)**	81 (8.7)	156 (24.2)	**90 (73.8)**	0 (0.0)	9 (10.8)
LTC	474 (11.3)	**1330 (89.8)**	70 (3.6)	9 (2.6)	**20 (60.6)**	0 (0.0)	204 (13.4)	**849 (91.3)**	29 (4.5)	0 (0.0)	**9 (100.0)**	0 (0.0)
Community	1307 (31.2)	0 (0.0)	**1459 (74.8)**	81 (23.3)	0 (0.0)	**51 (56.0)**	483 (31.8)	0 (0.0)	**459 (71.3)**	32 (26.2)	0 (0.0)	**74 (89.2)**

Data are presented as No. (%). Bold values indicate cases where colonization and infection were detected in the same health care setting.

Abbreviations: AMR, antimicrobial resistant; CPE, carbapenemase-producing Enterobacterales; ESBL, extended-spectrum β-lactamase–producing Enterobacterales; LTC, long-term care; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

methodologic strategies, and few studies have determined population-level infection risk. We report a higher rate of MRSA infection after colonization compared with a population-based MRSA study in US military veterans, which determined a 180-day postdischarge MRSA infection risk of 11.7% in those admitted to the ICU [15]. However, extrapolation of infection risk to the general population is challenging due to the homogeneity of the population studied [15].

By contrast, our reported VRE infection risk after colonization detection is lower than what has been described. One systematic review that included 16 VRE-based studies reported an 8% risk of VRE infection after colonization at 30 days, with a median time to infection of 17 days; however, most of these studies focused on high-risk populations (eg, organ transplant, malignancy) or high-risk settings (eg, ICU) [18], whereas most VRE colonization in our study was detected in the community.

Similar to MRSA, there was a higher risk of ESBL infection after colonization detection in our study as compared with previous studies, even in those that used population-level data. One study that used population-based surveillance data from western Sweden with a median follow-up time of 3.7 years reported a 5.6% infection rate after colonization, within a median 5.4 months; however, the authors exclusively examined blood and urine cultures and would not have accounted for other infections [17]. Our reported risk of ESBL infection in a sterile site is similar to that reported by another Swedish population-based study that examined ESBL bloodstream infections after colonization, which found a bloodstream infection rate of 3.8% if colonization was first detected in urine [16]. The authors also cited an incidence rate of infection that was highest in the first 90 days of follow-up, similar to our findings [16].

Finally, our reported risk of CPE infection is on par with findings from previous systematic reviews. One review based on 19 carbapenem-resistant Enterobacteriaceae (CRE) studies that mainly focused on high-risk populations and settings reported an infection rate of 19% at 30 days after colonization [18]. A review that included 10 CRE studies found a sterile/nonsterile infection rate of 16.5% after colonization [19]. Previous studies have also shown that carbapenemase-producing CRE are associated with a higher infection risk than non–carbapenemase-producing CRE due to specific clones likely associated with higher virulence [18, 20], which may explain the rapid time to infection after colonization detection with CPE in this study.

In terms of risk factors for infection after colonization detection, similar to our results, there have been variable effects reported in the literature for age, sex, and setting of colonization detection, depending on the organism studied. For example, older age has been shown to be associated with infection after colonization with MRSA (trend) [9] and ESBL [16, 21] but not VRE [22] or CPE [23]. There have also been variably reported sex-specific effects on infection risk with AMR

pathogens, with some studies showing an effect, usually in the direction of higher risk for males [16, 17], or more commonly no sex-specific influence [5, 9, 22–24]. With respect to the setting of colonization detection, most studies have focused exclusively on hospital-detected colonization and have not specifically examined risk based on setting of colonization detection. One CRE study did find an increased risk of infection for individuals recently admitted to the hospital or skilled nursing care facilities, many of whom were colonized [11]. Overall, immunocompromise was unsurprisingly associated with higher infection risk after colonization detection for most organisms studied, likely reflective of increased illness susceptibility in this population [25]. For all organisms studied, infection after colonization detection in the hospital occurred faster than if colonization was detected in the community; this was also largely expected as hospitalized patients may be more susceptible to infection in the context of acute illness.

When compared with previous reports, we found higher rates of infection after colonization detection for most organisms studied due to several factors, including our use of population-level data, which conferred less ascertainment bias, as well as our inclusion of multiple infection types and our ability to capture follow-up data from anywhere in Ontario. We observed higher rates of sterile/nonsterile site infections after colonization detection for the gram-negative organisms studied (ESBL and CPE) as compared with the gram-positive organisms (VRE and MRSA), which may reflect their increased virulence, as suggested by previously published differing mortality risks. A recent large-scale ICU-based study in patients with hospital-acquired bloodstream infections showed higher mortality risk with difficult-to-treat gram-negative infections (many of which were carbapenem resistant) than resistant gram-positive ones (including VRE and MRSA) [26]. The lack of association between CPE infection risk after colonization detection and immunocompromise in this study also supports increased virulence for this organism.

Although most infections occurred in the same health care setting as colonization detection, we did detect a substantial number of infections presenting in other settings, highlighting the importance of follow-up not limited to a single institution. In addition, our longer follow-up period as compared with most studies may explain our higher rates of infection as well as our longer median time to infection detection for some organisms. For VRE specifically, our reported rate of infection was lower than previous studies, likely due to their focus on high-risk populations and settings (particularly hospital-based settings, where this organism is most prevalent) [27], which may overestimate population risk. The increased infection risk associated with colonization detection in hospital and LTC settings as compared with the community was largely expected, given that such individuals are more likely to be immunocompromised, frail, and have more antibiotic exposures leading to increased selection pressure. Interestingly, we found a lower association with VRE infection after colonization detection in LTC as compared with the community setting. This may be due to a competing risk of death, as there is a high death rate in the elderly population who resides in LTC. Thus, some persons who are colonized and reside in LTC may die before developing infection with VRE, an infection that also tends to be most common in those who are immunosuppressed or have severe underlying illness [27].

Limitations

The most important limitation associated with use of administrative health care databases is an inability to apply clinical criteria for infection, meaning that some positive cultures, nonsterile site cultures in particular, could have represented colonization; however, nonsterile sites (eg, urine, which represented over one-third of such specimens in this study) do still carry substantial true infection risk. Second, as some clinical infections are never microbiologically confirmed, we may have underestimated the total rate of infection. Third, we were limited to following patients with known colonization given the lack of universal AMR surveillance, which limited our overall sample size. Fourth, our findings address infection risk after colonization detection in only the screened population; therefore, we cannot directly address general population risk. In addition, we were able to determine infection risk and time to infection only after colonization detection, as it was not possible to know precisely when individuals became colonized. Finally, we could not ensure a clonal relationship between colonizing and infecting strains of the AMR pathogens studied.

Conclusions and Future Directions

Colonization with an AMR pathogen has variable infection risk depending on the specific pathogen, but the overall risk is likely higher than what has been reported for most organisms, highlighting the importance of detecting colonization from both an infection control and empiric antibiotic selection perspective. For all organisms studied, the highest risk period of progression from colonization to infection was the first 90 days after colonization detection; however, we still observed infection risk up to 2 years after colonization detection, providing some insight into the time window for possible decolonization interventions. The increased risk of infection if AMR colonization was detected in a hospital or LTC setting emphasizes the importance of universal in-hospital screening programs, as well as consideration of universal screening in LTC. Future studies could use this same cohort to examine clinical predictors of progression from colonization to infection and adjust for the same covariates used in this study, in addition to other risk factors among patients who are colonized. Subsequent studies could also compare rates of infection with different AMR pathogens in

individuals who are colonized and noncolonized, adjusting for relevant covariates that may differ among pathogens.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: K. A. B. and N. D. Methodology: K. A. B. and N. D. Analysis: C. D. Resources: D. J. F. and C. D. Writing–original draft: C. B. Writing–review and editing: K. A. B., J. J., K. L. S., D. R. M., B. J. L., and N. D. Supervision: N. D. Project administration: S. M. L. Funding acquisition: K. A. B. and N. D.

Data availability. The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (eg, health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and therefore are inaccessible or may require modification.

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