Antibacterial Drugs and the Risk of Community-Associated Methicillin-Resistant Staphylococcus aureus in Children

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Objective: To investigate in children the association between antibacterial drugs and subsequent diagnosis of methicillin-resistant Staphylococcus aureus (MRSA) in the community.

Design: Population-based case-control study in children 1 to 19 years of age.

Setting: Primary care, General Practice Research Database, United Kingdom, 1994-2007.

Participants: Cases were children who had MRSA diagnosed as outpatients, and controls were individually matched on age and practice, with the matched case’s diagnosis date as the index date for both.

Main Exposures: Antibacterial agents prescribed 180 to 30 days prior to the index date, excluding prescriptions 30 days before the index date to prevent protopathic bias.

Outcome Measures: Rate ratios (RRs) estimated from the odds ratios of exposure in cases compared with controls using conditional logistic regression, adjusted for comorbid conditions, other prescription drug use, and hospitalization.

Results: The rate of MRSA was 4.5 per 100,000 per year. Of 297 cases and 9,357 controls, 52.5% and 13.6%, respectively, received antibacterial drug prescriptions during the 150-day exposure window. The adjusted RR with any antibacterial drug was 3.5 (95% confidence interval [CI], 2.6-4.8). The RRs increased with the number of prescriptions (2.2 [95% CI, 1.5-3.2], 3.3 [95% CI, 1.9-5.6], 11.0 [95% CI, 5.6-21.6], and 18.2 [95% CI, 9.4-35.4] for 1, 2, 3, and ≥4 prescriptions, respectively). The RR was particularly elevated for quinolones at 14.8 (95% CI, 3.9-55.8), with wide variation among antibacterial classes.

Conclusion: While close to half of children were diagnosed as having MRSA in the community without prior antibacterial drugs, such agents are associated with a dose-dependent increased risk, concordant with findings in adults.


Methicillin resistance is common in Staphylococcus aureus in hospitals; such resistance is increasingly reported in the community and is commonly referred to as community-associated methicillin-resistant Staphylococcus aureus (Ca-MRSA). Compared with its health care–associated counterpart, this emerging resistant organism generally affects younger and healthier individuals, including children. While Ca-MRSA is isolated mostly in skin and soft-tissue infections, it can also cause life-threatening invasive infections with fatal outcome. The pathogenesis of Ca-MRSA, however, is not yet completely understood.

So far, most of the literature on Ca-MRSA in children has been case series. Ca-MRSA has been detected in daycare attendees and outbreaks have occurred among young athletes. Pedi atric population–based studies are scarce but suggest that children represent a high-risk population with increasing Ca-MRSA incidence. Antibacterial agents have been suggested to play a role in the emergence of Ca-MRSA, and we have recently shown, in adults, a dose-dependent association of antibacterial drug prescriptions in pri-
mary care with later diagnoses of Ca-MRSA.21 However, there are only sparse data from children22 in support of this conceptual model,8 currently precluding its extension to children. This association may differ in children—both in strength and for classes of antibacterial agents—owing to differences in infectious disease incidence and treatment patterns. In this study we therefore investigated the association of antibacterial agents with a later diagnosis of Ca-MRSA in children, considering the number and class of antibacterial drug prescriptions.

### METHODS

#### THE GENERAL PRACTICE RESEARCH DATABASE

We analyzed the General Practice Research Database (GPRD) of the United Kingdom (England, Northern Ireland, Scotland, and Wales).23 This database contains demographic information, medical diagnoses, laboratory data, referral information, vaccinations, and prescriptions from more than 400 general practices with over 4 million active patients, about 7% of the population of the United Kingdom. The data are representative for the population of the United Kingdom and are widely used in research on prescription drug use and safety.24,25 antibacterial drug use,26-28 and infectious diseases.29-31

#### STUDY BASE AND CASE DEFINITION

From the database, we identified the cohort of children from birth to age 19 years from January 1, 1993, to December 31, 2007.29 We included children from the date their physician’s practice contributed data of sufficient quality to the database ("up to standard date"). Only children with known sex and year of birth were evaluated. The month of birth was available for 99% of children born in 1993 and for all children born later. However, for 32% of children in the cohort the month of birth was unknown because a large proportion of children entered the cohort in 1993. These children were assigned July 1 of their year of birth as their birthday.

Cases were cohort members with a diagnostic code indicative of Ca-MRSA during the study period from January 1, 1994, to December 31, 2007. We included 5 codes from the Read classification21 (+4JP..00, Sp25800, ZV02A00, and A3B1100) and Oxford Medical Information System24 code 0399TB in our case definition (Table 1). The earliest date of these diagnoses was defined as a case’s index date. We excluded diagnoses preceding a given code’s availability. Children with such erroneous diagnoses remained in the study population and became cases if they received a diagnosis with a correct date during follow-up, with the correct diagnosis date taken as the index date.

For each case, we individually matched controls on practice and month of birth, and we assigned their corresponding case’s diagnosis date as the index date. We analyzed all matching controls and only retained cases with at least 1 matching control. Cases and controls had to have at least 1 year of follow-up in the database prior to the index date.

#### EXPOSURE

We assessed exposure to antibacterial drugs in the 180 to 30 days prior to the index date in cases and controls. We ignored prescriptions in the 30-day period before the index date to prevent protopathic bias.23 We measured the intensity of exposure as the sum of antibacterial drug prescriptions and classified each prescription based on subchapters of chapter 5.1 of the British National Formulary (BNF)36 as “penicillin,” “penicillinase-resistant penicillin,” “broad-spectrum penicillin,” “cephalosporin,” “tetracycline,” “macrolide,” “quinolone,” “sulphonamide,” or “other antibacterial agent.”

A combination product containing antibacterial agents from more than 1 subchapter (eg, ampicillin and cloxacillin sodium) was counted in all antibacterial classes in which it was listed. Two or more prescriptions with an identical product code on the same date were considered as 1 prescription, and prescriptions with different product codes on the same date were considered as different prescriptions.

No child received antibacterial agents used for treatment of MRSA (eg, vancomycin) during the exposure time windows. We ignored prescriptions from other BNF chapters that contained antibacterial agents (eg, as a preservative in eye drops).

#### COVARIATES

We included sex and age in all adjusted analyses. We determined the following child-specific medical conditions and drug exposures in the 365-day period prior to the index date in cases and controls:

- Asthma, epilepsy, and diabetes mellitus were based on at least 1 diagnosis or prescription. A clinical record of any im-
munization or any vaccine prescription was defined as vaccination. We determined obesity, renal diseases, malignant diseases, eczema, S aureus carrier status, and cystic fibrosis from medical diagnoses. Likewise, we identified congenital malformations, comprising orofacial clefts, cardiovascular and nervous system malformations, other congenital malformations, and trisomy 21.

We separately considered prescription drug use based on 1 or more prescriptions of glucocorticoids, lipid-lowering drugs, diuretics, and any cardiovascular drugs that included positive inotropic, antiarrhythmic, antihypertensive, and oral anticoagulant drugs; aspirin; and clopidogrel bisulfate. The covariate cardiovascular and renal diseases consisted of cardiovascular drug use, diuretic use, and renal diseases. We defined 1 or more prescriptions of antipsychotic drugs, antidepressant drugs, or central nervous stimulants as psychotropic drug use.

Hospitalization consisted of hospitalizations and referrals to specialists, who in the United Kingdom frequently practice in hospital outpatient clinics, from 183 days before until and including the index date based on medical codes and the code representing “discharge details” from the consultation files.

DATA ANALYSIS

For the annual incidence rates of MRSA diagnoses, the number of MRSA cases served as the numerator and the sum of person-days of each child in the cohort served as the denominator. The incidence rate in infants was based on cases and person-time in children younger than 1 year.

We assessed antibacterial drug prescriptions and their association with MRSA in conditional logistic regression models, unadjusted and adjusted for potential confounders. Because MRSA is a rare disease, we report odds ratios as rate ratios (RRs).

We included a dichotomous variable indicating receipt of any number of antimicrobial drug prescriptions vs none in our first model. We assessed the number of prescriptions as a continuous covariate in a second model. In our third analysis, we included 4 indicator variables (categories) representing a given number of antibacterial drug prescriptions vs none. Children with more than 4 prescriptions were counted as having 4 prescriptions.

In our first analysis for antibacterial drug classes, children were considered to be exposed to a class regardless of prescriptions from other classes. Thus, each of the 9 classes was represented by an indicator for prescription vs no prescription. In a second analysis, children had to have prescriptions from a given class only, otherwise they were included in a combination class. This mutually exclusive definition thus yielded 9 variables for the different classes and 1 for all possible combinations. No antibacterial drug prescription in the exposure time window was the reference category in all statistical models. We used SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina) for our analyses.

SENSITIVITY ANALYSES

We varied the covariates and we restricted the study population to cases and controls free of certain covariates. We also modified the exposure window to 365 to 30 days and 90 to 30 days before the index date. In other analyses, we included only cases and corresponding controls with an index date later than 1998, 2000, or 2004. Finally, we restricted analyses to cases and corresponding controls based on diagnostic codes.

ETHICS APPROVAL

The study was approved by the faculty of medicine, McGill University institutional review board (Montreal, Quebec, Canada), and the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (ISAC, United Kingdom, Protocol 09_046R).
RESULTS

Ca-MRSA INCIDENCE IN CHILDREN IN THE UNITED KINGDOM

We identified 525 children with diagnostic codes indicative of MRSA and considered 514 with correct diagnosis dates from 248 individual general practices. During the study period, the annual number of children diagnosed as having MRSA generally increased, and the largest number of cases was diagnosed in 2006 (Figure 1). Based on cohort follow-up time, the average annual incidence was 4.5 cases per 100,000 person-years for children of all ages. In children younger than 1 year the rate was 31.5 cases per 100,000 person-years.

ASSOCIATION OF ANTIBACTERIAL DRUGS WITH Ca-MRSA IN CHILDREN

Only children with more than 1 year of follow-up were included in the case-control study (ie, children who were ≥1 year old) (Figure 2). We retained 297 cases (Table 1) and 9357 matched controls. Most cases were boys (60.6%), and their median age was 8.0 years (interquartile range, 3.6-14.5 years). Child-specific comorbid conditions were generally more prevalent in cases (Table 2), particularly epilepsy, which was about 15-fold more common than in controls. In contrast, a slightly larger proportion of controls had had hospitalizations.

About half of the cases (52.5%) and substantially fewer controls (13.6%) had received 1 or more antibacterial drug prescriptions in the 150-day exposure window (Table 3). Accounting for differences in sex and comorbid conditions, as well as hospitalizations, this difference translated to a more than 3 times higher risk of MRSA diagnosis in children with any prior antibacterial drug prescription compared with those without (adjusted RR, 3.9; 95% confidence interval [CI], 2.6-4.8). The risk of being diagnosed as having MRSA increased by about 2-fold with each antibacterial drug prescription (unadjusted RR, 2.2; 95% CI, 2.0-2.4), which remained similar after adjustment (adjusted RR, 1.8; 95% CI, 1.6-2.0). MRSA diagnoses were nonlinearly associated with increasing numbers of antibacterial drug prescriptions. Compared with no prescription, children with 1 prescription had a more than 10-fold greater risk of MRSA (adjusted RR, 11.5; 95% CI, 5.6-21.6), whereas those with 4 or more prescriptions had close to a 20-fold increase in risk (adjusted RR, 18.2; 95% CI, 9.4-35.4).

ASSOCIATION OF CLASSES OF ANTIBACTERIAL DRUGS WITH Ca-MRSA

We found a differential association with subsequent MRSA diagnosis for various classes of antibacterial agents (Table 4). When we accounted for potential confounders and prescriptions from other antibacterial drug classes in the exposure time window, both penicillinase-resistant penicillins and broad-spectrum penicillins were associated with a later diagnosis of MRSA, and the association was particularly strong for macrolides (RR, 5.2; 95% CI, 3.3-8.4) and quinolones (RR, 14.8; 95% CI, 3.9-55.8). In the same model, we did not detect an association for penicillins, cephalosporins, or sulfonamides, whereas the antibacterial agents summarized in the class “other antibacterial agents” were associated with MRSA.

Table 2. Characteristics of Children With Ca-MRSA Diagnoses and Matched Controls, General Practice Research Database, United Kingdom, 1994-2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=297)</th>
<th>Controls (n=9357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>122 (41.1)</td>
<td>4346 (46.4)</td>
</tr>
<tr>
<td>Follow-up time, mean (SD), y</td>
<td>4.64 (3.45)</td>
<td>4.64 (3.61)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>9.07 (5.94)</td>
<td>9.07 (5.49)</td>
</tr>
<tr>
<td>Male</td>
<td>180 (60.6)</td>
<td>4624 (49.4)</td>
</tr>
<tr>
<td>Asthma</td>
<td>83 (27.9)</td>
<td>886 (9.5)</td>
</tr>
<tr>
<td>Vaccination</td>
<td>105 (35.4)</td>
<td>1880 (20.1)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>32 (10.8)</td>
<td>66 (0.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (1.0)</td>
<td>27 (0.3)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0</td>
<td>14 (0.1)</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td>26 (8.8)</td>
<td>100 (1.1)</td>
</tr>
<tr>
<td>Eczea</td>
<td>51 (17.2)</td>
<td>309 (3.3)</td>
</tr>
<tr>
<td>S aureus carrier</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>14 (4.7)</td>
<td>32 (0.4)</td>
</tr>
<tr>
<td>Heart and renal disease</td>
<td>12 (4.0)</td>
<td>80 (0.9)</td>
</tr>
<tr>
<td>Use of psychotropic drugs</td>
<td>12 (4.0)</td>
<td>173 (1.8)</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs</td>
<td>0</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>3 (1.0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>7 (2.4)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

Abbreviation: Ca-MRSA, community-associated methicillin-resistant Staphylococcus aureus.

a Mean weighted, standard deviation unweighted.
Because very few children received tetracycline prescriptions, we could not assess this antibacterial class.

Defining antibacterial classes more strictly in a mutually exclusive way generally resulted in stronger associations for individual drug classes (Table 5). Consistently, without antibacterial drug prescriptions from other classes in the exposure time window, penicillins and sulfonamides were not associated with a later diagnosis of MRSA. We found an association for penicillinase-resistant penicillins (RR, 4.1; 95% CI, 2.1-8.0) and broad-spectrum penicillins (RR, 2.7; 95% CI, 1.7-4.1) as well as for macrolides (RR 5.7; 95% CI, 3.0-11.0). In contrast, exclusive use of cephalosporins was associated with a later diagnosis of MRSA (RR, 5.8; 95% CI, 1.8-18.1). Because no case received exclusively quinolones in the exposure time window, these could not be assessed with a stringent exposure definition. The same, expectedly, applied to tetracyclines. Exclusive prescription from the class “other antibacterial agents” was strongly associated with MRSA (RR, 12.3; 95% CI, 2.3-64.6), and children receiving prescriptions from various antibacterial classes were also more likely to be diagnosed as having MRSA than children without any antibacterial drug prescriptions (RR, 5.7; 95% CI, 3.6-8.9).

SENSITIVITY ANALYSES

Exposure to antibacterial agents remained associated with MRSA diagnoses in sensitivity analyses. Results of analyses using different sets of potential confounders and restricted to children without hospitalizations were equivalent to our main analysis. Children free of covariates were also at a dose-dependent risk of MRSA diagnosis after antibacterial drug exposure, and antibacterial classes were associated in the same way as in the main analysis.

Exposure in an expanded 365- to 30-day period prior to the index date led to a weaker association. Shorten-

### Table 3. Association of Number of Antibacterial Drug Prescriptions With Ca-MRSA Diagnoses in Children, General Practice Research Database, United Kingdom, 1994-2007

<table>
<thead>
<tr>
<th>Antibacterial Drug Prescriptions, No.</th>
<th>Cases (n = 297)</th>
<th>Controls (n = 9357)</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prescription</td>
<td>141 (47.5)</td>
<td>8083 (86.4)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;b&lt;/sup&gt; ≥1</td>
<td>156 (52.5)</td>
<td>1274 (13.6)</td>
<td>6.1 (4.8-7.9)</td>
<td>3.5 (2.6-4.8)</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;c&lt;/sup&gt; ≥4</td>
<td>46 (15.5)</td>
<td>46 (0.5)</td>
<td>49.9 (29.2-85.5)</td>
<td>18.2 (9.4-35.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Ca-MRSA, community-associated methicillin-resistant Staphylococcus aureus; RR, rate ratio.

<sup>a</sup>Adjusted for sex, age, asthma, vaccination, epilepsy, diabetes mellitus, eczema, glucocorticoids, cardiovascular and renal diseases, congenital malformations, psychotropic drugs, and hospitalization.

<sup>b</sup>Dichotomous variable for exposure.

<sup>c</sup>Categories of exposure.

### Table 4. Association of Different Classes of Antibacterial Drugs With Ca-MRSA Diagnoses in Children, General Practice Research Database, United Kingdom, 1994-2007

<table>
<thead>
<tr>
<th>Antibacterial Class</th>
<th>Cases (n = 297)</th>
<th>Controls (n = 9357)</th>
<th>Unadjusted</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prescription</td>
<td>141 (47.5)</td>
<td>8083 (86.4)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Penicillins</td>
<td>15 (5.1)</td>
<td>263 (2.8)</td>
<td>1.4 (0.7-2.7)</td>
<td>0.8 (0.4-1.8)</td>
</tr>
<tr>
<td>Penicillinase-resistant penicillins</td>
<td>44 (14.8)</td>
<td>170 (1.8)</td>
<td>5.2 (3.3-8.3)</td>
<td>3.6 (2.2-6.1)</td>
</tr>
<tr>
<td>Broad-spectrum penicillins</td>
<td>74 (24.9)</td>
<td>572 (6.1)</td>
<td>2.2 (1.6-3.1)</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>19 (6.4)</td>
<td>81 (0.9)</td>
<td>3.4 (1.8-6.7)</td>
<td>1.6 (0.7-3.7)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>0</td>
<td>126 (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Macrolides</td>
<td>56 (18.9)</td>
<td>178 (1.9)</td>
<td>7.0 (4.6-10.5)</td>
<td>5.2 (3.3-8.2)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>12 (4.0)</td>
<td>13 (0.1)</td>
<td>20.7 (5.9-72.5)</td>
<td>14.8 (3.9-55.8)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>14 (4.7)</td>
<td>91 (1.0)</td>
<td>1.64 (0.8-3.5)</td>
<td>1.3 (0.6-3.0)</td>
</tr>
<tr>
<td>Other antibacterial agents&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 (5.1)</td>
<td>37 (0.4)</td>
<td>8.5 (3.3-21.9)</td>
<td>11.1 (4.0-30.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Ca-MRSA, community-associated methicillin-resistant Staphylococcus aureus; CI, confidence interval; RR, rate ratio.

<sup>a</sup>Adjusted for prescriptions of all other antibacterial classes listed in the table and for sex, age, asthma, vaccination, epilepsy, diabetes mellitus, eczema, glucocorticoids, cardiovascular and renal diseases, congenital malformations, psychotropic drugs, and hospitalization.

<sup>b</sup>Comprises antipseudomonal penicillins, mecillinams, aminoglycosides, chloramphenicol, fusidic acid, polymyxins, or metronidazole and tinidazole, nitrofurantoin, methenamine hippurate, and fosfomycin.
We observed an association between antibacterial drug prescriptions and a subsequent diagnosis of MRSA in children in the community that was stronger for increasing numbers of prescriptions, varied for different classes of antibacterial agents, and remained consistent in sensitivity analyses. However, in nearly half of the cases the children had not received any antibacterial drug prescriptions prior to the index date showed a stronger association for antibacterial drug prescriptions with subsequent MRSA diagnoses. However, neither change affected the results qualitatively. Starting the study period in 1998, 2000, and 2004 instead of 1994 did not markedly alter the results. A restricted analysis of cases with Read code 4JP..00 “MRSA positive” and a separate analysis of cases having Read code A31100 “MRSA infection” were both consistent with the main analysis.

COMPARISON WITH OTHER STUDIES

We have previously demonstrated a comparable dose-dependent association of antibacterial agents with diagnoses of Ca-MRSA in adults.21 In children, we found associations for fewer antibacterial classes but particularly strong associations for macrolides, quinolones, and “other antibacterial agents.”

From 2000 through 2004, the annual incidence rate of Ca-MRSA was 15.2 cases per 100 000 adults per year.21 During the same period in the same database, the average incidence rate of MRSA diagnoses in children from birth to 19 years old was only about one-third (5.5 cases per 100 000 person-years).

Annual incidence of hospitalizations for Ca-MRSA skin infections in US children in 200620 was about 2.5-fold higher than our reported incidence of MRSA at unknown sites diagnosed in the community in children in the United Kingdom. In 2001 to 2002,7 pediatric incidence rates in white children older than 2 years in the United States were approximately twice as high as those for all children in our study, but similar to findings in our study, incidence rates were higher in very young children. Community-onset MRSA incidence in children younger than 15 years was drastically higher in San Francisco, California, in 2004 to 200519 compared with both previous studies in the United States and this study. Thus, Ca-MRSA seems to represent a larger public health problem for children in the United States than in the United Kingdom, but in both countries Ca-MRSA incidence is probably higher in young children than in older children.

STUDY STRENGTHS

We analyzed a well-defined, large, and representative cohort of children in the United Kingdom. We avoided considering antibacterial agents for an existing infection,
which later turned out to be MRSA, as associated with its development (protopathic bias) by excluding prescriptions in the 30 days preceding the diagnosis and the index date. We accounted for numerous child-specific comorbid conditions to minimize confounding. We matched control children on practice to account for differences in prescription and MRSA detection patterns between practices. By assigning the same index date to controls, we assessed antibacterial drug prescriptions in the same calendar time frame in cases and corresponding controls. To minimize bias by overadjustment, we modified covariates and excluded children with comorbid conditions in sensitivity analyses.

Trends in reporting or detecting may have caused or contributed to the observed increase in MRSA incidence. We therefore conducted sensitivity analyses restricting cases and corresponding controls to those with an index date later than 1998, 2000, and 2004.

STUDY LIMITATIONS

We cannot distinguish between asymptomatic carriers and children with clinically significant infections. However, we think that general practitioners (GPs) are unlikely to screen children for colonization and therefore a diagnosis of clinical significance is likely. We may miss children with MRSA who were directly referred to hospitals and in whom the diagnosis was not entered as a medical code. We lack microbiological test results confirming the medical diagnosis; therefore, diagnostic specificity and sensitivity are limited. While other diagnoses and diseases have been validated, we are not aware of any validation study on MRSA in the GPRD. However, our stratified analyses were generally consistent with the main results for the first and second most often assigned MRSA code.

We measured exposure based on GP prescriptions and not on records of prescriptions dispensed from pharmacies or actual drug ingestion. We lack prescription information from inpatients and those with prescriptions from emergency departments or specialists. Thus, exposure may have been overestimated or underestimated in some children. However, such errors would have to be differentially associated with a later MRSA diagnosis to affect our results.

Antibacterial drug prescriptions may represent an intermediate step on the causal pathway to MRSA diagnosed in the community. We therefore cannot consider the observed association as causal. However, in support of causality, the association was not only dose and class dependent but also responsive to modifying the length of the exposure time window, which implies time dependency.

Unfortunately, we could not study children younger than 1 year because they did not have sufficient follow-up time to determine comorbid conditions, prescription drug use, and hospitalizations. In these children, Ca-MRSA incidence was particularly high, indicating that they may have specific infection risks (eg, when being in the maternity ward).

In conclusion, antibacterial agents are not a necessary precondition for MRSA, but there is a robust association of antibacterial drug prescriptions with a subsequent diagnosis of MRSA for children in the community. Although we could not establish causality of the association, our results support efforts to minimize unnecessary antibacterial drug prescribing, particularly of second-line agents, to children in the community. Given limitations in case ascertainment, our Ca-MRSA incidence estimates should be cautiously interpreted.

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Author Contributions: Drs Schneider-Lindner and Suissa had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have given final approval of the submitted manuscript. Study concept and design: Schneider-Lindner, Hanley, and Suissa. Acquisition of data: Suissa. Analysis and interpretation of data: Schneider-Lindner, Quach, Hanley, and Suissa. Drafting of the manuscript: Schneider-Lindner. Critical revision of the manuscript for important intellectual content: Quach, Hanley, and Suissa. Statistical analysis: Schneider-Lindner, Hanley, and Suissa. Obtained funding: Suissa. Study supervision: Quach and Suissa.

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REFERENCES