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Population-Based Cohort Study of Anti-Infective Medication Use before and after the Onset of Type 1 Diabetes in Children and Adolescents

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A population-based cohort study was conducted in the Dutch PHARMO database to investigate prevalence and patterns of anti-infective medication use in children and adolescents with type 1 diabetes (T1D) before and after the onset of this disease. All patients <19 years with at least 2 insulin prescriptions (1999 to 2009) were identified (T1D cohort) and compared with an age- and sex-matched (ratio: 1 up to 4) diabetes-free reference group. The prevalence and average number of anti-infective use was studied from (up to) 8 years before until a maximum of 4 years after the onset of T1D. A total of 925 patients with T1D and 3,591 children and adolescents in the reference cohort (51% boys, mean age of 10.1 [standard deviation, 4.5] years) were included. The overall prevalence of anti-infective use (62.6 compared to 52.6%, $P < 0.001$) and average number of prescriptions (2.71 compared to 1.42 per child, $P < 0.001$) in the T1D cohort were significantly higher than those in the reference cohort after the onset of diabetes. This pattern was consistent across sex and age categories and already observed in the year before the onset of type 1 diabetes. Patients in the T1D cohort received more antibacterials (49.8 compared to 40%, $P < 0.001$), antimycotics (4.0 compared to 1.3%, $P < 0.001$), antivirals (2.5 compared to 0.4%, $P < 0.001$), and second-line antibiotics, such as aminoglycosides, quinolones, and third-generation cephalosporins and carbapenems. Our findings that elevated anti-infective use in the T1D cohort exists in the period before the onset of type 1 diabetes and the consumption of more second-line anti-infective compounds in this time period warrant further research.

One of the most common autoimmune disorders in children and adolescents is type 1 diabetes (T1D) (1, 2). In 2013, an estimated 500,000 children and adolescents 0 to 14 years old had type 1 diabetes worldwide, and the global incidence of type 1 diabetes among children 0 to 14 years of age increases by 3% annually (3). Associations between type 1 diabetes and infectious diseases have been reported in two ways. In several studies, infections have been discussed as important environmental determinants in the pathogenesis of type 1 diabetes (4–6). In other studies, high incidences of infections and consequently a higher prevalence of anti-infective medication use have been reported in patients with diabetes mellitus (both type 1 and type 2) (7–9).

Infections are an important component of the disease burden during childhood, and accordingly anti-infective medications are among the most commonly used classes of medicines in children and adolescents (10). So far, little attention has been paid to quantifying anti-infective medication use in children and adolescents with type 1 diabetes (both before and after the onset of this disease). Comparing the utilization patterns of anti-infective medications between patients with type 1 diabetes and a group of diabetes-free children and adolescents can provide insight into the additional burden of infectious diseases in patients with type 1 diabetes in daily clinical practice. Therefore, we conducted a population-based cohort study using community pharmacy prescription records to estimate levels of anti-infective medication use in children and adolescents with type 1 diabetes in the period before the onset until a maximum of 4 years thereafter and compared these utilization data with a group of age- and sex-matched diabetes-free children and adolescents.

MATERIALS AND METHODS

Data source, study design, and population. A population-based cohort study was conducted using the Dutch PHARMO Record Linkage System (RLS) (http://www.pharmo.nl). PHARMO RLS is a population-based patient-centric data network throughout the whole country including high-quality and complete information linked on a patient level of, among other things, patient demographics, drug dispensing records from community pharmacies, and hospital discharge records of more than 4 million individuals throughout the Netherlands (approximately 24% of the Dutch population) (11, 12). The drug dispensing records consist of data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. The hospital records are obtained from the Dutch National Medical Register (LMR), which comprises all hospital admissions in the Netherlands. Dates of hospital admissions and discharges, together with primary and secondary diagnoses, are documented in the hospital records. Diagnoses are coded according to the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM), whereas the drugs are coded according to the Anatomical Therapeutic Chemical codes (ATC codes) (http://www.whocc.no/atc_ddd_index). Information about these residents has been recorded since 1986 and has been used in many pharmacoepidemio-

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TABLE 1 Codes used to identify anti-infective medications

Anti-infective medications (ATC code[a])	Subgroup 1 (ATC code)	Subgroup 2 (ATC code)
Antibacterials for systemic use (J01)	Tetracyclines (J01A)	
	Amphenicols (J01B)	
	Beta-lactam antibacterials, penicillins (J01C)	Penicillins with extended spectrum (J01CA), beta-lactamase-sensitive penicillins (J01CE), beta-lactamase-resistant penicillins (J01CF), beta-lactamase inhibitors (J01CG), combinations of penicillins, including beta-lactamase inhibitors (J01CR)
	Other beta-lactam antibacterials (J01D)	First-generation cephalosporins (J01DB), second-generation cephalosporins (J01DC), third-generation cephalosporins (J01DD), fourth-generation cephalosporins (J01DE), monobactams (J01DF), carbapenems (J01DH), other cephalosporins and penems (J01DI)
	Sulfonamides and trimethoprim (J01E)	
	Macrolides (J01FA)	
	Aminoglycoside antibacterials (J01G)	
	Quinolone antibacterials (J01M)	
	Other antibacterials (J01X)	
Antimycotics for systemic use (J02)	Antimycotics for systemic use (J02A)	Antibiotics (J02AA), imidazole derivatives (J02AB), triazole derivatives (J02AC)
Antimycobacterials (J04)		
Antivirals for systemic use (J05)	Direct-action antivirals (J05A)	Thiosemicarbazones (J05AA), nucleosides and nucleotides excluding reverse transcriptase inhibitors (J05AB), protease inhibitors (J05AE), nucleoside and nucleotide reverse transcriptase inhibitors (J05AF), nonnucleoside reverse transcriptase inhibitors (J05AG), neuraminidase inhibitors (J05AH), antivirals for treatment of HIV infections, combinations (J05AR)
Antifungals for topical use (D01A)		
Antifungals for systemic use (D01B)	Antifungals for systemic use (D01BA)	
Antibiotics and chemotherapeutics for dermatological use (D06)		
Gynecological anti-infectives and antiseptics (G01)		

[a] ATC codes, Anatomical Therapeutic Chemical codes. All the changes in the ATC codes during the study period have been adjusted (http://www.whocc.no/atc_ddd_alterations_cumulative/atc_alterations/).

logic and outcome studies (11, 12). Hospital diagnoses and drug exposures retrieved from the prescription records in the PHARMO RLS have been validated in several studies (13–15).

In the current study, patients younger than 19 years old with at least 2 prescriptions for insulin (based on the ATC codes for insulin preparations [A10A]) between January 1999 and December 2009 were selected as patients with type 1 diabetes (T1D cohort). The date of first insulin prescription was selected as the index date (cohort entry date). For the comparative analysis, for each patient in the T1D cohort, up to 4 diabetes-free children and adolescents (without any prescription of glucose-lowering medications [ATC code A10] or hospitalization for diabetes [ICD-9-CM code 250] during the study period) with the same sex, age, and calendar time distribution were randomly sampled from the PHARMO RLS (reference cohort). Patients in both cohorts were eligible for inclusion in the study if they had at least 12 months of exposure history before and at least 12 months of follow-up after the index date. Patients in the T1D cohort were excluded from the study if they ever used oral glucose-lowering medications (in order to exclude potential patients with type 2 diabetes [ATC code A10B]) or glucagon prior to the index date (glucagon [ATC code H04AA01] is usually prescribed for patients with diabetes to manage hypoglycemia; therefore, in patients who had prescriptions of glucagon before the insulin prescriptions, the index date was not clear). Both cohorts were followed from the index date for a maximum of 4 years. Infants with an index date before the age of 12 months and at least 12 months of valid follow-up data after the index date in the PHARMO RLS were also included. For all included study participants, data for the period before the index date were retrieved as long as possible (with a maximum of 8 years).

Use of anti-infectives and statistical analysis. Exposure to anti-infectives was defined as a recorded receipt of a prescription for an anti-infective medication with an ATC code listed in Table 1. Children and adolescents who received at least one prescription for an anti-infective medication during the study period were defined as anti-infective users. The prevalence of anti-infective medication use in each cohort (T1D and the reference cohort) was defined as the number of children and adolescents with at least one anti-infective prescription in a particular year (or years) divided by the total number of children and adolescents in that cohort during that follow-up period. The overall prevalence of anti-infective use was calculated in each cohort from the index date till the end of follow-up and compared with Pearson's chi-square test. The study population was stratified into different age categories based on the age at the onset of type 1 diabetes (using age bands 0 to 4, 5 to 9, 10 to 14, and 15 to 18 years). The overall prevalences of anti-infective medication use (from the index date till the end of follow-up) by different sexes and age categories were also compared with an ordinal chi-square test within each cohort. The overall average number of anti-infective prescriptions was calculated in each cohort from the index date till the end of follow-up, compared with a two-sample *t* test, and further stratified by sex and age categories using the previous age bands. To assess patterns over time, annual prevalences of anti-infective medication use and the annual average number of anti-infective prescriptions per child were calculated from

TABLE 2 Baseline characteristics of the study participants

Baseline characteristic	T1D[a] cohort (n = 925)		Reference cohort (n= 3,591)	
	No.	%	No.	%
Sex				
Male	469	50.7	1,817	50.6
Female	456	49.3	1,774	49.4
Age category				
0–4 yrs	135	14.6	537	15
5–9 yrs	270	29.2	1,043	29
10–14 yrs	335	36.2	1,295	36.1
15–18 yrs	185	20	716	19.9
Yr of cohort entry				
1999–2004	385	41.6	1,452	40.4
2005–2009	540	58.4	2,139	59.6
No. of participants in each yr of the study period				
8 yrs before the index date	156	16.9	612	17.0
7 yrs before the index date	213	23.0	827	23.0
6 yrs before the index date	296	32.0	1,162	32.4
5 yrs before the index date	381	41.2	1,513	42.1
4 yrs before the index date	487	52.6	1,913	53.3
3 yrs before the index date	610	65.9	2,384	66.4
2 yrs before the index date	741	80.1	2,911	81.1
1 yr before the index date	925	100	3,591	100
First yr of follow up	925	100	3,591	100
Second yr of follow up	925	100	3,587	99.9
Third yr of follow up	812	87.8	3,139	87.4
Fourth yr of follow up	708	76.5	2,726	75.9

[a] T1D, type 1 diabetes.

8 years prior to the index date up to 4 years after the index date in both cohorts.

Anti-infectives were further categorized by therapeutic subgroups (Table 1). The overall (from the index date till the end of follow-up) and annual prevalences of different anti-infective subgroups for systemic use were calculated for both cohorts. Additionally, the annual proportions of different beta-lactam subgroups of the total beta-lactam antibacterial group were calculated in both cohorts. Monthly prescription rates did not reveal a significant seasonal pattern over the study period in both cohorts; therefore, only annual rates were presented in this study. Bonferroni correction was used to account for all tests that we used in this study. SPSS version 19.0 was used for the statistical analysis and calculating the prevalence rates in this study (SPSS Inc., Chicago, IL, USA).

RESULTS

From January 1999 through December 2009, we identified 925 children and adolescents with type 1 diabetes (T1D cohort) and compared them with a group of 3,591 age- and sex-matched diabetes-free individuals (reference cohort) from the PHARMO RLS. The mean age of the study population at the index date was 10.1 (standard deviation [SD], 4.5) years, and almost 51% of them were boys. The majority of the patients with type 1 diabetes in our study were 10 to 14 years old at the onset of the disease (Table 2).

The overall prevalence of anti-infective medication use from the index date till the end of follow-up was significantly higher in the T1D cohort (62.6%) than in the reference cohort (52.6%) ($P < 0.001$). Figure 1a compares the annual prevalences of anti-

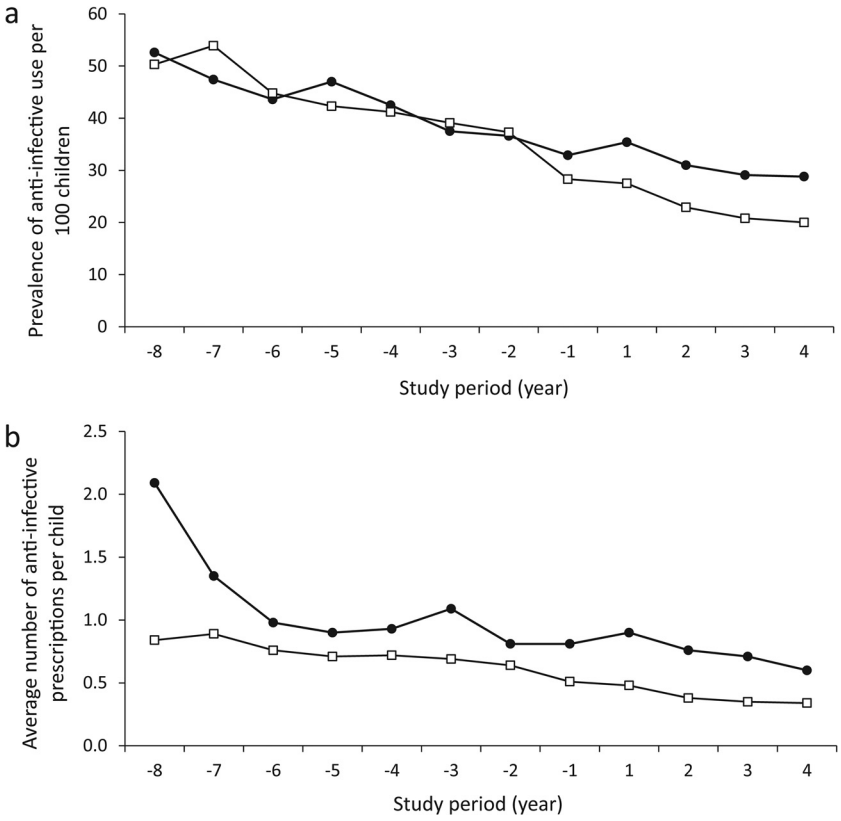

FIG 1 Annual prevalence of anti-infective medication use (a) and annual average number of anti-infective prescriptions per child (b) in the T1D (●) and the reference (□) cohorts. Minus signs in the *x* axis refer to years before the index date.

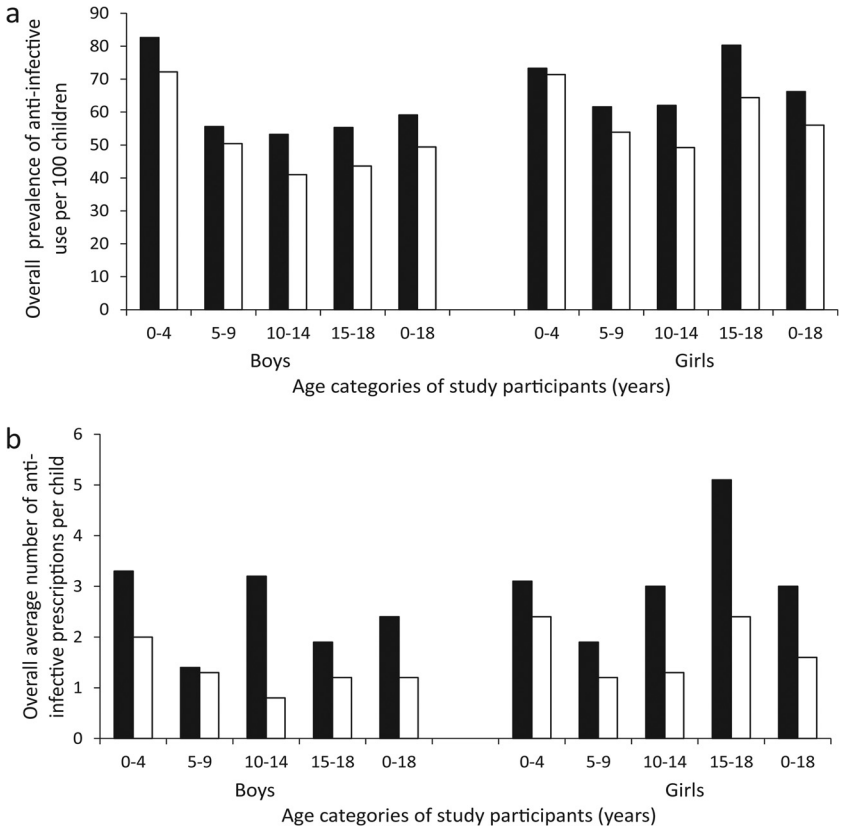

FIG 2 Overall (from the index date till the end of follow-up) prevalence of anti-infective medication use (a) and the average number of anti-infective prescriptions per child (b) in the T1D (black bars) and the reference (white bars) cohorts stratified by sex and age categories.

infective prescriptions between the two cohorts, showing a higher prevalence among the T1D cohort in all years after the diagnosis and in the year before the onset of diabetes. The overall average number of anti-infective prescriptions from the index date till the end of follow-up was significantly higher in the T1D cohort than in the reference cohort (2.71 compared to 1.42 per child, $P < 0.001$). Figure 1b displays the annual average number of anti-infective prescriptions in both cohorts, showing a pattern similar to that in Fig. 1a, although differences between the two cohorts were observed long before the disease onset.

As shown in Fig. 2a, anti-infective medications were used more frequently by girls with type 1 diabetes (66.2%) than by boys (59.1%) from the index date till the end of follow-up ($P = 0.024$). The same pattern across the two sexes was observed in the reference cohort. Within the cohorts, a significant difference in the prevalence of anti-infective medication use was observed among the different age categories ($P < 0.001$). Although the highest prevalence of anti-infective medication use from the index date till the end of follow-up was reported for boys who developed type 1 diabetes at the age of 0 to 4 years (Fig. 2a), girls who developed type 1 diabetes at the age of 15 to 18 years had the highest number of prescriptions per child in the same time period. This number was 2.7 times higher than boys in the 15-to-18-year category of the T1D cohort and 2.1 times higher than girls in the reference cohort with the same age category (Fig. 2b).

The overall prevalence of antibacterial prescriptions for systemic use in the T1D cohort was significantly higher than that in the reference cohort (49.8 compared to 40%, respectively [$P < 0.001$]). Not only were the annual prevalences of systemic antibacterials higher in the T1D cohort than in the reference cohort (Fig. 3), but also the choice of compounds was different, with more second-line agents in the T1D cohort, even in the whole period prior to the index date. For instance, children and adolescents in the T1D cohort had considerably higher prevalences of macrolides, aminoglycosides, quinolones, and second-line beta-lactam antibacterials (e.g., third-generation cephalosporins and carbapenems; Fig. 4).

From the index date till the end of follow-up, both systemic antimycotics (4.0 compared to 1.3% in the T1D and reference cohort, respectively [$P < 0.001$]) and systemic antivirals (2.5 versus 0.4%, $P < 0.001$) were used more frequently in the T1D cohort. During the 8 years before the index date, children and adolescents in the T1D cohort used more systemic antimycotic medications than the other cohort (Fig. 5). In the year before the index date, the prevalence of systemic antimycotics in the T1D cohort was 5.8 times higher than the other cohort (1.73 compared to 0.3%, respectively, $P < 0.001$). At the same time, the prevalence of systemic antivirals was 3.9 times higher in the T1D cohort than in the reference cohort (0.43 compared to 0.11%, respectively, $P < 0.001$). The prevalence of systemic antivirals remained the same for the reference cohort in the first year after the index date, but it increased considerably in the T1D cohort (5-fold increase). Figure 5 shows that in the first year after the index date, children and

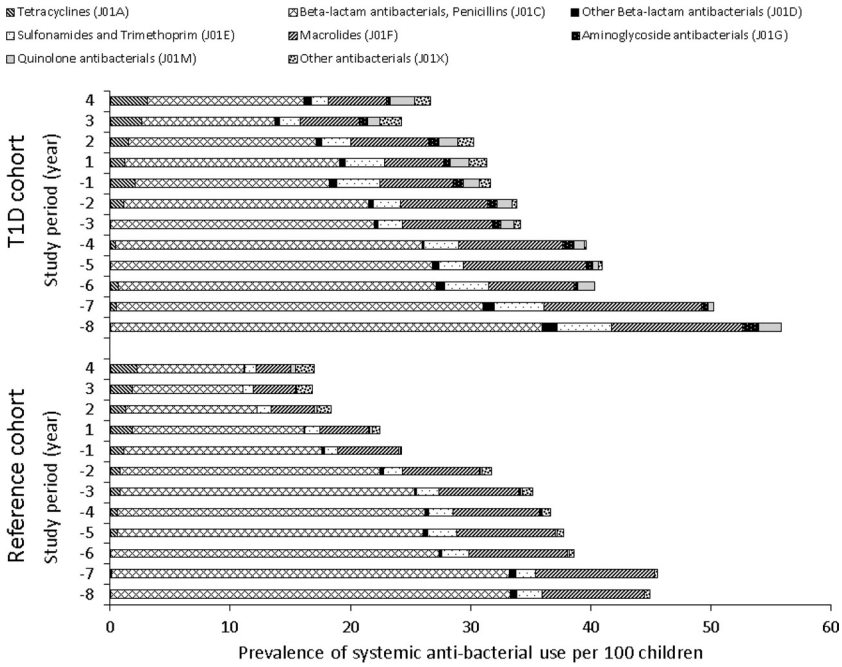

FIG 3 Annual prevalences of systemic antibacterial subgroups in the T1D and the reference cohorts (tetracyclines [J01A], beta-lactam antibacterial penicillins [J01C], other beta-lactam antibacterials [J01D], sulfonamides and trimethoprim [J01E], macrolides [J01F] aminoglycoside antibacterials [J01G], quinolone antibacterials [J01M], other antibacterials [J01X]). Minus signs in the *x* axis refer to years before the index date.

adolescents with type 1 diabetes had the highest prevalence of systemic antiviral use.

DISCUSSION

This study demonstrated that the overall prevalence and the average number of anti-infective prescriptions among children and adolescents with type 1 diabetes are significantly higher than among age- and sex-matched diabetes-free individuals in the PHARMO RLS. These differences were already observed at least in the year prior to the onset of type 1 diabetes and were even larger during the first year after diagnosis. Furthermore, the choice of compounds was also different between the two cohorts long before the disease onset. Children and adolescents with type 1 diabetes used more antimycotic, antiviral, and second-line antibacterial compounds, even in the years before the onset of this disease.

Anti-infective medication use after the onset of type 1 diabetes. The higher consumption of anti-infective medications in children and adolescents with type 1 diabetes corresponds with the more frequent occurrence of infections in these patients (7, 8). It is possible that regular contact with the physician after the diagnosis of type 1 diabetes increased the probability of diagnosing different infections, which resulted in prescribing more anti-infectives for these children during the follow-up time. But if this was the case, prevalence rates and average number of prescriptions would have remained high over the other 3 follow-up years, while these rates were lower than what we observed in the year prior to the diagnosis of type 1 diabetes.

Not only were the overall prevalence and average number of anti-infectives higher in the T1D cohort, but also the choice of the compound was different between the two cohorts. Children and adolescents with type 1 diabetes had prescriptions for more second-line anti-infectives compared with the reference cohort, including antibiotics which should be carefully prescribed in children and adolescents, such as quinolones (16, 17). This observation accords with earlier studies that mentioned a higher severity of infections in patients with diabetes (18). Specific factors like hyperglycemia-related impairment of the immune response, vascular insufficiency, sensory peripheral neuropathy, and autonomic neuropathy seem to be possible explanations for this increased severity of infections among diabetic patients (8, 18, 19). Another possible explanation for using more second-line anti-infectives is that children and adolescents with type 1 diabetes did not respond to the first-line anti-infectives that were initially prescribed and the physician was forced to prescribe a second-line anti-infective for them.

The observed differences in the prevalence and average number of anti-infective prescriptions between different sex and age categories in both cohorts are in line with the results of other studies (20–22). In our study, the highest prevalence for anti-infective prescriptions was observed for boys who developed type 1 diabetes at the age of 0 to 4 years. In the youngest age group (0 to 4 years), boys were more likely to receive anti-infective prescriptions, as we know that male gender is a well-known risk factor for recurrent infections in children (21, 23). In older-age categories, girls received more anti-infective prescriptions, which accords with the findings of Majed and Moser, which showed that prescribing rates for antibiotics in young females (older than 4 years) were substantially higher than in males of the same age (24). The increase in the prevalence and average number of anti-infective prescriptions in girls in older-age categories could be explained by a higher frequency of urinary tract infections (7). Increased susceptibility of patients with diabetes to vulvovaginal candidiasis could be the reason for the increased number of anti-infective prescriptions, especially antimycotics, as was observed in the oldest girls (25).

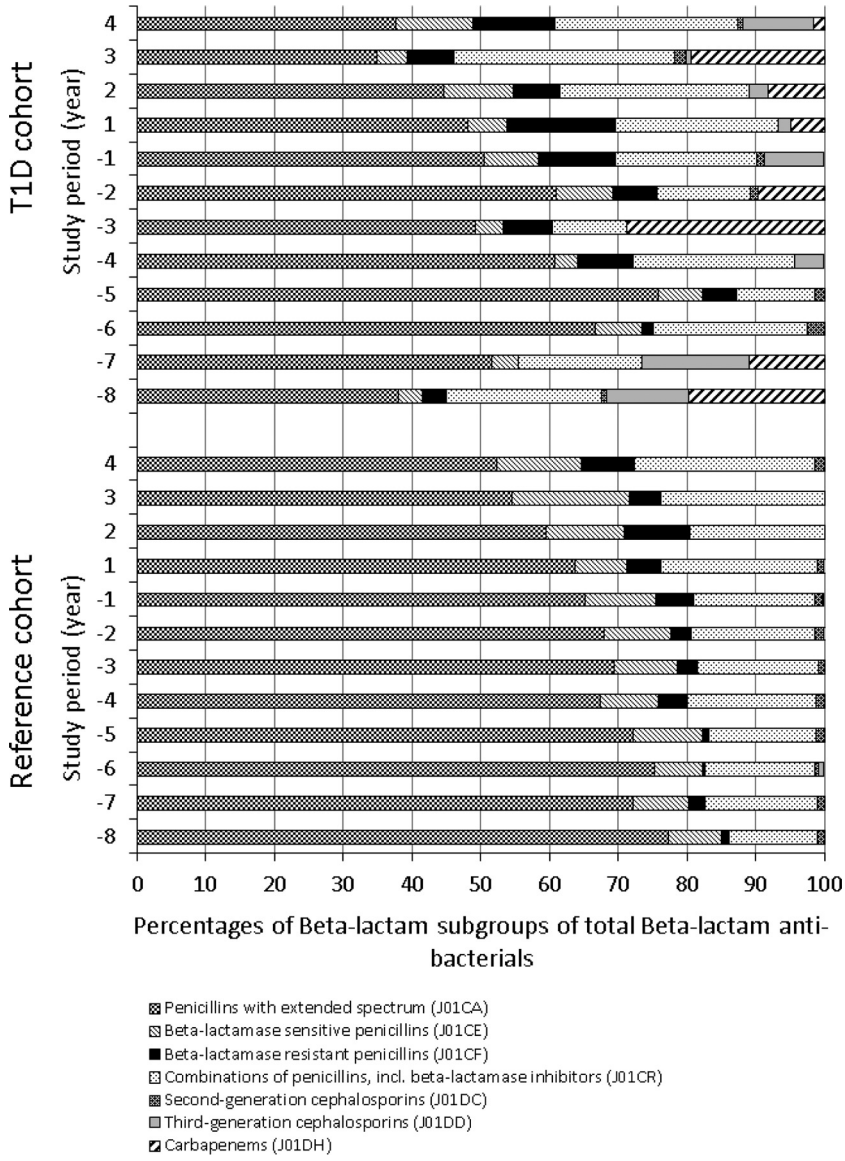

FIG 4 Annual proportion of beta-lactam subgroups of total beta-lactam antibacterials in the T1D and the reference cohorts (penicillins with extended spectrum [J01CA], beta-lactamase-sensitive penicillins [J01CE], beta-lactamase-resistant penicillins [J01CF], combinations of penicillins, including beta-lactamase inhibitors [J01CR], second-generation cephalosporins [J01DC], third-generation cephalosporins [J01DD], carbapenems [J01DH]). Minus signs in the *x* axis refer to years before the index date.

Anti-infective medication use before the onset of type 1 diabetes. The increase in prevalence (8.5% increase) and average number of anti-infective medications per child (11.1% increase) from the year before the index date to the first year of developing type 1 diabetes supports findings from previous studies which linked the occurrence of infections, especially viral infections, with the development of type 1 diabetes (5, 6). The raised prevalence rates and average numbers during this year seem to be consistent with a recent study which found that all children who developed islet autoimmunity and type 1 diabetes had at least 1 infection within 6 months before islet autoantibody seroconversion (4). Prior to the clinical presentation of type 1 diabetes, there is a variable asymptomatic period of beta cell destruction (26), so it is possible that this autoimmunity against the pancreatic beta cells is associated with observing more infections in the T1D cohort in the year before the diagnosis of type 1 diabetes. The association between viral infections and the pathogenesis of type 1 diabetes has been considered by several studies (5, 27, 28), but there has been little discussion about the association of bacterial or mycotic infections and type 1 diabetes in the literature. We found that the prevalences of antimycotic and antiviral medications in children and adolescents with type 1 diabetes in the year prior to the index date were 5.8 and 3.9 times higher than in the reference cohort, respectively.

In addition to infections, anti-infectives themselves may increase diabetes risk. To date, there has been little agreement on the association between anti-infective use and risk of developing type 1 diabetes (29–31). According to Kilkkinen et al., the use of phenoxymethyl penicillins and quinolones by mothers before pregnancy and the use of macrolides by mothers before pregnancy and

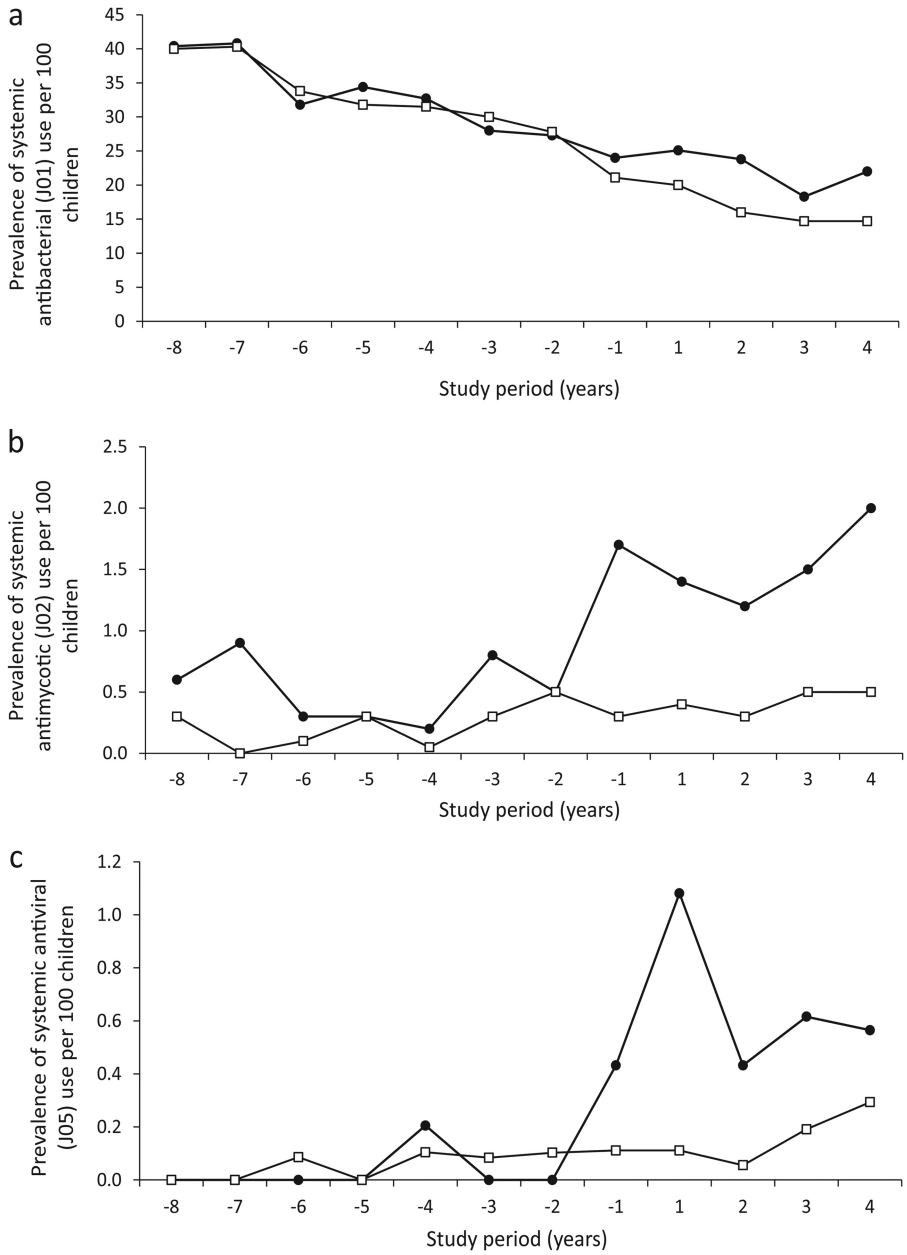

FIG 5 Annual prevalence of systemic antibacterial (J01) (a), systemic antimycotic (J02) (b), and systemic antiviral (J05) (c) medication use in the T1D (●) and the reference (□) cohorts. Minus signs in the *x* axis refer to years before the index date.

by their child were associated with an increased risk of type 1 diabetes in children (31). Furthermore, a recent FDA warning about fluoroquinolone antibiotics mentioned that several drugs in this class of antibiotics may disrupt blood glucose control in individuals with diabetes because of the insulinotropic or other effects of fluoroquinolones on beta cells in the pancreas. However, the incidence of hyperglycemia in patients taking quinolones (i.e., 6.9 per 1,000 people for moxifloxacin, 3.9 per 1,000 for levofloxacin, and 4.0 per 1,000 for ciprofloxacin) seems rather low and may only have partial contribution to the development of type 1 diabetes in the present cohort (32, 33). As can be seen from our results, children and adolescents in the T1D cohort had higher prevalence of quinolone use in the years prior to the diagnosis of type 1 diabetes and other follow-up years. Therefore, it is possible to hypothesize that fluctuating blood glucose and other effects of quinolones on beta cells and insulin secretion might accelerate beta cell destruction in genetically susceptible people or in those who already developed autoantibodies against beta cells. However, in the current study, we did not have information on autoantibodies and genetic-related risk factors for type 1 diabetes. Moreover, it is important to note that based on the recommendation of the American Academy of Pediatrics, the use of fluoroquinolones in a child or adolescent may be justified in special circumstances after careful assessment of the risks and benefits for the individual patient (16, 17).

Additionally, anti-infectives may affect other risk factors for

diabetes. For instance, in a recent study, Trasande et al. (34) showed that exposure to antibiotics during the first 6 months of life is associated with consistent increases in body mass from 10 to 38 months, which could be a risk factor for diabetes (35, 36).

Clinical relevance, implications, and suggestions for future research. Our findings support the recommendations of other studies calling for prevention and careful management of different types of infections in patients with diabetes, as infections can impair the maintenance of a strict glycemic control (37, 38). The correct choice of compound and efficient treatment of infections could be helpful in controlling blood glucose and preventing bacterial resistance (33, 39). Therefore, studies on the rational use of anti-infectives in children and adolescents with type 1 diabetes are recommended.

Moreover, further studies are needed to reveal the potential risk factors for developing type 1 diabetes. The current state of knowledge about the association between different types of infections (e.g., bacterial or mycotic infections) or anti-infective medications and type 1 diabetes is very limited. Our finding that elevated use of anti-infective medications exists already before the diagnosis of type 1 diabetes warrants further research to determine whether different types of infections or use of anti-infective medications can accelerate beta cell destruction in genetically susceptible children and adolescents and increase diabetes risk.

Strengths and limitations. To the best of our knowledge, this is the first population-based study to investigate the prevalence and patterns of anti-infective medication use in children and adolescents with type 1 diabetes (<19 years) in the period both before and after the onset of this disease. In order to have a better understanding of anti-infective use in children and adolescents with type 1 diabetes, we compared this group of patients with a group of age- and sex-matched diabetes-free children and adolescents who were included in the PHARMO database. PHARMO RLS is a large population-based database which has been shown to be a representative of the Dutch population in several studies (12), and the population-based design of our study (without too many exclusion criteria) is its main strength. Routinely collected detailed data on medication use reduced the probability of information bias and recall bias. Also, the use of insulin as a proxy for type 1 diabetes is strong since treatment of hyperglycemia is the only indication (40, 41). We assumed that most of the insulin users in our study had type 1 diabetes, because other types of diabetes needing insulin (e.g., latent autoimmune diabetes in adults [LADA], monogenic diabetes, mitochondrial diabetes, etc.) have low prevalences compared with that of type 1 diabetes (42–46). Therefore, misclassification of type of diabetes is probably a minor problem. Furthermore, Bonferroni correction has been used to account for all tests that we used in this study, and the results were still statistically significant.

There are several limitations in the current study that must be addressed. It is likely that our results underestimate the total prevalence of anti-infective medication use because anti-infective prescriptions that were prescribed in hospitals were not available. We had no information on the indication for prescribing these anti-infective agents, so we did not know whether these prescriptions were necessary for the patients and if the use of anti-infectives was rational in patients with type 1 diabetes. We may have misclassified undiagnosed cases of type 2 diabetes or children and adolescents with type 2 diabetes who do not use any medication for type 2 diabetes as diabetes-free children in the reference cohort. Furthermore, there are a few children and adolescents ($n = 10$) with only 2 insulin prescriptions during a longer follow-up time who may be misclassified as patients with type 1 diabetes. As this number is low (1% of our patients with type 1 diabetes), it has no material influence on our results. The last limitation of our study is related to our reference cohort. In the current study, we randomly selected a group of age- and sex-matched diabetes-free children and adolescents from the PHARMO RLS. We could not include diabetes-free children and adolescents who never obtained any prescription from pharmacies until the end of our study period (probably the most healthy children). The rates of anti-infective use we found in the reference cohort are therefore not generalizable to the general diabetes-free children and adolescents in the Netherlands, and the gap between children and adolescents with type 1 diabetes and diabetes-free children and adolescents in the general population will be even higher than what we reported as the difference between the 2 cohorts.

Conclusions. In conclusion, we showed that the annual prevalence and average number of anti-infective prescriptions in children and adolescents with type 1 diabetes were higher than in a group of diabetes-free age- and sex-matched children and adolescents both before and after the onset of type 1 diabetes. Furthermore, the choice of compounds was also different between the two cohorts. Our findings that elevated anti-infective use in the T1D cohort exists before the onset of type 1 diabetes and the consumption of more second-line anti-infective compounds in this time period warrant further research. The combined efforts of clinicians, microbiologists, academia, governmental organizations, and pharmaceutical companies are needed to find potential prevention strategies against type 1 diabetes and treat infections in patients with type 1 diabetes properly.

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