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The Clinical and Economic Burden of Antibiotic Use in Pediatric Patients With Varicella Infection: A Retrospective Cohort Analysis of Real-World Data in England

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Background. Varicella is a highly infectious disease, particularly affecting children, that can lead to complications requiring antibiotics or hospitalization. Antibiotic use for varicella management is poorly documented. This study assessed antibiotic use for varicella and its complications in a pediatric population in England.

Methods. Data were drawn from medical records in the Clinical Practice Research Datalink and Hospital Episode Statistics data sets. The study included patients <18 years old with varicella diagnosed during 2014–2018 and 3-month follow-up available. We determined varicella-related complications, medication use, healthcare resource utilization, and costs from diagnosis until 3 months after diagnosis.

Results. We identified 114 578 children with a primary varicella diagnosis. Of these, 7.7% (n = 8814) had a varicella-related complication, the most common being ear, nose, and throat related (37.1% [n = 3271]). In all, 25.9% (n = 29 706 of 114 578) were prescribed antibiotics. A higher proportion of patients with complications than without complications were prescribed antibiotics (64.3% [n = 5668 of 8814] vs 22.7% [n = 24 038 of 105 764]). Mean annualized varicella-related costs were £2 231 481 for the study cohort. Overall, antibiotic prescriptions cost approximately £262 007.

Conclusions. This study highlights high antibiotic use and healthcare resource utilization associated with varicella management, particularly in patients with complications. A national varicella vaccination program in England may reduce varicella burden and related complications, medication use, and costs.

Keywords. varicella; pediatric; costs; antibiotics; England.

Varicella (chickenpox) is a highly infectious disease caused by the varicella-zoster virus. An estimated 2–16 per 1000 individuals are infected annually worldwide. Although the condition typically presents during early childhood, varicella can be contracted at any age [1, 2]. The highest burden of illness is in young children, with >90% of children experiencing infection before the age of 9 years [3]. In 2014, the World Health Organization estimated that >4 million varicella cases had severe complications, with >4000 related deaths per year globally [4].

The World Health Organization recommends universal vaccination as one of the main preventive interventions where varicella is a public health problem, yet only 39 countries have universal varicella vaccination (UVV) programs [2]. Varicella vaccination has been part of the recommended pediatric immunization schedule in the United States for >25 years, which has resulted in a substantial decrease in disease burden [5]. Within Europe, several countries have a lower varicella prevalence as a result of UVV programs [1, 6]. Other countries, such as the United Kingdom and France, are yet to implement a UVV program, resulting in high annual varicella incidence and hospital admissions [1]. The United Kingdom has an annual incidence of 13 000 cases per 100 000 population in children <5 years old [6]. In England, the average annual incidence of varicella hospital admissions is 7.6 (95% confidence interval, 7.3–7.9) per 100 000 population [6, 7].

Because most varicella cases are considered mild and self-limiting, the majority may be managed without seeking care. However, more severe cases may result in complications, such as skin and soft-tissue infections, pneumonia, or neurological conditions [8], which may require treatment in primary or secondary care with antibiotics, antivirals, analgesics, or antihistamines [9–12].

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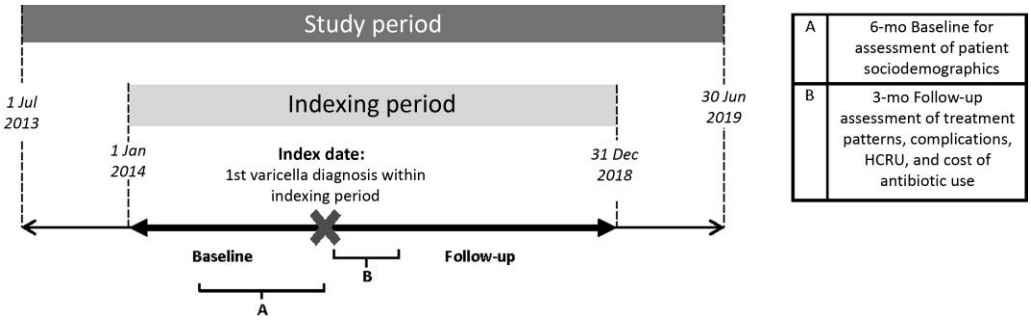

Figure 1. Schematic of the study design. Abbreviation: HCRU, healthcare resource utilization.

Although clinical and economic impact estimates attributable to varicella have been produced for some European countries, the extent to which antibiotics are used to manage varicella is not well documented [6, 8, 13]. A study from Latin America and Europe among children 1–14 years old with varicella reported that 13% of outpatients and 69% of inpatients were prescribed an antibiotic [10]. More recently, a pediatric study at a hospital in Rome found that 43% of patients admitted for varicella received antibiotics, and a study in primary care in Belgium reported that 27% of patients with varicella were prescribed antibiotics [9, 14].

Antibiotic use is rising globally, propagated by the prescription of antibiotics to patients with unconfirmed bacterial diagnoses [15]. By exposing patients to antibiotics for unnecessary reasons, the risk of antimicrobial resistance increases [16]. Similarly, overexposure to antibiotics for respiratory infections increases the risk of associated adverse events, such as clostridium difficile infection, fungal infections, and diarrhea [17]. This study aimed to assess the burden of varicella and varicella-related complications and the associated antibiotic use, healthcare resource utilization (HCRU), and costs in the treatment and management of varicella in a pediatric population in England.

METHODS

Study Design and Sample

An observational retrospective cohort study design was used to identify pediatric patients with varicella infection. Patient demographic and clinical data from linked primary care electronic medical records and secondary care administrative data were obtained from the Clinical Practice Research Datalink (CPRD Aurum) and Hospital Episode Statistics (HES) data sets, respectively [18, 19]. Patients in England with a recorded varicella infection between January 2014 and December 2018 (indexing period) were identified within each data set. The indexing period provided a clear start and end date for cohort inclusion and defined our cohort size (Figure 1). To be eligible for inclusion, patients had to have their first varicella infection diagnosis (defined in "Measures") recorded in the indexing period within a primary or secondary care setting, be <18 years old at first varicella diagnosis, have ≥3 months of follow-up recorded within the database after the index date (date of first varicella diagnosis), and have primary care record activity and linkage to HES. A 3-month follow-up period (including the index date) was chosen to ensure the capture of varicella-related complications and any diagnosis delays. Patients with 1 varicella diagnosis, or who had received ≥1 dose of a varicella vaccine before or on the index date. were excluded from the study.

Patient demographics were assessed from 6 months before (and including) the index date, where available, until the date of the patient's last database entry or the end of the follow-up period (whichever was earliest). For patients >28 days old, a minimum preindex period of 28 days was required to assess treatment patterns, varicella complications, HCRU and antibiotic use (Figure 1). Baseline sociodemographic and clinical characteristic variables included index year, age, sex, region, ethnicity, chronic comorbid conditions, body mass index, and index of multiple deprivation (a measure of relative poverty).

Data Source

CPRD Aurum is a longitudinal and representative anonymized electronic health record database of primary care interactions in England. CPRD Aurum contains data routinely collected from primary care practices that use the Education Management Information System (EMIS) Web electronic patient record system software (about 10% of National Health Service [NHS] general practitioners [GPs]) [19]. Because all data are fully anonymized, GPs do not need patient consent to add their data to the database; however, patients may opt out. For this study, CPRD Aurum was linked to HES data sets, which detailed inpatient admissions, outpatient appointments, and emergency department (ED) attendances at NHS-funded centers in England [18]. Approximately 99% of CPRD Aurum practices have consented to participate in the linkage scheme.

Table 1. Patient Sociodemographic and Clinical Characteristics

Variable	Patients, No. (%)[a]		
	Total (N = 114 578)	No Complication Recorded (n = 105 764)	Any Varicella-Related Complication Recorded (n = 8814)
Index year			
2014	24 537 (21.4)	22 739 (21.5)	1798 (20.4)
2015	25 372 (22.1)	23 446 (22.2)	1926 (21.9)
2016	19 996 (17.5)	18 408 (17.4)	1588 (18.0)
2017	23 090 (20.2)	21 284 (20.1)	1806 (20.5)
2018	21 583 (18.8)	19 887 (18.8)	1696 (19.2)
Age, mean (SD), y	4.0 (2.8)	4.1 (2.8)	2.8 (2.3)
Age group, y			
≤ 1	11 641 (10.2)	9757 (9.2)	1884 (21.4)
2–4	53 230 (46.5)	48 526 (45.9)	4704 (53.4)
5–6	28 167 (24.6)	26 719 (25.3)	1448 (16.4)
7–9	15 090 (13.2)	14 517 (13.7)	573 (6.5)
10–12	4858 (4.2)	4701 (4.4)	157 (1.8)
13–18	1592 (1.4)	1544 (1.5)	48 (0.5)
Sex			
Male	58 762 (51.3)	53 956 (51.0)	4806 (54.5)
Female	55 816 (48.7)	51 808 (49.0)	4008 (45.5)
Immunocompromised	1955 (1.7)	1803 (1.7)	154 (1.8)
Any varicella-related complication recorded	8814 (7.7)	0 (0.0)	8814 (100.0)

Abbreviation: SD, standard deviation.

[a]Data represent no. (%) of patients unless otherwise specified.

Measures

Outcome measures (counts), including all varicella-related complications, prescribed medications, HCRU, and costs, were assessed from the index date to 3 months after the index date. Any recorded complications before the index date were removed from follow-up analysis to account for chronic illnesses or ongoing infections.

Varicella infection and varicella-related complications were identified via the Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) terminological structure and the *International Classification of Diseases, Tenth Revision,* as well as Read-2 and EMIS diagnostic codes. Complications were split into categories, including skin disorders, systemic bacterial infections, neurological conditions, upper and lower respiratory tract infections, ear, nose, and throat (ENT) conditions, musculoskeletal disorders, ophthalmic conditions, and gastrointestinal disorders. Within each category, complications were selected based on a literature review [8, 12, 20–33], and further validated with clinical experts (Supplementary Table 1). A further condensed list was also compiled of common complications resulting from varicella in children (termed "specific complications" and including conditions such as superficial bacterial infections and conjunctivitis) (Supplementary Table 1).

Medication classes of interest included antivirals, antibiotics (stratified by systemic antibiotics and nonsystemic/topical antibiotics), emollients, analgesics, and antihistamines. Specific systemic antibiotics were selected from the National Institute of Health and Care Excellence list of common antibiotics used for the treatment of pediatric patients with the complications included in our analysis [32]. Medications included those prescribed in primary care only; medications prescribed or administered in secondary care were not available in the HES data sets. For each medication class, the time to prescribed medication following varicella diagnoses or varicella-related complications was recorded, together with the duration of treatment. CPRD Aurum prescriptions are linked to a diagnosis using the SNOMED-CT terminological structure, as well as Read-2 and local EMIS codes to ascertain which condition the medication was prescribed for and its use; not all medications are linked, however, so this study used both linked and nonlinked codes.

The varicella-specific costs (those linked to varicella or a varicella-related complication diagnostic code) for HCRU and medication included confirmed GP consultations (face-to-face or telephone consultations), outpatient and inpatient attendances, ED visits, and medication prescribed during the 3-month follow-up period. The cost of a single GP consultation in primary care was taken from the document on the unit costs of health and social care compiled and provided by the Personal Social Service Research Unit [34]. The cost of medication prescribed in primary care was taken from the NHS Drug Tariff, which reports the basic price and quantity of each drug from which a per-unit cost

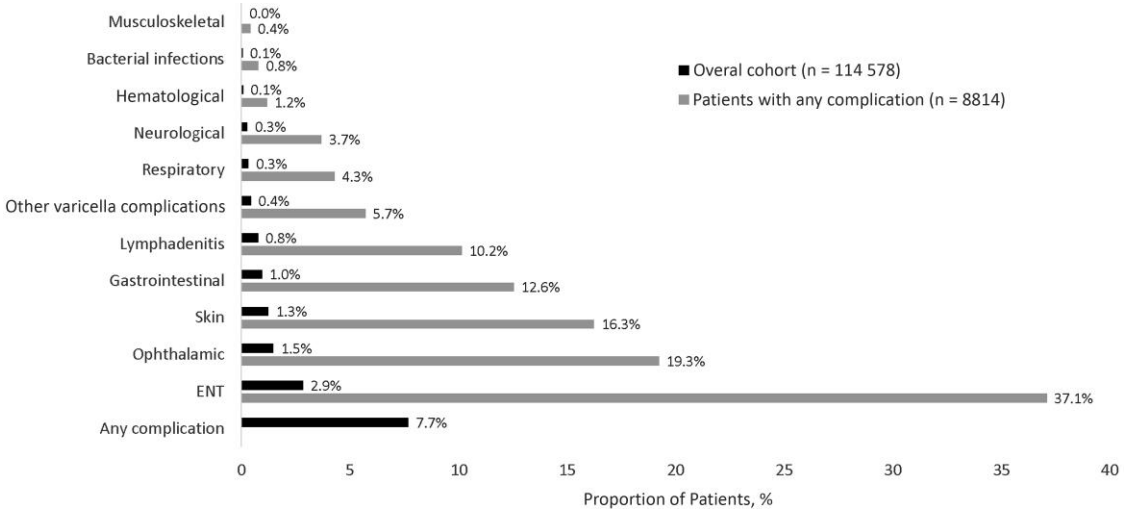

Figure 2. Proportion of patients with complications, by type, within the overall cohort, and by those with any varicella-related complication recorded within 3 months after varicella diagnosis. Abbreviation: ENT, ear, nose, and throat.

can be derived [35, 36]. Costs for hospitalizations, outpatient and ED visits were derived using NHS healthcare resource group Local Payment Grouper software, in conjunction with national tariffs for 2019–2020 [37].

Data Analysis

Categorical variables were summarized by frequencies and proportions, while counts, number of missing, means, medians, standard deviations (SDs), and ranges were reported for continuous variables as appropriate. Direct healthcare costs were calculated via the application of unit costs for GP consultations, other outpatient attendances, and hospitalizations (length of stay), together with prescription costs, aggregated for all resource users in each category. This is a descriptive study; no hypotheses were tested.

Ethical Considerations

The study received approval by an independent scientific advisory committee (hosted by CPRD [identification no. 21_000372]). No direct subject contact or primary collection of individual human subject data occurred.

RESULTS

Study Population

From 2014 to 2018, there were 114 578 children identified in CPRD Aurum with a primary varicella diagnosis who met the inclusion criteria (Table 1). Approximately half (51.3% [n = 58 762]) of the patients were male, and the mean (SD) age in the cohort was 4.0 (2.8) years, with 81.3% (n = 93 038) of patients <6 years old.

Overall, 7.7% (n = 8814) of patients had ≥1 varicella-related complication (either on the index date or during the 3-month follow-up period). The proportions of complications observed in the overall study cohort over the 3-month follow-up period are presented in Figure 2. Among patients with complications, the highest proportion of patients presented with ENT complications (37.1% [n = 3271]), ophthalmic complications (19.3% [n = 1698]), and bacterial skin infections (16.3% [n = 1433]). The most frequently observed complications within these categories included conjunctivitis (19.1% [n = 1684]), otitis media (18.2% [n = 1604]), tonsilitis (14.3% [n = 1256]), and pharyngitis (8.7% [n = 764]). In patients first presenting in secondary care (n = 346), the most observed complications were bacterial skin infections (36.7% [n = 127]), ENT complications (14.5% [n = 50]), and neurological complications (14.5% [n = 50]). The median times to first varicella-related complications ranged from 5.5 days (interquartile range [IQR] 1–35 days) for bacterial skin infections to 41 days for both ENT (IQR, 18–65 days) and gastrointestinal disorders (IQR, 19–63 days).

Baseline sociodemographic and clinical characteristics were largely similar between patients with and those without a varicella-related complication recorded. Most notable was a difference in age, with a lower mean (SD) age in patients with a complication than in those without (2.8 [2.3] vs 4.1 [2.8] years, respectively); a higher proportion of patients with a complication than without a complication were <4 years old (74.8% [n = 6588 of 8814] vs 55.1% [n = 58 283 of 105 764]). Furthermore, a higher proportion of patients with complications than patients without complications required secondary care (hospitalization, 21.8% [n = 1922 of 8814] vs 1.8% [n = 1890 of 105 764], respectively; ED visit, 18.7% [n = 1650 of 8814] vs 3.5% [n = 3717 of 105 764]; outpatient

Table 2. Treatment Use Within 3 Months After Varicella Diagnosis by Complication Status

Treatment[a]	Patients, No. (%)				
	Overall (N = 114 578)	Any Varicella-Related Complication Recorded (n = 8814)	No Complication Recorded (n = 105 764)	Specific Complication Recorded[b] (n = 5567)	No Specific Complication Recorded (n = 109 011)
All antibiotics	29 706 (25.9)	5668 (64.3)	24 038 (22.7)	3711 (66.7)	25 995 (23.9)
Systemic antibiotics	22 517 (19.7)	4352 (49.4)	18 165 (17.2)	3334 (59.9)	19 183 (17.6)
Specific systemic antibiotics[c]	21 621 (96.0)	4306 (98.9)	17 315 (95.3)	3300 (99.0)	18 321 (95.5)
Nonsystemic/topical antibiotics	10 589 (9.2)	2400 (27.2)	8189 (7.7)	1068 (19.2)	9521 (8.7)
Antivirals	1730 (1.5)	139 (1.6)	1591 (1.5)	80 (1.4)	1650 (1.5)
Acyclovir	1713 (99.0)	134 (96.4)	1579 (99.3)	77 (96.3)	1636 (99.2)
Analgesics	14 589 (12.7)	1405 (15.9)	13 184 (12.5)	891 (16.0)	13 698 (12.6)
Antihistamines	20 260 (17.7)	1402 (15.9)	18 858 (17.8)	848 (15.2)	19 412 (17.8)
Emollients	12 760 (11.1)	1337 (15.2)	11 423 (10.8)	856 (15.4)	11 904 (10.9)

[a]Treatments include those prescribed during the 3-month follow-up period in primary care only and are presumed to be linked to varicella or varicella-related complications.

[b]Specific complications include encephalitis, pneumonia, cerebellar ataxia, superficial bacterial infections, sepsis, febrile convulsions, meningitis, bronchitis, cerebritis, otitis media, tonsilitis, gastroenteritis, and other varicella-coded complications.

[c]Specific systemic antibiotics include amoxicillin, azithromycin, benzylpenicillin, ceftriaxone, clarithromycin, co-amoxiclav, doxycycline, erythromycin, flucloxacillin, and phenoxymethylpenicillin.

attendance, 7.2% [n = 633 of 8814] vs 2.1% [n = 2165 of 105 764]).

Medication

Medications prescribed in a primary healthcare setting within 3 months after (or on) the index date for the overall cohort and stratified by complication status are presented in Table 2. Approximately a quarter of patients (25.9% [n = 29 706]) received ≥1 antibiotic, with 19.7% (n = 22 517) prescribed systemic and 9.2% (n = 10 589) prescribed nonsystemic/topical antibiotics. Other prescriptions included analgesics (12.7% [n = 14 589]), antihistamines (17.7% [n = 20 260]), and emollients (11.1% [n = 12 760]). A low proportion of patients received antivirals (1.5% [n = 1713]), largely acyclovir.

A greater proportion of patients with complications than without complications were prescribed antibiotics (64.3% [n = 5668 of 8814] vs 22.7% [n = 24 038 of 105 764], respectively), with similar proportions receiving other medications (Table 2). Antibiotic prescriptions declined with increasing age, ranging from 35.0% (n = 4071) in children ≤1 year old (n = 11 641) to 15.2% (n = 242) in those 13–18 years old (n = 1592; Table 3). A similar trend was observed in the prescription of nonsystemic/topical antibiotics. However, a higher percentage of children 13–18 years old (10.9% [n = 174]) were prescribed antivirals, compared with other age groups (range, 1.3%–2.2%).

Common systemic antibiotics prescribed within 3 months of the follow-up period for the overall cohort and stratified by complication status are presented in Supplementary Table 2. The most frequently prescribed antibiotic was amoxicillin (46.6% [n = 10 504]), followed by flucloxacillin (25.9% [n = 5826]) (Supplementary Table 2).

HCRU and Costs

Most patients (90.4% [n = 103 526]) in the overall cohort had a confirmed varicella-related GP consultation (either face to face or by telephone) on the index date or during the 3-month follow-up; a greater proportion of patients indexed in secondary care required ED and outpatient visits than those indexed in primary care (Table 4).

The total medication and HCRU cost related to varicella or a varicella complication for resource users within the cohort in the 3-month follow-up period (including the index date) was £11 157 406, resulting in a mean annualized cost of £2 231 481 (range, £1 947 176–£2 470 681) when accounting for the number of patients indexed each year (Table 5). Of the total costs across all study years, HCRU costs accounted for 96% (£10 744 081). GP consultations contributed most to HCRU costs (£9 263 506), representing 86% of the total with a mean (SD) per patient cost of £89.50 (£69.40). In comparison, the cost of varicella-related hospitalizations, other outpatient visits, and ED visits were £546 831, £392 643, and £541 101, respectively, with mean per-patient costs of £143.50, £140.30, and £100.80, respectively.

Overall, total varicella-related medication costs were £413 325, more than half of which (63%) were attributed to antibiotics (£262 007), followed by antihistamines (£77 798), analgesics (£44 059), and antivirals (£29 652). Per patient, the most expensive medications were antivirals (mean [SD], £17.14 [£23.39]), while the mean (SD) per patient cost for all antibiotics was £8.82 (£28.23), with systemic antibiotics costing £8.39

Table 3. Treatment Use Within 3 Months After Varicella Diagnosis by Age[b]

Treatment[a]	Patients by Age Group, No. (%)						
	Overall	≤1 y	2–4 y	5–6 y	7–9 y	10–12 y	13–18 y
All patients	(N = 114 578)	(n = 11 641)	(n = 53 230)	(n = 28 167)	(n = 15 090)	(n = 4858)	(n = 1592)
All antibiotics	29 706 (25.9)	4071 (35.0)	15 565 (29.2)	6405 (22.7)	686 (17.80)	737 (15.2)	242 (15.2)
Systemic antibiotics	22 517 (19.7)	2925 (25.1)	11 889 (22.3)	4896 (17.4)	2017 (13.5)	584 (12.0)	206 (12.9)
Specific systemic antibiotics[b]	21 621 (96.0)	2865 (98.0)	11 491 (96.7)	4654 (95.1)	1896 (94.0)	544 (93.2)	171 (83.0)
Nonsystemic/topical antibiotics	10 589 (9.2)	1789 (15.4)	5595 (10.5)	2058 (7.3)	891 (5.9)	199 (4.1)	57 (3.6)
Antivirals	1730 (1.5)	171 (1.5)	673 (1.3)	370 (1.3)	233 (1.5)	109 (2.2)	174 (10.9)
Acyclovir	1713 (99.0)	168 (98.3)	666 (99.0)	369 (99.7)	228 (97.9)	108 (99.1)	174 (100.0)
Analgesics	14 589 (12.7)	1471 (12.6)	6217 (11.7)	3795 (13.5)	2281 (15.1)	671 (13.8)	154 (9.7)
Antihistamines	20 260 (17.7)	1590 (13.7)	8255 (15.5)	5454 (19.4)	3417 (22.6)	1164 (24.0)	380 (23.9)
Emollients	12 760 (11.1)	1749 (15.0)	6551 (12.3)	2698 (9.6)	1316 (8.7)	350 (7.2)	96 (6.0)
Only patients receiving antibiotics	(n = 29 706)	(n = 4071)	(n = 15 565)	(n = 6405)	(n = 2686)	(n = 737)	(n = 242)
Systemic antibiotics	22 517 (75.8)	2925 (71.9)	11 889 (76.4)	4896 (76.4)	2017 (75.1)	584 (79.2)	206 (85.1)
Specific systemic antibiotics	21 621 (72.8)	2865 (70.4)	11 491 (73.8)	4654 (72.7)	1896 (70.6)	544 (73.8)	171 (70.7)
Nonsystemic/topical antibiotics	10 589 (35.7)	1789 (43.9)	5595 (36.0)	2058 (32.1)	891 (33.2)	199 (27.0)	57 (23.6)

[a]Treatments include those prescribed during the 3-month follow-up period in primary care only and are presumed to be linked to varicella or varicella-related complications.

[b]Specific systemic antibiotics included amoxicillin, azithromycin, benzylpenicillin, ceftriaxone, clarithromycin, co-amoxiclav, doxycycline, erythromycin, flucloxacillin, and phenoxymethylpenicillin.

Table 4. Varicella-Related Healthcare Resource Utilization 3 Months After Varicella Diagnosis by Indexed Care setting

Type of HCRU	Patients, No. (%)		
	Overall (n = 114 578)	Indexed in Primary Care (n = 113 726)	Indexed in Secondary Care (n = 852)
GP consultation	103 526 (90.4)	103 207 (90.8)	319 (37.4)
ED visit	5367 (4.7)	4963 (4.4)	404 (47.4)
Hospitalization	3812 (3.3)	2970 (2.6)	842 (98.8)
OP attendance	2798 (2.4)	2648 (2.3)	150 (17.6)

Abbreviations: ED, emergency department; GP, general practitioner; OP, outpatient.

Table 5. Varicella-Related Medication and Healthcare Resource Utilization Costs for Resource Users in the 3 Months After Varicella Diagnosis

Type of Costs	Total Cost, £	Per-Patient Cost, Mean (SD), £
Medication costs		
Antivirals	29 652	17.1 (23.4)
All antibiotics	262 007	8.8 (28.2)
Systemic	188 918	8.4 (30.8)
Nonsystemic/topical	72 852	6.9 (14.0)
Analgesics	44 059	3.0 (4.5)
Antihistamines	77 798	3.8 (32.4)
Total varicella-related medication costs	413 325	8.1 (30.6)
HCRU costs		
GP consultations	9 263 506	89.5 (69.4)
ED visits	541 101	100.8 (67.5)
Inpatient stays/hospitalizations	546 831	143.5 (952.4)
OP attendances	392 643	140.3 (248.6)
Total varicella-related HCRU costs	10 744 081	…
Total costs	11 157 406	…

Abbreviations: ED, emergency department; GP, general practitioner; HCRU, healthcare resource utilization; OP, outpatient; SD, standard deviation.

(£30.81) per patient, and nonsystemic/topical antibiotics costing £6.88 (£13.96) per patient.

DISCUSSION

This real-world study aimed to assess and characterize the clinical and economic burden of pediatric varicella cases and use of antibiotics for the treatment and management of varicella and its complications within England. Overall, 8% of the cohort had ≥1 complication recorded. Antibiotics were the most prescribed medication (26%), with higher usage in patients with complications than in those without. Total HCRU costs exceeded £11 million. HCRU (GP, inpatient, outpatient, and ED visits) contributed to 96% of the total costs, 86% of which related to GP consultations. Medications accounted for 4% of total costs, with antibiotics representing 63% of total medication costs. These results illustrate substantial HCRU and antibiotic use among pediatric patients with varicella.

Consistent with other studies, most complications in our study were ENT (37%), ophthalmic (19%), or skin (16%) disorders [9, 28]. Slightly higher rates of complications have been observed within both single-country and multicountry studies, albeit with different study designs. In a multicountry retrospective record review of antibiotic use, 12% of outpatients with a varicella diagnosis experienced an infectious complication, increasing to 79% within the inpatient setting [10].

A retrospective study in Belgium investigating only hospitalized pediatric patients with varicella also found that 65% of children had ≥1 complication, predominantly skin infections (27%) [8]. This contrasts with an electronic medical record study of pediatric patients with varicella in a primary care setting in Belgium, which reported complications among 13% of patients, in whom the most common complications were upper or lower respiratory infections (61%) and skin infections (39%) [9].

While there was moderate use of analgesic (13%), antihistamine (18%), and emollient (11%) across the cohort, antibiotics were the most prescribed medications (26%), with antivirals prescribed in <2% of patients overall, but in 11% of older patients. Furthermore, antibiotic use was higher among patients with complications than among those without (64% vs 23%, respectively). The prescription of antibiotics for infections with a probable viral origin, such as acute respiratory tract infections, is a common occurrence, and these results are consistent with studies that have also reported that antibiotics are regularly prescribed for the management of varicella-related complications [9, 10]. For example, in the primary care study in Belgium, 27% of patients with varicella were prescribed antibiotics, with the highest rate in patients with complications (64%) and in those <1 year of age (42%) [9]. A study of pediatric inpatients at a single hospital in Italy found that 43% of patients with varicella were prescribed antibiotics [14].

Our findings underscore global concerns over the use of antibiotics in varicella management and the potential contribution to antimicrobial resistance. Concerns over antimicrobial resistance have led to policies that include stewardship programs aimed at improving antibiotic use to conserve effectiveness and reduce the emergence of resistant strains. Vaccination programs have been successful in reducing antibiotic use through the prevention and control of infections [38]. For example, implementation of pneumococcal vaccination programs have reported dramatic reductions in cases of childhood invasive pneumococcal disease, antibiotic use, and the proportions of pneumococcus showing resistance to some antimicrobial agents [39–41].

Furthermore, reduction in the use of antibiotics through vaccination programs can have other downstream effects and societal impacts, regardless of their contribution to antimicrobial resistance, including impact on the microbiome and children's health [42, 43]. Disruption to the microbiome can have wide-reaching effects into adulthood, affecting metabolism and immune development [42]. Moreover, disruption of gut microbiota increases risk of osmotic diarrhea and *Clostridium difficile,* which present a significant morbidity and mortality risk among young children [17, 44, 45].

The cost to the healthcare system of varicella in our study cohort was almost £11 million, representing a considerable financial burden to the NHS. A UVV could help reduce this burden. A recent modeling study on the impact of UVV on the economic burden of varicella in England and Wales over 50 years found that UVV was cost-effective compared with no UVV [46]. UVV resulted in higher overall costs but better clinical outcomes (quality-adjusted life-years), with incremental cost-effectiveness ratios from the payer perspective ranging from £6809–£16 698, depending on strategy, compared with no UVV [46]. A UVV program in the United States resulted in net societal savings of $23.4 billion in its first 25 years [47]. Furthermore, the introduction of a UVV program in the United States was associated with 97% reduction in varicella cases [5] with an estimated $259 million reduction in antibiotic and antiviral prescription costs per year [48].

This study is subject to several limitations. First, within the CPRD Aurum database, there are no standardized definitions for diagnoses; therefore, study-specific code lists and algorithms were developed to identify variables of interest. Where feasible, study definitions were aligned with previously published studies and code lists were verified through medical input. Second, although the reason for the prescribed medication is recorded using SNOMED diagnostic codes in CPRD, and code lists were used to identify prescriptions for varicella or varicella-related complications, not all prescriptions had a unique diagnosis code that was explicitly identifiable, and both linked and unlinked medications prescribed on the index date or during the 3-month follow-up period were included. Accordingly, overestimation or underestimation of associated medication use and costs is possible. Third, this is a descriptive study, and therefore we did not include a control group, which may result in overestimation or underestimation of the burden of varicella-related complications, medication use, and costs relative to the general population. For example, complications categorized as varicella related may be overestimated if they can occur in the absence of varicella, while other complications that are difficult to link to varicella (such as rare conditions, secondary infections, and longer-term burdens outside the observation window) may be underestimated.

Relating to medication prescriptions, because this is a retrospective study using electronic medical record data, we could not confirm whether prescriptions were issued for varicella or unrelated conditions. Furthermore, CPRD captures prescription data, which may not accurately reflect dispensed or consumed medications. It was assumed that all medications prescribed were dispensed and consumed according to prescribing information. In addition, only medications prescribed in the primary care setting were recorded in the study data. Medications initiated in the hospital or outpatient setting were not captured within the data. Moreover, analgesics, antihistamines, and emollients are readily available over the counter. Therefore, the use of these medications may have been underestimated. Finally, the findings of this study may not be generalizable to the entire UK population, as CPRD Aurum covers only approximately 10% of GP practices in England; it

is considered, however, to be highly representative of the whole population [19].

In conclusion, this real-world study provided an assessment of the varicella-related complications, antibiotic use, and costs associated with varicella management among pediatric patients in England. The findings highlight the relatively high antibiotic use in the management of varicella, especially for patients with varicella-related complications. In addition, this study also illustrates high HCRU as well as direct medical costs associated with the management of varicella in England. Policymakers should consider the introduction of a UVV program in England that could reduce the overall burden of varicella and the associated complication frequency and mitigate the need for antibiotic use in varicella management.

Supplementary Data

Supplementary materials are available at *The Journal of 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

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Potential conflicts of interest. S. A. K. and M. P. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. V. B. was an employee of Adelphi Real World at the time of study design and initiation and is currently employed by and owns stocks/shares in Bayer. C. S. C. was an employee of Adelphi Real World during study completion. S. B. D. has provided consultancy and/or investigator roles in relation to product development for Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, iLiAD, and Sanofi, with fees paid to St George's, University of London. S. B. D. is a member of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) RSV subcommittee and a member of the Medicines and Healthcare products Regulatory Agency's (MHRA's) Paediatric Medicine Expert Advisory Group (PMEAG), but the reviews expressed herein do not necessarily represent those of DHSC, JCVI, MHRA, or PMEAG. A. P., O. M., and T. H. are employees of Adelphi Real World; the company received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to conduct the study.

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