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# Association of child weight and adverse outcomes following antibiotic prescriptions in children: A national data study in Wales, UK.



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**Abstract**

**Objective**: To examine if the weight of a child determines adverse events following oral antibiotics prescription.

**Design:** Population respective cohort using linked GP, hospital data, and linkage with the Welsh Demographic Service for demographic information. Data linkage was performed using Wales health data, extracted from the SAIL (Secure Anonymised Information Linkage) databank.

Inclusion: Children aged (0 to 12 years) prescribed oral antibiotics by their GP in Wales.

Exposure: Antibiotic prescription (Penicillins, Cephalosporins, Macrolides, Dihydropyrimidines, Nitroimidazoles, Nitrofurans, Lincosamides).

Outcome: Adverse event as defined by; patients' death within 5 days, records of emergency admission within 5 days, and GP records of adverse drug reactions or prescription of another antibiotic within 14 days.

Analysis : Logistic regression of adverse events versus no adverse events at follow up time.

**Results**: There were 141,773 prescriptions of the selected antibiotics and 77,050 children (50.72% male) included with follow up data of which there were 26,087 (18.40% of all prescriptions) children experienced adverse outcomes. There was a higher odds of adverse event for lower weight children and those who were younger, female, Asian origin or deprived.

**Conclusion**: The findings support the hypothesis that smaller children for their age (e.g. low weight, female, Asian) are more likely to experience adverse events following antibiotics prescription. This work suggests child weight, rather than just age, should be used when prescribing antibiotics to children.

**Key message**

1. What is already known on this topic – summarise the state of scientific knowledge on thics subject before you did your study and why this study needed to be done:

   Prior research have emphasized the importance of precise dosing in paediatric antibiotic prescriptions, considering both age and weight, due to concerns about antimicrobial resistance and under-dosing in overweight children.

2. What this study adds – summarise what we now know as a result of this study that we did not know before:

   This study reveals that low-weight children, females, minority ethnic groups, and those from deprived socioeconomic backgrounds face higher risks of adverse events following oral antibiotic prescriptions.

3. How this study might affect research, practice or policy – summarise the implications of this study:

   The findings suggest revising paediatric antibiotic prescribing guidelines to prioritize weight measurements, aiming to enhance dosing accuracy and reduce adverse outcomes in children.

## Introduction

### Background

The escalating concern over antimicrobial resistance has prompted increased scrutiny of antibiotic prescription practices worldwide (1). Striking a delicate equilibrium between safety and efficacy holds utmost significance when administering antibiotics to children, as any deviation from this balance can lead to unwanted consequences (2). Selecting antibiotics based on a recognized formulary, tailoring dosages to individual patient characteristics, and considering adverse drug reactions specific to each patient are crucial considerations in paediatric antibiotic therapy. More than a third of British children annually undergo antibiotic therapy, with oral penicillins constitute a substantial majority. They are frequently prescribed to address common respiratory tract infections (3–5). While most antibiotics have a low risk-to-benefit ratio for infectious illnesses (6), appropriate dosing is important.

The practice of prescribing oral penicillins as fractions of adult doses in children's age groups was established in the 1960s and maintained until 2011when concerns were raised about suboptimal dosing of amoxicillin for overweight children (7). Prescribing recommendations underwent revision in 2014 because of concerns about potential under-dosing (8). In 2014, the dosage was increased twofold in all age groups (9).

Paediatric drug dosing often demands precision with consideration of both age/development and weight. The British National Formulary for Children (BNFC) (10) details an age-banded system for most commonly prescribed oral antibiotics in primary care. This simplifies prescribing by eliminating the need for real-time weight measurement. However, this could lead to suboptimal dosing due to the non-linear relationship between age and weight in children(11). Age and weight necessitate consistent documentation and special attention in paediatric antibiotic prescriptions due to distinct growth trajectories compared to adults (12). In continental Europe, prescriptions are typically weight-based, offering a potentially more tailored approach (8). Given that boys generally have higher average

weights than girls (13), and children's weights exhibit significant variability (14); individualised dosing that considers both age and weight is crucial to safe prescribing of antibiotics. It would likely result in meeting more of the antibiotics' therapeutic indices (15). This necessitates a focused evaluation of dosing strategies to enhance accuracy in paediatric pharmacotherapy.

**Objective**

This study examines adverse outcomes associated with oral antibiotic prescribing practices in paediatric primary care in Wales, with a specific emphasis on child weight. It examines major factors such as the age bands of children (based on the British National Formulary for children guidance), weight categories (grouped by centiles for sex and age), ethnicity, deprivation quintile, and sex. Our study employs a sophisticated statistical approach known as a multilevel multivariate logistic regression model (16). This model is tailored to handle within-patient correlation and heterogeneity, which is crucial given that multiple records for individual patients are present within our study period. Specifically, we aim to investigate the likelihood of adverse events following oral antibiotic prescriptions in general practice.

## Method

### Sample selection

In this retrospective cohort study, we used routinely-collected GP prescription data for antibiotics prescribed for children in Wales between the period of January 2014 and October, 2023. Prescriptions were identified using Read codes (version 2). The list of codes used are available in Appendix 3 (17). The inclusion criteria for the study included children between the ages of 0 and 12 years within the study period who had been issued with primary care prescription for oral antibiotics. Child weight data from National Community Child Health Database (NCCHD) and WLGP were linked using to the reference. Records with erroneous weights were excluded. Weights were considered erroneous if they were greater than 112kg or were recorded more than thirty days before or after oral antibiotics prescription date. The data linkage was carried out using the an encrypted Anonymised Linking Field (ALF) encrypted key in the SAIL databank (18). The antibiotics studied include common oral antibiotics classes used in children such as beta lactams (penicillins and cephalosporins), macrolides, dihydropyrimidines (trimethoprim), nitroimidazole (metronidazole), nitrofuran (nitrofurantoin) and lincosamides. A flow diagram of the cohort selection can be found in Figure.

### Risk Factors and data linkage

Patient demographic information such as age and gender were linked from the WLGP dataset; deprivation quintile data was linked from the Welsh Demographic Service Dataset (WDSD) (19); patient ethnicity data was linked from the Patient Episode Dataset for Wales (PEDW) (20); and, patient birth-weight data was linked from the National Community Child Health Database (NCCHD) (21). A brief description of the risk factors and their sources can be found in Appendix 4. This study acknowledges the multifaceted nature of pediatric antibiotic therapy and specifically focuses on key

determinants, including: (a) Deprivation quintile. Given that socioeconomic inequalities exist and can be a major problem in appropriate healthcare delivery on a national scale (22). For this we utilized a quintile categorization of populations into five groups based on their Welsh Index of Multiple Deprivation (WIMD) scores. These quintiles are used to represent different levels of deprivation, with the first quintile representing the least deprived areas and the fifth quintile representing the most deprived areas. (b) Ethnicity. As knowledge and use of antibiotics has been shown to differ in different ethnic groups (23). (c) Sex. There are physiological and anatomical differences between males and females, this could influence pharmacology of the prescribed antibiotics in respective sexes (24,25). (d) weight categories. the weight categories used were: Low Weight Category (LWC grouped by sex and age group; with weights equal or less than the 25$^{th}$ percentile), Normal Weight Category (NWC grouped by sex and age group; with weights above the 25$^{th}$ percentile and less than the 75$^{th}$ percentile) and, High Weight Category (HWC grouped by sex and age group; with weights equal or greater than the 75$^{th}$ percentile). And, (e) age bands. The age band categories studies were 0 to 28 days (neonates), 1 to 11 months, 1 to 4 years, and, 5 to 12 years. These represents the age bands in which children are often grouped during GP antibiotics prescription, based on the British National Formulary (BNF) for children (10). No imputation techniques were applied to the variables in this study to handle missing values. This decision was made to maintain the representativeness of the sample and avoid introducing assumptions.

**Adverse events identification**

Four binary foundation phase indicator variables were derived from the linked dataset; however, no formal assessment of causality was carried out. These include: (a) Patient death identified within 5 days of the initial antibiotic prescription; (b) Repeated antibiotic prescribing within 14 days of an initial antibiotic prescription; (c) non-elective hospital/emergency admission within 5 days of antibiotics prescription; and, (d) GP record of toxicity, poisoning, overdose, allergy or hypersensitivity reactions within 14 days of antibiotics prescription (read codes 2 used to identify

these events in the WLGP dataset can be found in Appendix 1). The data source used to generate these adverse events can be found in Appendix 5.

## Statistical analysis

A multilevel logistic regression model was used to measure the associated weight of each risk factor to the general adverse events outcome (as well as certain specific adverse event outcome based on availability of sufficient oral antibiotics prescription data). Sensitivity analysis using the excluded data (records greater than 30 days more or less than the date of antibiotics prescription and weight records more than 112kg) was carried out, additional information on this can be found in Appendix 2. Data preparation was carried out on a DB2 SQL platform and the statistical analysis was performed on R version 4.0.3. using the following libraries: RODBC (26), tidyverse (27), lubridate (28), and caret (29).

## Logistic regression

We conducted a multilevel logistic regression for all the outcomes using the factors of interest as the covariates. The regression model was applied to generate Odds Ratio plots, using normal weight category as the reference in the weight category column, the highest quintile (deprivation quintile 5) as the reference for deprivation quintiles column, White ethnicity compared with all other ethnicities in the ethnic group column, and the 1 to 4 years age band compared with all other age bands in the age band column. These categories were selected as references based on the fact that they were the most common groups in their respective categories. The risk factors of adverse events following oral antibiotics prescription were presented with adjusted Odds Ratio (aOR) and 95% Confidence Interval (CI)

## Ethical Considerations

All access to SAIL datasets for research purposes is subject to Independent Information Governance Review Panel (IGRP) approval which involves a panel that considers ethical implications. Due to the anonymity of the data which is specifically collated by SAIL for research purposes, no additional ethical approval of this research was required (30)

## Results

### Sample characteristics

The study comprised 77,050 children meeting the inclusion criteria of a GP prescription for oral antibiotics (there were 141,773 prescriptions associated with 26,087 (18.40% of all ) general adverse drug outcomes.), coupled with a weight record from NCCHD and WLGP within 30 days of prescription. Of these, 39,080 were boys, among whom 20.70% experienced at least one adverse event, and 37,970 were girls, with 21.82% experiencing at least one adverse event. Among the participants, 22,742 fell into the low weight category (LWC), with 18.55% experiencing at least one adverse event, while 41,741 were categorized as normal weight children (NWC), among whom 20.47% experienced at least one adverse event. Additionally, 22,658 children were classified as high weight category (HWC), with 20.71% experiencing at least one adverse event. The overall summary of the study population can be found in Table 1.

### Logistic regression

Children in the low weight category had higher odds of an adverse reaction (aOR [95% CI]: 1.05 (1.00, 1.10)) compared to those categorized in the normal weight category; while children in the high weight category had lower odds 0.95 (0.91, 0.99). Females had higher odds 1.15 (1.06, 1.24) than males having adjusted for all other factors. Children in 5 to 12 years age band had lower odds 0.64 (0.59, 0.65) than those in the 1 to 4 months age band. Asians, mixed and other ethnicities had higher odds than the whites (with odds ratios of 1.35 (1.02, 1.84), 1.20 (0.95, 1.52) and 1.92 (1.47, 2.52) respectively). Children in the deprivation quintiles 1 and 2 had higher odds of an adverse event than those in the deprivation quintile 5 (with odds ratios of 1.15 (1.02, 1.30) and 1.08 (0.96, 1.23) respectively). The risk factors, odds ratios, upper and lower confidence intervals can be found in Table 2.

## Discussion

Children who were of low weight, female, of Asian, mixed, or other ethnic backgrounds, residing in deprivation quintile 1 or aged between one and eleven months had higher odds of adverse events following oral antibiotic prescriptions compared to their respective reference groups having adjusted for age, sex, ethnic group, deprivation quintiles, and weight category. Conversely, children categorized as high weight and older children (ages 5 to 12 years) demonstrated lower odds of experiencing adverse events. Similarly, those of low weight, smaller children (aged up-to 28 days or between one to eleven months), of Asian, mixed, or other ethnicities, or residing in deprivation quintile 1 were found to have an increased odds of a hospital/emergency admission within 5 days of the initial oral antibiotic prescribed. This was in sharp contrast to the result from investigating the repeat primary care prescription of oral antibiotics within 14 days of the initial oral antibiotic as children who were of low weight, residing in deprivation quintile 4, or female were found to have higher odds of this subset of adverse event. The reason for the observed trend is unknown and requires further investigation, ideally in a more ethnically diverse population with a more equal representation of the various age bands.

Our findings align with Bielicki et al.'s assertion that weight, in addition to age bands, is a crucial variable in antibiotic prescription for children (8). Specifically, our results indicate that children classified as low weight for their sex and age band exhibit elevated odds of adverse events, consistent with existing literature (31). Conversely, our observation that high weight category children have lower odds of adverse events compared to those of normal weight provides further support to this notion. Taken together, these findings underscore the importance of considering weight alongside age when prescribing oral antibiotics to children, offering a potential avenue to mitigate adverse events in this population.

Studies have shown that babies of Asian (Indian, Pakistani, Bangladeshi, Chinese, and other Asian ethnic groups) ethnicity tend to have lower body weights in comparison to those of Caucasian ancestry (32,33). This observation may suggest that the increased odds of general adverse events among minority ethnic groups could be attributed, at least in part, to the lower birth weight prevalent in these populations (34). Children of other ethnicity show a tendency towards very high odds (OR 1.84 (1.53, 2.19)) of adverse events. However, the prevalence of this ethnic group in Wales is small (0.86%) and results in a wide confidence interval so the likely odds ratio is inconclusive and would require further investigation.

Based on our findings, children living in more deprived socioeconomic conditions (deprivation quintile 1) have greater odds of a general adverse event when compared to those of the least deprived quintiles. This pattern is similar to those shown recent studies (35,36).

Sex also appears to be associated with general adverse event outcome in children prescribed with oral antibiotics; with our result suggesting that females have higher odds than males to experience a general adverse event. Given that boys tend to have a higher weight trajectory than girls (37); and, there is no difference in dosage based on sex, the observed increase in odds is likely linked to the weight difference between the sexes. This would further emphasize the need to prioritize weight measurement when prescribing oral antibiotics to children.

**Strengths and limitations**

This study was carried out by linking routinely collected data for the whole population of Wales over a period of 10 years. It provides a valuable resource to help inform policy aimed at improving paediatric health outcomes and preventing the incidences of adverse events. Important patient demographics such as sex, deprivation quintiles, age group, and weight have been investigated to help healthcare professionals improve individualized care for children in need of oral antibiotics.

Two major limitations were identified in this study. Firstly, a formal causality assessment was not conducted (38). A significant challenge in pharmacovigilance is accurately pinpointing the root cause of adverse reactions to specific drugs (39). Despite implementing rigorous measures to establish a clear link between observed adverse reactions and the prescribed oral antibiotic, the absence of formal causality assessment limits the strength of our conclusions. Secondly, the study suffered from inadequate representation of minority ethnic groups in Wales (40), which hindered a comprehensive assessment of ethnicity's impact on the measured outcome. Addressing these limitations in future research endeavors is crucial to enhance the robustness and generalizability of findings.

This study lays the groundwork for understanding the importance of weight measurement in the prescription of oral antibiotics. While a detailed exploration of the correlation between risk factors and adverse events necessitates focusing on specific classes of antibiotics and their indications, future research examining individual oral antibiotics can offer further insights to inform healthcare policies and enhance patient care.

**Conclusion**

Our study sheds light on the significant role of weight as a crucial variable in determining adverse events following oral antibiotic prescriptions in children. Our findings highlight that children who are of low weight, female, of certain minority ethnic backgrounds, residing in deprived socioeconomic conditions, or children in the low weight category are at heightened risk of adverse events. Conversely, children categorized as high weight and older children demonstrate lower odds of experiencing adverse events. These results underscore the importance of considering weight alongside other demographic factors when prescribing oral antibiotics to children. By prioritizing weight measurement, healthcare providers can better tailor antibiotic prescriptions, potentially mitigating adverse drug reactions and improving outcomes for pediatric patients.

This finding does not overlook the fact that weight may serve as a proxy for various underlying conditions and factors that can predispose children to adverse outcomes following oral antibiotic prescriptions. While weight itself may not be the direct issue, it signifies potential links with factors such as malnutrition, intrauterine growth restriction (IUGR), neglect, prematurity, immunocompromise, and other health conditions. By disregarding weight and dosing based solely on averages, we overlook the complexities of individual health profiles and miss opportunities to tailor treatments accordingly. Weight, as a measure of growth and development, is integral to monitoring overall health status. Our study underscores the importance of recognizing weight as more than just a number—it represents a critical aspect of a child's health that warrants careful consideration in antibiotic prescription practices to optimize outcomes and mitigate adverse events.

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**List of Abbreviations**

GP: General practice.

BNFC: British National Formulary for Children.

NCCHD: National Community Child Health Database.

ALF: Anonymised Linkage Field.

SAIL: Secure Anonymised Information Linkage.

WLGP: Welsh Longitudinal General Practice Dataset.

PEDW: Patient Episode Dataset for Wales

WDSD: Welsh Demographic Service Dataset

WIMD: Welsh Index of Multiple Deprivation

LWC: Low Weight Category

NWC: Normal Weight Category

HWC: High Weight Category

BNF: British National Formulary

ADDE: Annual District Death Extract

EDDS: Emergency Department Datasets

DB2 SQL: Structured Query Language developed by IBM

CI: Confidence Interval

aOR: Adjusted Odds Ratio

IGRP: Independent Information Governance Review Panel

WHO: World Health Organization

**Figure, Tables, and, Appendices Caption**

**Figures:**

One figure was provided with the manuscript:

1. Flow chart showing inclusion and exclusions from WLGP, NCCHD.

**Tables:**

Two tables were provided with the manuscript:

1. Table 1: Demographic data for study cohort. LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups
2. Table 2: Table showing the odds ratios of the risk factors for the respective adverse events (95% CI). LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups. Reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, Weight categories: normal weigh category.

**Appendices:**

Five supplementary documents were provided with the manuscript:

1. Appendix 1: Read Codes for records of adverse events in the GP
2. Appendix 2: Information on the excluded group
3. Appendix 3: Read codes for the oral antibiotics
4. Appendix 4: Risk factors for adverse events in children prescribed oral antibiotics in the GP

5. Appendix 5: Adverse events data source

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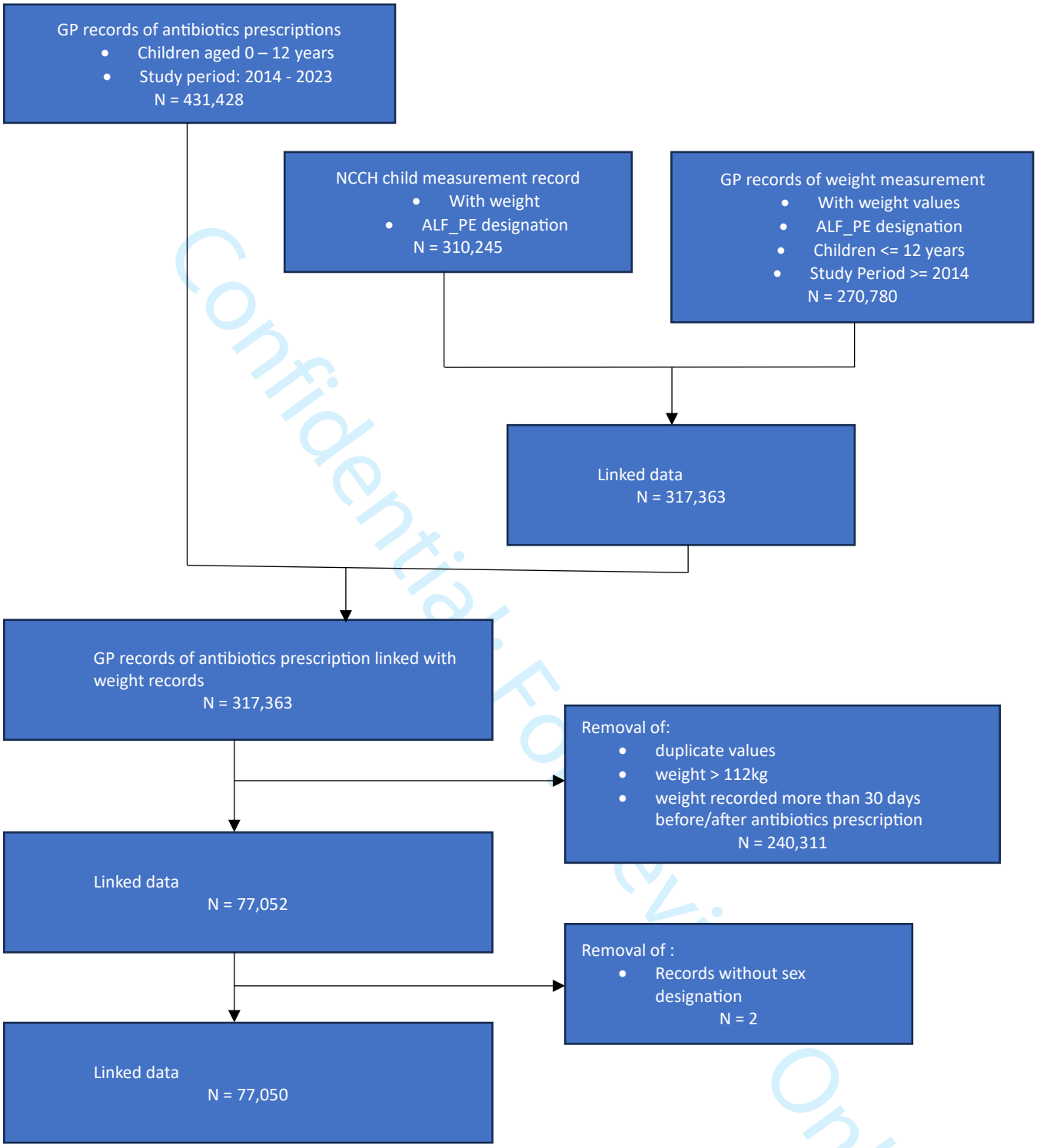



*Figure 1: Flow chart showing inclusion and exclusions from WLGP, NCCHD*

| Variables | Total number | Total all outcomes N (%) | Total repeat antibiotics N (%) | Total hospital/emergency admission N (%) | Total number of NAs |
|---|---|---|---|---|---|
| Sex | | | | | 0 |
| Female | 37,970 | 8,284 ( 21.82 ) | 6,576 (17.32 ) | 2,371 (6.24 ) | |
| Male | 39,080 | 8,091 ( 20.70 ) | 6,031 (15.43 ) | 2,758 (7.06 ) | |
| Age bands | | | | | 0 |
| 0 - 28 days | 377 | 53 ( 14.06 ) | 26 (6.90 ) | 28 (7.43 ) | |
| 1 - 11 months | 5,060 | 1,038 ( 20.51 ) | 613 (12.11 ) | 515 (10.18 ) | |
| 1 - 4 years | 31,754 | 8,141 ( 25.64 ) | 6,107 (19.23 ) | 2,764 (8.70 ) | |
| 5 - 12 years | 46,388 | 7,803 ( 16.82 ) | 6,298 (13.58 ) | 1,946 (4.20 ) | |
| Deprivation quintiles | | | | | 4,285 |
| 1 | 20,347 | 4,311 ( 21.19 ) | 3,203 (15.74 ) | 1,524 (7.49 ) | |
| 2 | 16,398 | 3,442 ( 20.99 ) | 2,634 (16.06 ) | 1,091 (6.65 ) | |
| 3 | 14,436 | 2,980 ( 20.64 ) | 2,297 (15.91 ) | 899 (6.23 ) | |
| 4 | 11,467 | 2,435 ( 21.23 ) | 1,965 (17.14 ) | 630 (5.49 ) | |
| 5 | 11,887 | 2,420 ( 20.36 ) | 1,907 (16.04 ) | 688 (5.79 ) | |
| Weight categories | | | | | 0 |
| Low Weight Category | 22,742 | 4,219 ( 18.55 ) | 3,031 (13.33 ) | 1,524 (6.70 ) | |
| Normal Weight Category | 41,741 | 8,543 ( 20.47 ) | 6,587 (15.78 ) | 2,524 (6.05 ) | |
| High Weight Category | 22,658 | 4,692 ( 20.71 ) | 3,708 (16.37 ) | 1,278 (5.64 ) | |
| Ethnic group | | | | | 52,480 |
| Asians | 619 | 143 ( 23.10 ) | 105 (16.96 ) | 70 (11.31 ) | |
| Blacks | 171 | 39 ( 22.81 ) | 25 (14.62 ) | 18 (10.53 ) | |
| Mixed | 296 | 74 ( 25.00 ) | 53 (17.91 ) | 36 (12.16 ) | |
| other Races | 212 | 70 ( 33.02 ) | 48 (22.64 ) | 37 (17.45 ) | |
| Whites | 23,271 | 5,731 ( 24.63 ) | 4,364 (18.75 ) | 1,994 (8.57 ) | |

*Table 1: Demographic data for study cohort. LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups*

| Variables | General adverse events | | | | Repeat antibiotics | | | | Hospital/emergency admissions | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | Lower CI | Upper CI | P values | OR | Lower CI | Upper CI | P values | OR | Lower CI | Upper CI | P values |
| Weight categories | | | | | | | | | | | | |
| LWC | 1.0512 | 1.0001 | 1.1284 | 0.2470 | 0.8491 | 0.7616 | 0.9466 | 0.0133 | 1.1837 | 1.0611 | 1.3203 | 0.0112 |
| NWC | - | - | - | - | - | - | - | - | - | - | - | - |
| HWC | 0.9492 | 0.9087 | 0.9989 | 0.1510 | 0.9512 | 0.8571 | 1.0556 | 0.4300 | 1.0374 | 0.9334 | 1.1530 | 0.5680 |
| Sex | | | | | | | | | | | | |
| Female | 1.1527 | 1.0637 | 1.2491 | 0.0036 | 1.3138 | 1.1617 | 1.4859 | 0.0003 | 0.7718 | 0.6820 | 0.8735 | 0.0006 |
| Male | - | - | - | - | - | - | - | - | - | - | - | - |
| Ethnic groups | | | | | | | | | | | | |
| Asian | 1.3527 | 1.0176 | 1.8425 | 0.1080 | 0.7656 | 0.5673 | 1.0331 | 0.1430 | 1.3614 | 1.0082 | 1.8385 | 0.0911 |
| Black | 1.0684 | 0.7579 | 1.5062 | 0.7510 | 0.5448 | 0.3339 | 0.8890 | 0.0413 | 1.9211 | 1.1759 | 3.1383 | 0.0287 |
| Mixed | 1.2007 | 0.9511 | 1.5158 | 0.1970 | 0.4963 | 0.3265 | 0.7545 | 0.0060 | 2.0497 | 1.3478 | 3.1173 | 0.0049 |
| Other ethnicities | 1.9223 | 1.4669 | 2.5192 | 0.0001 | 0.6262 | 0.4213 | 0.9307 | 0.0520 | 1.6812 | 1.1288 | 2.5039 | 0.0320 |
| Whites | - | - | - | - | - | - | - | - | - | - | - | - |
| Deprivation quintiles | | | | | | | | | | | | |
| 1 | 1.1500 | 1.0159 | 1.3017 | 0.0636 | 0.8921 | 0.7463 | 1.0665 | 0.2930 | 1.1444 | 0.9562 | 1.3696 | 0.2170 |
| 2 | 1.0840 | 0.9574 | 1.2274 | 0.2850 | 0.9700 | 0.7925 | 1.1871 | 0.8040 | 1.0563 | 0.8622 | 1.2941 | 0.6570 |
| 3 | 0.9745 | 0.8680 | 1.0941 | 0.7140 | 0.9411 | 0.7986 | 1.1091 | 0.5430 | 1.0738 | 0.9096 | 1.2677 | 0.4800 |
| 4 | 1.0682 | 0.9433 | 1.2098 | 0.3830 | 1.1664 | 0.9630 | 1.4127 | 0.1860 | 0.8576 | 0.7071 | 1.0400 | 0.1900 |
| 5 | - | - | - | - | - | - | - | - | - | - | - | - |
| Age bands | | | | | | | | | | | | |
| 0 - 28 days | 0.9279 | 0.5920 | 1.4544 | 0.7840 | 0.3994 | 0.1844 | 0.8650 | 0.0508 | 2.6493 | 1.2210 | 5.7486 | 0.0386 |
| 1 - 11 months | 1.2607 | 1.0569 | 1.5037 | 0.0307 | 0.8358 | 0.6500 | 1.0746 | 0.2400 | 1.2446 | 0.9674 | 1.6013 | 0.1530 |
| 0 - 4 years | - | - | - | - | - | - | - | - | - | - | - | - |
| 5 - 12 years | 0.6349 | 0.5938 | 0.6788 | 0.0000 | 1.4133 | 1.2776 | 1.5635 | 0.0000 | 0.7081 | 0.6396 | 0.7840 | 0.0000 |

*Table 2: Table showing the odds ratios of the risk factors for the respective adverse events (95% CI). LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups. Reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, Weight categories: normal weigh category.*

**Appendix 1**: Read Codes for records of adverse events in the GP

| read codes | description |
|---|---|
| SL05. | Cephalosporin group poisoning - |
| SL050 | Cefalexin poisoning |
| SL051 | Cephaloglycin poisoning |
| SL052 | Cephaloridine poisoning |
| SL053 | Cephalothin poisoning |
| SL052 | Cephalosporin poisoning NOS |
| TJ05z | Adverse reaction to cephalosporin NOS |
| T105. | Adverse reaction to cephalosporin group |
| TJ050 | Adverse reaction to cefacior |
| TJ051 | Adverse reaction to cefadroxil |
| TJ052 | Adverse reaction to cefotaxime |
| TJ053 | Adverse reaction to cefoxitin |
| TJ054 | Adverse reaction to cefsulodin sodium |
| TJ055 | Adverse reaction to ceftazidime |
| TJ056 | Adverse reaction to ceftizoxime |
| TJ057 | Adverse reaction to cephalexin |
| TJ058 | Adverse reaction to cephalothin |
| 1J059 | Adverse reaction to cephamandole |
| TJ05A | Adverse reaction to cephazolin |
| TJ05B | Adverse reaction to cephradine |
| TJ05z | Adverse reaction to cephalosporin NOS |
| U6001 | [X] Adverse reaction to cephalosporin NOS |
| Xa5ru | Macrolide allergy |
| Xa5rv | Erythromycin allergy |
| Xa5rw | Clarithromycin allergy |
| Xa5rx | Azithromycin allergy |
| Xa6Pw | Macrolide overdose |
| Xa6Px | Erythromycin overdose |
| Xa6Q1 | Azithromycin overdose |
| Xa6Q5 | Clarithromycin overdose |
| Xa5TR | Macrolide adverse reaction |
| Xa5TS | Erythromycin adverse reaction |
| Xa5TT | Clarithromycin adverse reaction |
| Xa5TU | Azithromycin adverse reaction |
| TJ03z | Adverse reaction to macrolide NOS |
| XM1Fr | Adverse reaction to macrolide group |
| TJ03. | Adverse reaction to erythromycin and other macrolides |
| TJ030 | Adverse reaction to erythromycin |
| TJ031 | Adverse reaction to oleandomycin |
| TJ032 | Adverse reaction to spiramycin |
| XE1oI | Erythromycin and macrolide poisoning |
| SL03z | Erythromycin or macrolide poisoning NOS |
| TJ03. | Adverse reaction to erythromycin and other macrolides |
| U6003 | [X]Macrolides causing adverse effects in therapeutic use |

| | |
|---|---|
| Xa5s3 | Nitrofurantoin allergy |
| 14LI. | H/O: nitrofurantoin allergy |
| Xa6QP | Nitrofuran derivative overdose |
| Xa5Ta | Nitrofurantoin adverse reaction |
| Xa56l | Accidental nitrofuran derivative poisoning |
| Xa56m | Intentional nitrofuran derivative poisoning |
| Xa56n | Nitrofuran derivative poisoning of undetermined intent |
| TJ1z2 | Adverse reaction to nitrofurantoin |
| Xa6QQ | Accidental nitrofuran derivative overdose |
| Xa6QR | Intentional nitrofuran derivative overdose |
| Xa56l | Accidental nitrofuran derivative poisoning |
| Xa56m | Intentional nitrofuran derivative poisoning |
| Xa6QS | Nitrofuran derivative overdose of undetermined intent |
| Xa56n | Nitrofuran derivative poisoning of undetermined intent |
| Xa5tS | Nitroimidazole allergy |
| Xa5tT | Metronidazole allergy |
| Xa5tV | Nimorazole allergy |
| Xa5Uz | Nitroimidazole adverse reaction |
| Xa5V0 | Metronidazole adverse reaction |
| Xa5V1 | Tinidazole adverse reaction |
| Xa5V2 | Nimorazole adverse reaction |
| SL00. | Penicillin poisoning |
| SL000 | Ampicillin poisoning |
| SL001 | Cloxacillin poisoning |
| SL002 | Carbenicillin poisoning |
| SL003 | Penicillin G poisoning |
| SL00z | Penicillin poisoning NOS |
| SL003 | Penicillin G poisoning |
| SL340 | Penicillinase poisoning |
| e1... | PENICILLINASE SENS PENICILLINS |
| e11.. | BENZYLPENICILLIN(PENICILLIN G) |
| e12.. | *BENETHAMINE PENICILLIN |
| e13.. | *BENZATHINE PENICILLIN |
| e14.. | *PHENETHICILLIN |
| e15.. | PHENOXYMETHYLPENICILLIN |
| e16.. | PROCAINE PENICILLIN |
| TJ00. | Adverse reaction to penicillins |
| TJ000 | Adverse reaction to natural penicillins |
| TJ001 | Adverse reaction to cloxacillin |
| TJ002 | Adverse reaction to flucloxacillin |
| TJ003 | Adverse reaction to amoxycillin |
| TJ004 | Adverse reaction to ampicillin |
| TJ005 | Adverse reaction to bacampicillin |
| TJ006 | Adverse reaction to ciclacillin |
| TJ007 | Adverse reaction to mezlocillin |
| TJ008 | Adverse reaction to pivampicillin |
| TJ009 | Adverse reaction to talampicillin |
| TJ009 | Adverse reaction to talampicillin |
| TJ00A | Adverse reaction to azlocillin |
| TJ00B | Adverse reaction to carbenicillin |

| | |
|---|---|
| TJ00C | Adverse reaction to carfecillin sodium |
| TJ00D | Adverse reaction to piperacillin |
| TJ00E | Adverse reaction to ticarcillin |
| TJ00F | Adverse reaction to mecillinam |
| TJ00G | Adverse reaction to pivmecillinam |
| TJ00z | Adverse reaction to penicillin NOS |
| U6000 | [X]Penicillins causing adverse effects in therapeutic use |
| Xa5s2 | Trimethoprim allergy |
| Xa6QL | Trimethoprim overdose |
| Xa6QM | Accidental trimethoprim overdose |
| Xa6QN | Intentional trimethoprim overdose |
| Xa6QO | Trimethoprim overdose of undetermined intent |
| Xa56h | Trimethoprim poisoning |
| Xa56i | Accidental trimethoprim poisoning |
| Xa56j | Intentional trimethoprim poisoning |
| Xa56k | Trimethoprim poisoning of undetermined intent |
| 14LE. | H/O: trimethoprim allergy |
| Xa5TZ | Trimethoprim adverse reaction |
| TJ0yC | Adverse reaction to trimethoprim |
| Xa6QM | Accidental trimethoprim overdose |
| Xa6QN | Intentional trimethoprim overdose |
| Xa56j | Intentional trimethoprim poisoning |
| Xa6QO | Trimethoprim overdose of undetermined intent |
| Xa56k | Trimethoprim poisoning of undetermined intent |

APPENDIX 2: Information on the excluded group

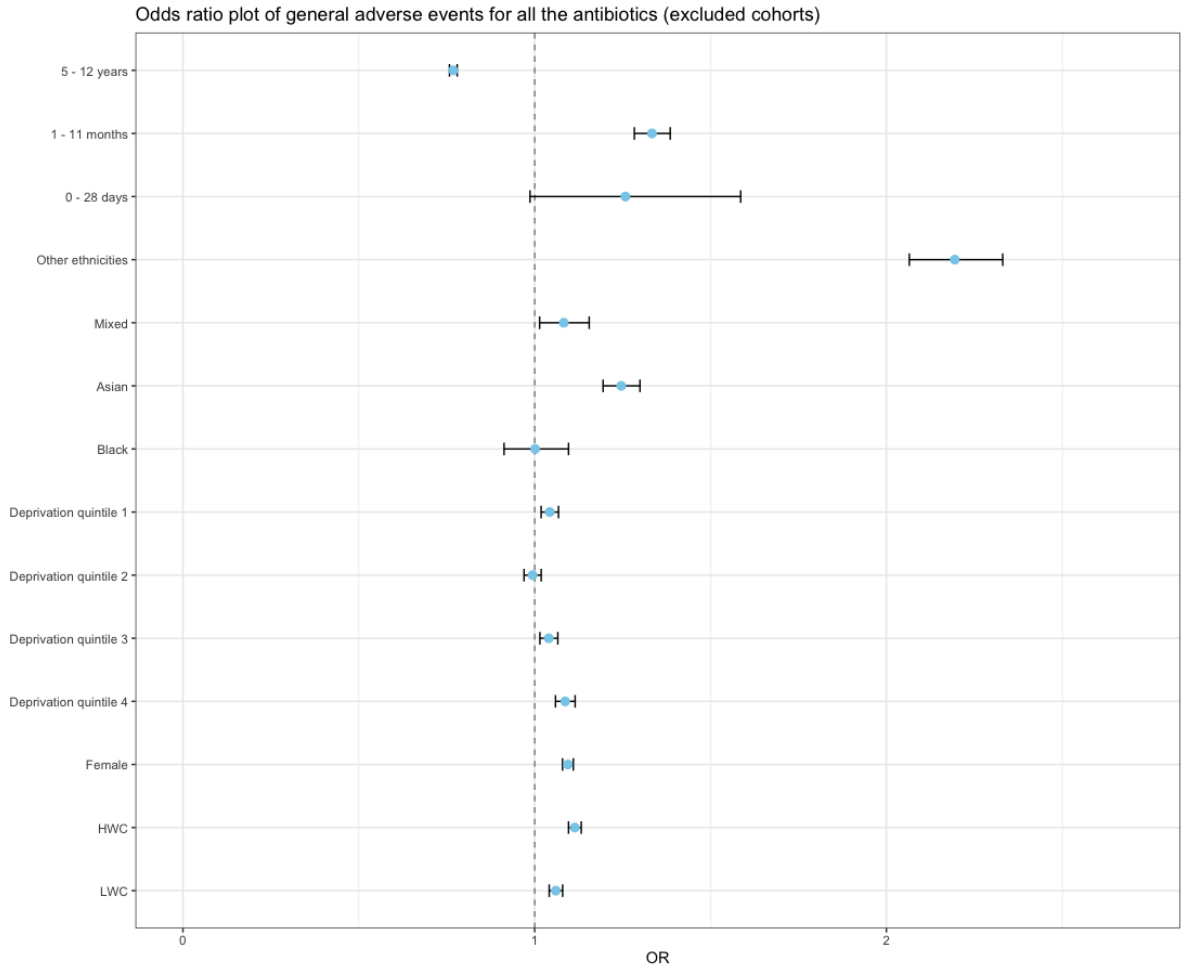
*Table 1: Characteristics of the excluded group*

| | Final cohort (77,050) | | Excluded group (314,225) | |
|---|---|---|---|---|
| Sex | | | | |
| Male | 39,080 | 50.72% | 160,654 | 51.13% |
| Female | 37,970 | 49.28% | 153,571 | 48.87% |

*Table 2: adjusted odds ratio for an adverse drug event*

| variables | OR | Lower CI | Upper CI | P values |
|---|---|---|---|---|
| Weight category | | | | |
| HWC | 1.1142 | 1.0963 | 1.1324 | 0.0000 |
| LWC | 1.0603 | 1.0414 | 1.0796 | 0.0000 |
| NWC | - | - | - | - |
| Sex | | | | |
| Female | 1.0944 | 1.0792 | 1.1099 | 0.0000 |
| Male | - | - | - | - |
| Ethnicity | | | | |
| Asian | 1.2461 | 1.1945 | 1.2995 | 0.0000 |
| Black | 1.0015 | 0.9130 | 1.0963 | 0.9791 |
| Mixed | 1.0827 | 1.0140 | 1.1551 | 0.0445 |
| Other ethnicities | 2.1945 | 2.0652 | 2.3308 | 0.0000 |
| White | - | - | - | - |
| Deprivation quintile | | | | |
| 1 | 1.0427 | 1.0184 | 1.0678 | 0.0036 |
| 2 | 0.9939 | 0.9698 | 1.0186 | 0.6821 |
| 3 | 1.0400 | 1.0148 | 1.0658 | 0.0085 |
| 4 | 1.0867 | 1.0592 | 1.1151 | 0.0000 |
| Age band | | | | |
| 0 - 28 days | 1.2581 | 0.9867 | 1.5858 | 0.1109 |
| 1 - 11 months | 1.3336 | 1.2835 | 1.3854 | 0.0000 |
| 0 – 4 years | - | - | - | - |
| 5 - 12 years | 0.7687 | 0.7577 | 0.7798 | 0.0000 |

*Figure 1: Forest plot of odds ratio of combined adverse events after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.*



**APPENDIX 3:** Read codes for the oral antibiotics

| Read codes | Description |
|---|---|
| e15.. | PHENOXYMETHYLPENICILLIN |
| e151. | PHENOXYMETHYLPENICILLIN 250mg capsules |
| e152. | PHENOXYMETHYLPENICILLIN 125mg capsules |
| e153. | PHENOXYMETHYLPENICILLIN 250mg tablets |
| e154. | PHENOXYMETHYLPENICILLIN 62.5mg/5mL syrup |
| e155. | PHENOXYMETHYLPENICILLIN 125mg/5mL syrup |
| e156. | PHENOXYMETHYLPENICILLIN granules 125mg/sachet |
| e157. | PHENOXYMETHYLPENICILLIN 250mg/5mL syrup |
| e158. | *APSIN VK 250mg tablets |
| e159. | *APSIN VK 125mg/5mL syrup |
| e15A. | PHENOXYMETHYLPENICILLIN 125mg tablets |
| e15B. | *RIMAPEN 250mg tablets |
| e15a. | APSIN VK 250mg/5mL syrup |
| e15b. | *CRYSTAPEN V 125mg/5mL syrup |
| e15c. | *CRYSTAPEN V 250mg/5mL syrup |
| e15d. | *DISTAQUAINE V-K 125mg tablets |
| e15e. | *DISTAQUAINE V-K 250mg tablets |
| e15f. | DISTAQUAINE V-K 62.5mg/5mL syrup |
| e15g. | DISTAQUAINE V-K 125mg/5mL syrup |
| e15h. | *DISTAQUAINE 250mg/5mL syrup |
| e15i. | *ECONOCIL VK 250mg capsules |
| e15j. | *ECONOCIL VK 125mg tablets |
| e15k. | *ECONOCIL VK 250mg tablets |
| e15l. | *STABILLIN V-K 250mg tablets |
| e15m. | STABILLIN V-K 62.5mg/5mL syrup |
| e15n. | *STABILLIN V-K 125mg/5mL syrup |
| e15o. | *STABILLIN V-K 250mg/5mL syrup |
| e15p. | *V-CIL-K 250mg capsules |
| e15q. | *V-CIL-K 125mg tablets |
| e15r. | *V-CIL-K 250mg tablets |
| e15s. | V-CIL-K PAEDIATRIC 62.5mg/5mL syrup |
| e15t. | V-CIL-K PAEDIATRIC 125mg/5mL syrup |
| e15u. | *V-CIL-K 250mg/5mL syrup |
| e15v. | *TENKICIN 250mg tablets |
| e15w. | PHENOXYMETHYLPENICILLIN 125mg/5mL s/f oral solution |
| e15x. | PHENOXYMETHYLPENICILLIN 250mg/5mL s/f oral solution |
| e221. | FLUCLOXACILLIN 250mg capsules |
| e222. | FLUCLOXACILLIN 500mg capsules |
| e223. | FLOXAPEN 250mg capsules |
| e224. | FLOXAPEN 500mg capsules |
| e225. | FLOXAPEN 125mg/5mL syrup |
| e226. | FLOXAPEN FORTE 250mg/5mL syrup |
| e22A. | FLUCLOXIN 125mg/5mL oral suspension |
| e22B. | FLUCLOXACILLIN 250mg/5mL oral suspension |
| e22C. | FLUCLOXACILLIN 125mg/5mL s/f oral solution |
| e22D. | FLUCLOXACILLIN 250mg/5mL s/f oral solution |
| e22a. | *LADROPEN 250mg capsules |
| e22b. | *LADROPEN 500mg capsules |
| e22c. | *STAFOXIL 250mg capsules |

| | |
|---|---|
| e22d. | *STAFOXIL 500mg capsules |
| e22e. | *STAPHLIPEN 250mg capsules |
| e22f. | *STAPHLIPEN 500mg capsules |
| e22j. | FLUCLOXACILLIN 125mg/5mL syrup |
| e22k. | FLUCLOXACILLIN 250mg/5mL syrup |
| e22l. | *FLUCLOMIX 250mg capsules |
| e22m. | FLUCLOMIX 500mg capsules |
| e22n. | LADROPEN 125mg/5mL suspension 100mL |
| e22t. | *GALFLOXIN 250mg capsules |
| e22u. | *GALFLOXIN 500mg capsules |
| e22v. | FLUCLOXACILLIN 125mg/5mL oral suspension |
| e22w. | *ZOXIN 250 capsules |
| e22x. | *ZOXIN 500 capsules |
| e22y. | *FLUCLOXIN 250mg capsules |
| e22z. | *FLUCLOXIN 500mg capsules |
| e311. | AMOXICILLIN 250mg capsules |
| e312. | AMOXICILLIN 500mg capsules |
| e313. | *AMOXIDIN 250mg capsules |
| e314. | *AMOXIDIN 500mg capsules |
| e315. | AMOXIL 250mg capsules |
| e316. | AMOXIL 500mg capsules |
| e317. | AMOXIL 500mg dispersible tablets |
| e318. | *AMOXIL 125mg/5mL syrup |
| e319. | *AMOXIL SF 125mg/5mL syrup |
| e31A. | *AMIX 125mg/5mL suspension |
| e31B. | *AMIX 250mg/5mL suspension |
| e31C. | *AMRIT 125mg/5mL suspension |
| e31D. | *AMRIT 250mg/5mL suspension |
| e31E. | *AMRIT 250mg capsules |
| e31F. | *AMRIT 500mg capsules |
| e31G. | *AMOPEN 250mg capsules |
| e31H. | *AMOPEN 500mg capsules |
| e31I. | *AMOPEN 125mg/5mL suspension |
| e31J. | *AMOPEN 250mg/5mL suspension |
| e31K. | FLEMOXIN SOLUTAB 375mg dispersible tablets |
| e31L. | FLEMOXIN SOLUTAB 750mg dispersible tablets |
| e31M. | AMOXIL FIZTAB 125mg chewable tablets |
| e31N. | AMOXIL FIZTAB 250mg chewable tablets |
| e31O. | AMOXIL FIZTAB 500mg chewable tablets |
| e31P. | AUGMENTIN 250/62 in 5mL suspension |
| e31Q. | CO-AMOXICLAV 125/31mg in 5mL suspension |
| e31R. | *AMOXYMED 250mg capsules |
| e31S. | *AMOXYMED 125mg/5mL syrup |
| e31T. | AUGMENTIN 625mg tablets |
| e31U. | CO-AMOXICLAV 625mg tablets |
| e31V. | ALMODAN 125mg/5mL sugar free syrup |
| e31W. | ALMODAN 250mg/5mL sugar free syrup |
| e31X. | CO-AMOXICLAV 400/57mg in 5mL sugar free suspension |
| e31Y. | AUGMENTIN-DUO 400/57 in 5mL sugar free suspension |
| e31a. | *AMOXIL SF 250mg/5mL syrup |
| e31b. | AMOXIL 125mg/1.25mL paediatric suspension |
| e31c. | *AMOXIL SF 750mg sachets |

| | |
|---|---|
| e31d. | *AMOXIL SF 3g sachets |
| e31h. | AUGMENTIN 375mg tablets |
| e31i. | AUGMENTIN 375mg dispersible tablets |
| e31j. | AUGMENTIN JUNIOR 125/62 in 5mL suspension |
| e31k. | AUGMENTIN 125/31 in 5mL paediatric suspension |
| e31n. | *ALMODAN 250mg capsules |
| e31o. | *ALMODAN 500mg capsules |
| e31p. | *ALMODAN 125mg/5mL syrup |
| e31q. | *ALMODAN 250mg/5mL syrup |
| e31t. | CO-AMOXICLAV 375mg tablets |
| e31u. | CO-AMOXICLAV 375mg dispersible tablets |
| e31v. | CO-AMOXICLAV 125mg/5mL suspension |
| e31w. | CO-AMOXICLAV 125mg/mL suspension |
| e31z. | CO-AMOXICLAV 250/62 in 5mL suspension |
| e321. | AMPICILLIN 250mg capsules |
| e322. | AMPICILLIN 500mg capsules |
| e323. | AMPICILLIN 125mg/5mL mixture |
| e324. | AMPICILLIN 250mg/5mL mixture |
| e325. | *AMFIPEN 250mg capsules |
| e326. | *AMFIPEN 500mg capsules |
| e327. | *AMFIPEN 125mg/5mL syrup |
| e328. | *AMFIPEN 250mg/5mL syrup |
| e329. | *AMFIPEN 250mg injection |
| e32A. | *RIMACILLIN 250mg capsules |
| e32B. | *RIMACILLIN 500mg capsules |
| e32C. | *RIMACILLIN 125mg/5mL syrup |
| e32D. | *RIMACILLIN 250mg/5mL syrup |
| e32E. | *AMPICILLIN 250mg injection |
| e32F. | AMPICILLIN 500mg injection |
| e32G. | AMPICILLIN 125mg/1.25mL paediatric suspension |
| e32H. | AMPICILLIN 125mg/5mL sugar free suspension |
| e32J. | AMPICILLIN 250mg/5mL sugar free suspension |
| e32K. | Ampicillin 125mg/5mL oral suspension |
| e32b. | *AMPILAR 250mg capsules |
| e32c. | *AMPILAR 500mg capsules |
| e32d. | *AMPILAR 125mg/5mL syrup |
| e32e. | *AMPILAR 250mg/5mL syrup |
| e32f. | *BRITCIN 250mg capsules |
| e32g. | *BRITCIN 500mg capsules |
| e32h. | PENBRITIN 250mg capsules |
| e32i. | PENBRITIN 500mg capsules |
| e32j. | *PENBRITIN 125mg tablets |
| e32k. | PENBRITIN 125mg/5mL syrup |
| e32l. | PENBRITIN 250mg/5mL syrup |
| e32m. | PENBRITIN 100mg/mL paediatric suspension |
| e32p. | *VIDOPEN 250mg capsules |
| e32q. | *VIDOPEN 500mg capsules |
| e32r. | *VIDOPEN 125mg/5mL syrup |
| e32s. | *VIDOPEN 250mg/5mL syrup |
| e32v. | *AMPITRIN 250mg capsules |
| e32w. | *AMPITRIN 500mg capsules |
| e32x. | AMPITRIN 125mg/5mL oral suspension |
| e32y. | AMPITRIN 250mg/5mL oral suspension |
| e32z. | *AMPICILLIN 125mg tablets |

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| e334. | *FLU-AMP 250/250mg capsules |
| e335. | MAGNAPEN 500mg capsules |
| e336. | *MAGNAPEN 250mg/5mL syrup |
| e339. | CO-FLUAMPICIL 250mg/250mg capsules |
| e33a. | CO-FLUAMPICIL 125/125mg syrup |
| e33h. | *UNASYN 375mg tablets |
| e33i. | *SULTAMICILLIN 375mg tablets |
| e3A.. | AMOXICILLIN [2] |
| e3A1. | *RESPILLIN 250mg capsules |
| e3A2. | *RESPILLIN 500mg capsules |
| e3A3. | RESPILLIN 125mg/5mL oral suspension |
| e3A4. | RESPILLIN 250mg/5mL oral suspension |
| e3A5. | RESPILLIN 125mg/5mL sugar free suspension |
| e3A6. | RESPILLIN 250mg/5mL sugar free suspension |
| e3A7. | *AMICLAV 250mg/125mg tablets |
| e3A8. | *RANCLAV 375mg tablets |
| e3A9. | *RANCLAV 625mg tablets |
| e3AA. | RANCLAV 125mg/31mg sugar free suspension |
| e3AB. | RANCLAV 250mg/62mg sugar free suspension |
| e3z.. | AMOXICILLIN [GENERIC ADDITIONS] |
| e3z1. | *AMORAM 250mg capsules |
| e3z2. | *AMORAM 500mg capsules |
| e3z3. | *AMORAM 125mg/5mL suspension |
| e3z4. | *AMORAM 250mg/5mL suspension |
| e3z5. | AMIX 250mg capsules |
| e3z6. | AMIX 500mg capsules |
| e3z7. | *GALENAMOX 250mg capsules |
| e3z8. | *GALENAMOX 500mg capsules |
| e3z9. | GALENAMOX 125mg/5mL suspension |
| e3zA. | GALENAMOX TP 250mg capsules |
| e3zB. | GALENAMOX TP 500mg capsules |
| e3zC. | *ZOXYCIL 250 capsules |
| e3zD. | *ZOXYCIL 500 capsules |
| e3zE. | AMOXICILLIN 125mg/sachet sugar free powder |
| e3zF. | AMOXIDENT 250mg capsules |
| e3zG. | AMOXIDENT 500mg capsules |
| e3za. | GALENAMOX 250mg/5mL suspension |
| e3zb. | GALENAMOX 125mg/5mL sugar free suspension |
| e3zc. | GALENAMOX 250mg/5mL sugar free suspension |
| e3zf. | *RIMOXALLIN 125mg/5mL syrup |
| e3zg. | *RIMOXALLIN 250mg capsules |
| e3zh. | *RIMOXALLIN 500mg capsules |
| e3zj. | *RIMOXALLIN 250mg/5mL syrup |
| e3zk. | AMOXICILLIN 125mg/5mL sugar free suspension |
| e3zl. | AMOXYCILLIN 500mg dispersible tablets |
| e3zm. | AMOXICILLIN 125mg/5mL syrup |
| e3zn. | AMOXICILLIN 250mg/5mL syrup |
| e3zo. | AMOXICILLIN 125mg/1.25mL paediatric suspension |
| e3zp. | AMOXYCILLIN powder 750mg/sachet |
| e3zq. | AMOXICILLIN powder 3g/sachet |
| e3zu. | AMOXICILLIN 250mg/5mL sugar free suspension |
| e3zv. | AMOXYCILLIN 125mg s/f chewable tablets |
| e3zw. | AMOXYCILLIN 250mg s/f chewable tablets |
| e3zx. | AMOXYCILLIN 500mg s/f chewable tablets |

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| e3zy. | AMOXYCILLIN 375mg s/f dispersible tablets |
| e3zz. | AMOXYCILLIN 750mg s/f dispersible tablets |
| e52.. | PIVMECILLINAM HYDROCHLORIDE |
| e521. | SELEXID 200mg tablets |
| e522. | SELEXID 100mg/sachet suspension |
| e52v. | PIVMECILLINAM 100mg/sachet suspension |
| e52w. | PIVMECILLINAM HYDROCHLORIDE 200mg tablets |
| e69.. | CEFALEXIN |
| e691. | CEFALEXIN 250mg capsules |
| e692. | CEFALEXIN 500mg capsules |
| e693. | CEFALEXIN 250mg tablets |
| e694. | CEFALEXIN 500mg tablets |
| e695. | CEFALEXIN 125mg/5mL mixture |
| e696. | CEFALEXIN 250mg/5mL mixture |
| e697. | CEFALEXIN 500mg/5mL syrup |
| e698. | CEPOREX 250mg capsules |
| e699. | CEPOREX 500mg capsules |
| e69A. | *TENKOREX 250mg capsules |
| e69B. | *TENKOREX 500mg capsules |
| e69C. | *TENKOREX 125mg/5mL suspension |
| e69D. | *TENKOREX 250mg/5mL suspension |
| e69E. | *TENKOREX 500mg tablets |
| e69F. | *KIFLONE 500mg tablets |
| e69G. | *KIFLONE 250mg capsules |
| e69H. | *KIFLONE 500mg capsules |
| e69J. | *KIFLONE 125mg/5mL syrup |
| e69K. | *KIFLONE 250mg/5mL syrup |
| e69a. | CEPOREX 250mg tablets |
| e69b. | CEPOREX 500mg tablets |
| e69c. | CEPOREX 125mg/1.25mL paediatric drops |
| e69d. | *CEPOREX 125mg/5mL suspension |
| e69e. | *CEPOREX 250mg/5mL suspension |
| e69f. | CEPOREX 125mg/5mL syrup |
| e69g. | CEPOREX 250mg/5mL syrup |
| e69h. | CEPOREX 500mg/5mL syrup |
| e69i. | KEFLEX 250mg capsules |
| e69j. | KEFLEX 500mg capsules |
| e69k. | KEFLEX 250mg tablets |
| e69l. | KEFLEX 500mg tablets |
| e69m. | KEFLEX 125mg/5mL suspension |
| e69n. | KEFLEX 250mg/5mL suspension |
| e69o. | KEFLEX-C 125mg chewable tablets |
| e69p. | KEFLEX-C 250mg chewable tablets |
| e69q. | *CEPOREX 1g tablets |
| e69v. | CEFALEXIN 125mg/5mL syrup |
| e69w. | CEFALEXIN 250mg/5mL syrup |
| e69x. | *CEPHALEXIN 1g tablets |
| e69y. | CEPHALEXIN 125mg/1.25mL paediatric drops |
| e61.. | CEFACLOR |
| e611. | *DISTACLOR 250mg capsules |
| e612. | DISTACLOR 125mg/5mL suspension |
| e613. | DISTACLOR 250mg/5mL suspension |
| e614. | CEFACLOR 250mg capsules |
| e615. | CEFACLOR 125mg/5mL suspension |

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| e616. | CEFACLOR 250mg/5mL suspension |
| e617. | DISTACLOR 500mg capsules |
| e618. | CEFACLOR 500mg capsules |
| e619. | DISTACLOR MR 375mg m/r tablets |
| e61A. | KEFTID 250mg capsules |
| e61B. | KEFTID 500mg capsules |
| e61C. | CEFACLOR 125mg/5mL sugar free suspension |
| e61D. | CEFACLOR 250mg/5mL sugar free suspension |
| e61E. | KEFTID 125mg/5mL sugar free suspension |
| e61F. | KEFTID 250mg/5mL sugar free suspension |
| e61G. | BACTICLOR MR 375mg m/r tablets |
| e61a. | CEFACLOR 375mg m/r tablets |
| e61b. | DISTACLOR MR 500mg m/r tablets |
| e61c. | *CEFACLOR 500mg m/r tablets |
| e62.. | CEFADROXIL |
| e621. | *BAXAN 500mg capsules |
| e622. | *BAXAN 125mg/5mL suspension |
| e623. | *BAXAN 250mg/5mL suspension |
| e624. | *BAXAN 500mg/5mL suspension |
| e625. | CEFADROXIL 125mg/5mL suspension |
| e626. | CEFADROXIL 250mg/5mL suspension |
| e627. | CEFADROXIL 500mg capsules |
| e62w. | *CEFADROXIL 500mg capsules |
| e62x. | *CEFADROXIL 500mg capsules |
| e62z. | CEFADROXIL 500mg/5mL suspension |
| e684. | ZINNAT 125mg tablets |
| e685. | ZINNAT 250mg tablets |
| e686. | CEFUROXIME 125mg tablets |
| e687. | CEFUROXIME 250mg tablets |
| e689. | ZINNAT 125mg/5mL suspension |
| e68a. | CEFUROXIME 125mg/5mL suspension |
| e68b. | ZINNAT 125mg/sachet suspension |
| e68c. | CEFUROXIME 125mg/sach for suspension |
| e6h.. | CEFIXIME |
| e6h1. | CEFIXIME 200mg tablets |
| e6h2. | CEFIXIME 100mg/5mL suspension |
| e6h3. | SUPRAX 200mg tablets |
| e6h4. | SUPRAX 100mg/5mL paediatric suspension 37.5mL |
| e6h5. | SUPRAX 100mg/5mL paediatric suspension 75mL |
| e6h6. | SUPRAX 100mg/5mL paediatric suspension 50mL |
| e6h7. | SUPRAX 100mg/5mL paediatric suspension 100mL |
| e911. | ERYTHROMYCIN 250mg e/c tablets |
| e912. | ERYTHROMYCIN 500mg tablets |
| e913. | ERYTHROMYCIN STEARATE 250mg tablets |
| e914. | ERYTHROMYCIN STEARATE 500mg tablets |
| e915. | ARPIMYCIN 125mg/5mL sugar free suspension |
| e916. | ARPIMYCIN 250mg/5mL sugar free suspension |
| e917. | ARPIMYCIN 500mg/5mL sugar free suspension |
| e918. | *ERYCEN 250mg tablets |
| e919. | *ERYCEN 500mg tablets |
| e91A. | ERYTHROPED FORTE granules 500mg/sachet |
| e91B. | ERYTHROPED P.I. granules 125mg/sachet |
| e91C. | ERYTHROPED P.I. 125mg/5mL sugar free suspension 140mL |

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| e91D. | ERYTHROPED 250mg/5mL sugar free suspension 140mL |
| e91E. | ERYTHROMYCIN 125mg/5mL sugar free suspension |
| e91F. | ERYTHROMYCIN 250mg/5mL sugar free suspension |
| e91G. | *ROMMIX-125 suspension |
| e91H. | *ROMMIX-250 tablets |
| e91I. | KERYMAX 250mg e/c granules in capsules |
| e91J. | *ROMMIX-500 tablets |
| e91L. | *ERYTHROMYCIN 250mg capsules |
| e91M. | ERYTHROMYCIN 125mg/sachet granules |
| e91N. | ERYTHROMYCIN 250mg/sachet granules |
| e91P. | ERYTHROMYCIN 500mg/sachet granules |
| e91Q. | ERYTHROMYCIN 1g/sachet granules |
| e91R. | ERYTHROMYCIN 500mg/5mL sugar free suspension |
| e91S. | TILORYTH 250mg e/c granules in capsules |
| e91T. | ERYMIN 250mg/5mL sugar free suspension |
| e91U. | ARPIMYCIN 125mg/5mL suspension |
| e91V. | ARPIMYCIN 250mg/5mL suspension |
| e91W. | ARPIMYCIN 500mg/5mL suspension |
| e91X. | ERYTHROMYCIN 250mg e/c granules in capsules |
| e91Y. | ERYTHROPED FORTE SF 500mg/5mL sugar free suspension |
| e91Z. | PRIMACINE 125mg/5mL suspension 100mL |
| e91a. | ERYMAX 250mg e/c granules in capsules |
| e91b. | ERYTHROCIN 250mg tablets |
| e91c. | ERYTHROCIN 500mg tablets |
| e91e. | *ERYTHROLAR 250mg tablets |
| e91f. | *ERYTHROLAR 500mg tablets |
| e91g. | ERYTHROLAR 250mg/5mL suspension |
| e91h. | *ERYTHROMID 250mg tablets |
| e91i. | *ERYTHROMID DS 500mg tablets |
| e91j. | ERYTHROPED P.I. 125mg/5mL suspension |
| e91k. | ERYTHROPED 250mg/5mL suspension 140mL |
| e91l. | ERYTHROPED 250mg/sachet sugar free granules |
| e91m. | ERYTHROPED FORTE 500mg/5mL suspension |
| e91n. | ERYTHROPED A 500mg tablets |
| e91o. | *ILOSONE 250mg capsules |
| e91p. | *ILOSONE 500mg tablets |
| e91q. | *ILOSONE 125mg/5mL suspension |
| e91r. | ILOSONE FORTE 250mg/5mL suspension |
| e91s. | *ILOTYCIN 250mg tablets |
| e91t. | RETCIN 250mg tablets |
| e91u. | ERYTHROMYCIN 125mg/5mL suspension |
| e91v. | ERYTHROMYCIN 250mg/5mL suspension |
| e91w. | ERYTHROMYCIN 500mg/5mL suspension |
| e91x. | ERYTHROPED A 1g/sachet granules |
| e91y. | ERYMAX SPRINKLE 125mg capsules |
| e91z. | ERYTHROPED 250mg/sachet granules |
| e921. | CLARITHROMYCIN 250mg tablets |
| e922. | KLARICID 250mg tablets 14CP |
| e923. | CLARITHROMYCIN 125mg/5mL paediatric suspension |
| e924. | KLARICID 125mg/5mL paediatric suspension |
| e927. | CLARITHROMYCIN 500mg tablets |
| e928. | KLARICID 500mg tablets |

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| e929. | CLARITHROMYCIN 500mg m/r tablets |
| e92A. | KLARICID XL 500mg m/r tablets |
| e92B. | CLARITHROMYCIN 250mg/sachet granules |
| e92C. | KLARICID adult 250mg/sachet granules |
| e92D. | CLARITHROMYCIN 250mg/5mL paediatric suspension |
| e92E. | KLARICID 250mg/5mL paediatric suspension |
| e92F. | CLARITHROMYCIN 125mg granules straw |
| e92G. | *CLAROSIP 125mg granules straw |
| e92H. | CLARITHROMYCIN 187.5mg granules straw |
| e92I. | CLAROSIP 187.5mg granules straw |
| e92J. | CLARITHROMYCIN 250mg granules straw |
| e92K. | CLAROSIP 250mg granules straw |
| e92L. | XETININ XL 500mg m/r/ tablets |
| e92M. | FEBZIN XL 500mg m/r tablets |
| e92N. | MYCIFOR XL 500mg m/r tablets |
| e931. | AZITHROMYCIN 250mg capsules |
| e932. | AZITHROMYCIN 40mg/mL suspension |
| e933. | ZITHROMAX 250mg capsules |
| e934. | ZITHROMAX 40mg/mL suspension 15mL |
| e935. | ZITHROMAX 40mg/mL suspension 22.5mL |
| e936. | ZITHROMAX 40mg/mL suspension 30mL |
| e937. | AZITHROMYCIN 500mg tablets |
| e938. | *ZITHROMAX 500mg tablets |
| e939. | CLAMELLE AZITHROMYCIN 500mg tablets |
| e95.. | ERYTHROMYCIN [2] |
| e951. | PRIMACINE 125mg/5mL suspension 140mL |
| e952. | PRIMACINE 250mg/5mL suspension 100mL |
| e953. | PRIMACINE 250mg/5mL suspension 140mL |
| e954. | PRIMACINE 500mg/5mL suspension 100mL |
| e955. | PRIMACINE 500mg/5mL suspension 140mL |
| ea11. | DALACIN C 75mg capsules |
| ea12. | DALACIN C 150mg capsules |
| ea13. | DALACIN C 75mg/5mL paediatric suspension |
| ea1v. | CLINDAMYCIN 75mg capsules |
| ea1w. | CLINDAMYCIN 150mg capsules |
| ea1x. | *CLINDAMYCIN 75mg/5mL syrup |
| ec11. | CO-TRIMOXAZOLE 480mg tablets |
| ec12. | CO-TRIMOXAZOLE 480mg dispersible tablets |
| ec13. | CO-TRIMOXAZOLE 960mg tablets |
| ec14. | CO-TRIMOXAZOLE 960mg dispersible tablets |
| ec15. | CO-TRIMOXAZOLE 120mg tablets |
| ec16. | CO-TRIMOXAZOLE 480mg/5mL mixture |
| ec17. | CO-TRIMOXAZOLE 240mg/5mL mixture |
| ec1A. | CO-TRIMOXAZOLE 240mg/5mL sugar free suspension |
| ec1B. | CO_TRIMOXAZOLE 480mg/5mL suspension |
| ec21. | *BACTRIM 480mg tablets |
| ec22. | BACTRIM 480mg dispersible tablets |
| ec23. | BACTRIM 960mg double strength tablets |
| ec24. | BACTRIM PAEDIATRIC 120mg tablets |
| ec25. | *BACTRIM 480mg/5mL suspension |
| ec26. | BACTRIM 240mg/5mL paediatric syrup |
| ec29. | CHEMOTRIM 240mg/5mL suspension |

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| ec2a. | *COMOX 480mg tablets |
| ec2b. | COMOX 480mg dispersible tablets |
| ec2c. | *COMOX FORTE 960mg tablets |
| ec2d. | COMOX 240mg/5mL paediatric suspension |
| ec2e. | FECTRIM STANDARD 480mg dispersible tablets |
| ec2f. | FECTRIM FORTE 960mg dispersible tablets |
| ec2g. | FECTRIM 120mg paediatric tablets |
| ec2h. | *LARATRIM 480mg tablets |
| ec2i. | *LARATRIM FORTE 960mg tablets |
| ec2j. | *LARATRIM 480mg/5mL suspension |
| ec2k. | LARATRIM 240mg/5mL paediatric suspension |
| ec2l. | SEPTRIN 480mg tablets |
| ec2m. | SEPTRIN 480mg dispersible tablets |
| ec2n. | SEPTRIN FORTE 960mg tablets |
| ec2o. | SEPTRIN PAEDIATRIC 120mg dispersible tablets |
| ec2p. | SEPTRIN 480mg/5mL adult suspension |
| ec2q. | SEPTRIN 240mg/5mL paediatric suspension |
| ec2t. | *COMIXCO 80/400 tablets |
| ec2u. | *COMIXCO 160/800 tablets |
| ec2v. | COMIXCO 40/200/5mL paediatric suspension |
| ec2w. | COMIXCO 80/400 dispersible tablets |
| ecc1. | TRIMETHOPRIM 100mg tablets |
| ecc2. | TRIMETHOPRIM 200mg tablets |
| ecc3. | *TRIMETHOPRIM 300mg tablets |
| ecc4. | TRIMETHOPRIM 50mg/5mL sugar free suspension |
| ecc6. | *IPRAL 100mg tablets |
| ecc7. | *IPRAL 200mg tablets |
| ecc8. | IPRAL SF 50mg/5mL paediatric suspension |
| ecc9. | *MONOTRIM 100mg tablets |
| ecca. | *MONOTRIM 200mg tablets |
| eccb. | MONOTRIM 50mg/5mL sugar free suspension |
| eccd. | *SYRAPRIM 100mg tablets |
| ecce. | *SYRAPRIM 300mg tablets |
| eccf. | *SYRAPRIM 100mg/5mL injection |
| eccg. | TIEMPE 100mg tablets |
| ecch. | TIEMPE 200mg tablets |
| ecci. | *TRIMOGAL 100mg tablets |
| eccj. | *TRIMOGAL 200mg tablets |
| ecck. | *TRIMOPAN 100mg tablets |
| eccl. | *TRIMOPAN 200mg tablets |
| eccm. | TRIMOPAN 50mg/5mL sugar free suspension |
| eccn. | *TRIPRIMIX 200mg tablets |
| ef11. | METRONIDAZOLE 200mg tablets |
| ef12. | METRONIDAZOLE 400mg tablets |
| ef1A. | METRONIDAZOLE 200mg/5mL suspension |
| ef1D. | METRONIDAZOLE 500mg tablets |
| ef1c. | FLAGYL 200mg tablets |
| ef1d. | FLAGYL 400mg tablets |
| ef1g. | FLAGYL S suspension 100mL |
| ef1l. | *METROLYL 200mg tablets |
| ef1m. | *METROLYL 400mg tablets |
| ef1r. | *NIDAZOL 200mg tablets |
| ef1s. | VAGINYL 200mg tablets |
| ef1t. | VAGINYL 400mg tablets |

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| ef1u. | *ZADSTAT 200mg tablets |
| eg1.. | NITROFURANTOIN |
| eg11. | NITROFURANTOIN 50mg tablets |
| eg12. | NITROFURANTOIN 100mg tablets |
| eg13. | FURADANTIN 50mg tablets |
| eg14. | FURADANTIN 100mg tablets |
| eg15. | FURADANTIN 25mg/5mL sugar free suspension |
| eg16. | MACRODANTIN 50mg capsules |
| eg17. | MACRODANTIN 100mg capsules |
| eg18. | URANTOIN 50mg tablets |
| eg19. | URANTOIN 100mg tablets |
| eg1A. | MACROBID 100mg m/r capsules |
| eg1B. | GENFURA 50mg tablets |
| eg1C. | GENFURA 100mg tablets |
| eg1w. | NITROFURANTOIN 100mg m/r capsules |
| eg1x. | NITROFURANTOIN 25mg/5mL sugar free suspension |
| eg1y. | NITROFURANTOIN 50mg capsules |
| eg1z. | NITROFURANTOIN 100mg capsules |
| eg61. | CIPROXIN 250mg tablets |
| eg64. | CIPROXIN 500mg tablets |
| eg65. | CIPROXIN 750mg tablets |
| eg67. | CIPROFLOXACIN 100mg tablets |
| eg68. | *CIPROXIN 100mg tablets |
| eg69. | CIPROFLOXACIN 5g/100mL oral suspension |
| eg6A. | CIPROXIN 5g/100mL oral suspension |
| eg6v. | CIPROFLOXACIN 750mg tablets |
| eg6w. | CIPROFLOXACIN 500mg tablets |
| eg6x. | CIPROFLOXACIN 250mg tablets |

**APPENDIX 4:** Risk factors for adverse events in children prescribed oral antibiotics in the GP

| Risk factors | Variable from routine data | source |
|---|---|---|
| Deprivation quintile | Welsh index of multiple deprivation 2014 overall index quartile. | Welsh Demographic Service Dataset (WDSD) |
| Ethnicity | Ethnic group description | Patient Episode Dataset for Wales (PEDW) |
| Sex | Gender codes | Welsh Longitudinal General Practice Dataset (WLGP) – Welsh Primary Care |
| Weight | Patient weight values within 30 days of oral antibiotics prescription date | National Community Child Health Database (NCCHD)<br><br>WLGP |
| Age band | Patient age at oral antibiotics prescription date (prescription date – Week of Birth (WOB)) | WLGP |

Cohort selection (inclusion and exclusion criteria)

- Children born in Wales.
- Study population include children (aged 0 to 12 years) with a GP oral antibiotics prescription record (WLGP dataset)
- Weight record in NCCHD/WLGP.
- Weight record was within 30 days before or after oral antibiotics prescription.

Datasets used: WDSD, WLGP, PEDW, NCCHD.

**APPENDIX 5:** Adverse events data source

| Adverse events | Variable from routine data | source |
|---|---|---|
| Patient death within 5 days | Death date | Annual District Death Extract (ADDE) |
| Repeat GP antibiotic prescription within 14 days | Event date, antibiotics codes | Welsh Longitudinal General Practice Dataset (WLGP) |
| Non-elective hospital/emergency admission within 5 days of initial prescription | Admission date | Emergency Department Dataset (EDDS), Patient Episode Dataset for Wales (PEDW) |
| GP record of toxicity, poisoning, overdose, allergy or hypersensitivity within 14 days | Event date, event code | WLGP |

These records merged (row-bind) to the main dataset and arranged chronologically to detect the adverse outcomes.

Datasets used: ADDE, WLGP, and, PEDW.

BMJ Paediatrics Open

# Association of child weight and adverse outcomes following antibiotic prescriptions in children: A national data study in Wales, UK.



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| Keywords: | Statistics, Infant, Health Policy |
| | |

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**Abstract**

**Objective**: To examine if the weight of a child determines adverse events following oral antibiotics prescription.

**Design:** Population respective cohort using linked GP, hospital data, and linkage with the Welsh Demographic Service for demographic information. Data linkage was performed using Wales health data, extracted from the SAIL (Secure Anonymised Information Linkage) databank.

Inclusion: Children aged (0 to 12 years) prescribed oral antibiotics by their GP in Wales.

Exposure: Antibiotic prescription (Penicillins, Cephalosporins, Macrolides, Dihydropyrimidines, Nitroimidazoles, Nitrofurans, Lincosamides).

Outcome: Adverse event as defined by; patients' death within 5 days, records of emergency admission within 5 days, and GP records of adverse drug reactions or prescription of another antibiotic within 14 days.

Analysis : Logistic regression of adverse events versus no adverse events at follow up time.

**Results**: There were 139,571 prescriptions of the selected antibiotics and 71,541 children (51.39% male) included with follow up data of which there were 25,445 (18.23% of all prescriptions) children experienced adverse outcomes. There was a higher odds of adverse event for lower weight children and those who were younger, female, Asian origin or deprived.

**Conclusion**: The findings support the hypothesis that smaller children for their age (e.g. low weight, female, Asian) are more likely to experience adverse events following antibiotics prescription. This work suggests child weight, in addition to age, should be used when prescribing antibiotics to children in primary care.

**Key message**

1. What is already known on this topic – summarise the state of scientific knowledge on thics subject before you did your study and why this study needed to be done:

   Prior research have emphasized the importance of precise dosing in paediatric antibiotic prescriptions, considering both age and weight, due to concerns about antimicrobial resistance and under-dosing in overweight children.

2. What this study adds – summarise what we now know as a result of this study that we did not know before:

   This study reveals that low-weight children, females, and minority ethnic groups face higher risks of adverse events following oral antibiotic prescriptions.

3. How this study might affect research, practice or policy – summarise the implications of this study:

   The findings suggest revising paediatric antibiotic prescribing guidelines to prioritize weight measurements, aiming to enhance dosing accuracy and reduce adverse outcomes in children.

## Introduction

### Background

The escalating concern over antimicrobial resistance has prompted increased scrutiny of antibiotic prescription practices worldwide (1). Striking a delicate equilibrium between safety and efficacy holds utmost significance when administering antibiotics to children, as any deviation from this balance can lead to unwanted consequences (2). Selecting antibiotics based on a recognized formulary, tailoring dosages to individual patient characteristics, and considering adverse drug reactions specific to each patient are crucial considerations in paediatric antibiotic therapy. More than a third of British children annually undergo antibiotic therapy, with oral penicillins constitute a substantial majority. They are frequently prescribed to address common respiratory tract infections (3–5). While most antibiotics have a low risk-to-benefit ratio for infectious illnesses (6), appropriate dosing is important.

The practice of prescribing oral penicillins as fractions of adult doses in children's age groups was established in the 1960s and maintained until 2011when concerns were raised about suboptimal dosing of amoxicillin for overweight children (7). Prescribing recommendations underwent revision in 2014 because of concerns about potential under-dosing (8). In 2014, the dosage was increased twofold in all age groups (9).

Paediatric drug dosing often demands precision with consideration of both age/development and weight. The British National Formulary for Children (BNFC) (10) details an age-banded system for most commonly prescribed oral antibiotics in primary care. This simplifies prescribing by eliminating the need for real-time weight measurement. However, this could lead to suboptimal dosing due to the non-linear relationship between age and weight in children(11). Age and weight necessitate consistent documentation and special attention in paediatric antibiotic prescriptions due to distinct growth trajectories compared to adults (12). In continental Europe, prescriptions are typically weight-based, offering a potentially more tailored approach. Given that boys generally have higher average weights

than girls (13), and children's weights exhibit significant variability (14); individualised dosing that considers both age and weight is crucial to safe prescribing of antibiotics. It would likely result in meeting more of the antibiotics' therapeutic indices (15). This necessitates a focused evaluation of dosing strategies to enhance accuracy in paediatric pharmacotherapy.

**Objective**

This study examines the association of adverse outcomes associated with oral antibiotic prescribing practices in paediatric primary care in Wales, with a specific emphasis on child weight. It examines major factors such as the age bands of children (based on the British National Formulary for children guidance), weight categories (grouped by centiles for sex and age), ethnicity, deprivation quintile, and sex. Our study employs a sophisticated statistical approach known as a multilevel multivariate logistic regression model (16). This model is tailored to handle within-patient correlation and heterogeneity, which is crucial given that multiple records for individual patients are present within our study period. Specifically, we aim to investigate the likelihood of adverse events following oral antibiotic prescriptions in general practice.

## Method

### Sample selection

In this retrospective cohort study, we used routinely-collected GP prescription data for antibiotics prescribed for children in Wales between the period of January 2014 and October, 2023. Prescriptions were identified using Read codes (version 2). The list of codes used are available in Appendix 1(17). The inclusion criteria for the study included children between the ages of 0 and 12 years within the study period who had been issued with primary care prescription for oral antibiotics. Child weight data from WLGP were linked using to the reference. Records with erroneous weights were excluded. Weights were considered erroneous if they were greater than 112kg or were recorded more than thirty days before or after oral antibiotics prescription date. The data linkage was carried out using the an encrypted Anonymised Linking Field (ALF) encrypted key in the SAIL databank (18). The antibiotics studied include common oral antibiotics classes used in children such as beta lactams (penicillins and cephalosporins), macrolides, dihydropyrimidines (trimethoprim), nitroimidazole (metronidazole), nitrofuran (nitrofurantoin) and lincosamides. A flow diagram of the cohort selection can be found in Figure 1.

### Risk Factors and data linkage

Patient demographic information such as age and gender were linked from the WLGP dataset; deprivation quintile data was linked from the Welsh Demographic Service Dataset (WDSD) (19); patient ethnicity data was linked from the Patient Episode Dataset for Wales (PEDW) (20); and, patient birth-weight data was linked from the National Community Child Health Database (NCCHD) (21). A brief description of the risk factors and their sources can be found in Appendix 2. This study acknowledges the multifaceted nature of pediatric antibiotic therapy and specifically focuses on key determinants, including: (a) Deprivation quintile. Given that socioeconomic inequalities exist and can be a major problem in appropriate healthcare delivery on a national scale (22). For this we utilized a

quintile categorization of populations into five groups based on their Welsh Index of Multiple Deprivation (WIMD) scores. These quintiles are used to represent different levels of deprivation, with the first quintile representing the least deprived areas and the fifth quintile representing the most deprived areas. (b) Ethnicity. As knowledge and use of antibiotics has been shown to differ in different ethnic groups (23). (c) Sex. There are physiological and anatomical differences between males and females, this could influence pharmacology of the prescribed antibiotics in respective sexes (24,25). (d) weight categories. the weight categories used were: Low Weight Category (LWC grouped by sex and age group; with weights equal or less than the 25$^{th}$ percentile), Normal Weight Category (NWC grouped by sex and age group; with weights above the 25$^{th}$ percentile and less than the 75$^{th}$ percentile) and, High Weight Category (HWC grouped by sex and age group; with weights equal or greater than the 75$^{th}$ percentile). And, (e) age bands. The age band categories studies were 0 to 28 days (neonates), 1 to 11 months, 1 to 4 years, and, 5 to 12 years. These represents the age bands in which children are often grouped during GP antibiotics prescription, based on the British National Formulary (BNF) for children. No imputation techniques were applied to the variables in this study to handle missing values. This decision was made to maintain the representativeness of the sample and avoid introducing assumptions.

NA values for deprivation quintiles and ethnicity were categorised under a separate category labelled as Missing.

**Adverse events identification**

Four binary foundation phase indicator variables were derived from the linked dataset; however, no formal assessment of causality was carried out. These include: (a) Patient death identified within 5 days of the initial antibiotic prescription; (b) Repeated antibiotic prescribing within 14 days of an initial antibiotic prescription; (c) non-elective hospital/emergency admission within 5 days of antibiotics prescription; and, (d) GP record of toxicity, poisoning, overdose, allergy or hypersensitivity reactions within 14 days of antibiotics prescription (read codes 2 used to identify

these events in the WLGP dataset can be found in Appendix 3). The data source used to generate these adverse events can be found in Appendix 4.

## Statistical analysis

A multilevel logistic regression model was used to measure the associated weight of each risk factor to the general adverse events outcome (as well as certain specific adverse event outcome based on availability of sufficient oral antibiotics prescription data). A sensitivity analysis was performed on the data, which included records that were more than 30 days before or after the antibiotic prescription date and weight values above 112kg. This analysis aimed to assess the impact of using potentially erroneous weight values for the children. Additional details can be found in Appendix 5. Data preparation was carried out on a DB2 SQL platform and the statistical analysis was performed on R version 4.0.3. using the following libraries: RODBC (26), tidyverse (27), lubridate (28), and caret (29).

## Logistic regression

We conducted a multilevel logistic regression for all the outcomes using the factors of interest as the covariates. The regression model was applied to generate Odds Ratio plots, using normal weight category as the reference in the weight category column, the highest quintile (deprivation quintile 5) as the reference for deprivation quintiles column, White ethnicity compared with all other ethnicities in the ethnic group column, and the 1 to 4 years age band compared with all other age bands in the age band column. These categories were selected as references based on the fact that they were the most common groups in their respective categories. The risk factors of adverse events following oral antibiotics prescription were presented with adjusted Odds Ratio (adjusted for age band, weight category, sex, deprivation quintile, and ethnicity) and 95% Confidence Interval (CI)

## Ethical Considerations

All access to SAIL datasets for research purposes is subject to Independent Information Governance Review Panel (IGRP) approval which involves a panel that considers ethical implications. Due to the anonymity of the data which is specifically collated by SAIL for research purposes, no additional ethical approval of this research was required (30)

Patient and Public Involvement

Patient and Public Involvement (PPI) was not directly incorporated into the design or conduct of this study. The data utilized for the design and implementation of this analysis was obtained from the SAIL databank, subject to approval from its Independent Information Governance Review Panel (IGRP) which includes members of the public.

We recognize the most effective way making the findings of this research relevant, accessible and impactful is to involve individuals and organisations which directly interface with these issues. For the dissemination of our findings, we plan to collaborate with the National Centre for Population Health and Wellbeing Research to involve their PPI group in interpreting the findings, identifying key messages, and advising how best to communicate with relevant charities and organizations, such as the Children's Commissioner for Wales. Additionally, we will seek the expertise of Dr. David Tuthill, a consultant paediatrician at the Children's Hospital for Wales in Cardiff, to facilitate outreach and promote awareness of our results among healthcare professionals.

## Results

### Sample characteristics

The study comprised 71,541 children meeting the inclusion criteria of a GP prescription for oral antibiotics (there were 139,571 prescriptions associated with 25,445 (18.2% of all ) general adverse drug outcomes.), coupled with a weight record from WLGP within 30 days of prescription. Of these, 36,762 were boys, among whom 21.3% experienced at least one adverse event, and 34,779 were girls, with 23.1% experiencing at least one adverse event. Among the participants, 22,140 fell into the low weight category (LWC), with 21.0% experiencing at least one adverse event, while 37,240 were categorized as normal weight children (NWC), among whom 21.1% experienced at least one adverse event. Additionally, 22,778 children were classified as high weight category (HWC), with 20.0% experiencing at least one adverse event. The overall summary of the study population can be found in Table 1.

| Variables | Total number | Total all outcomes N (%) | Total repeat antibiotics N (%) | Total hospital/emergency admission N (%) |
|---|---|---|---|---|
| **Sex** | | | | |
| **Female** | 34,779 | 8,037 (23.11) | 7,165 (20.60) | 1,455 (4.18) |
| **Male** | 36,762 | 7,846 (21.34) | 6,791 (18.47) | 1,737 (4.72) |
| **Age bands** | | | | |
| **0 - 28 days** | 442 | 55 (12.44) | 32 (7.24) | 24 (5.43) |
| **1 - 11 months** | 10,333 | 2,051 (19.85) | 1,557 (15.07) | 704 (6.81) |
| **1 - 4 years** | 27,295 | 6,670 (24.44) | 5,809 (21.28) | 1,413 (5.18) |
| **5 - 12 years** | 41,041 | 7,862 (19.40) | 7,238 (17.64) | 1,146 (2.79) |
| **Deprivation quintiles** | | | | |
| **1** | 18,133 | 3,926 (21.65) | 3,412 (18.82) | 840 (4.63) |
| **2** | 14,158 | 3,043 (21.49) | 2,670 (18.86) | 629 (4.44) |
| **3** | 12,038 | 2,636 (21.90) | 2,139 (19.51) | 482 (4.00) |
| **4** | 10,636 | 2,392 (22.49) | 2,145 (20.17) | 389 (3.66) |
| **5** | 10,829 | 2,371 (21.89) | 2,139 (19.75) | 425 (3.92) |
| **Missing** | 7734 | 1,707 (22.07) | 1,395 (18.04) | 446 (5.77) |
| **Weight categories** | | | | |
| **Low Weight Category** | 22,140 | 4,651 (21.01) | 3,960 (17.89) | 1,055 (4.77) |
| **Normal Weight Category** | 37,240 | 7,844 (21.06) | 6,870 (18.45) | 1,516 (4.07) |
| **High Weight Category** | 22,788 | 4,556 (19.99) | 4,078 (17.90) | 727 (3.19) |
| **Ethnic group** | | | | |
| **Asians** | 18,914 | 4945 (26.14) | 4,255 (22.50) | 1231 (6.51) |
| **Blacks** | 605 | 118 (19.5) | 99 (16.36) | 30 (4.96) |
| **Mixed** | 1,828 | 324 (17.72) | 280 (15.32) | 83 (4.54) |
| **other Races** | 627 | 127 (20.26) | 112 (17.86) | 27 (4.31) |
| **Whites** | 39,071 | 8,135 (20.82) | 7,258 (18.58) | 1,414 (3.62) |
| **Missing** | 10,496 | 2,234 (21.28) | 1952 (18.60) | 407 (3.88) |

*Table 1: Demographic data for study cohort. LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African,*

*White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic group*

Logistic regression

Children in the low weight category had higher odds of an adverse reaction (aOR [95% CI]: 1.06 (1.01, 1.11)) compared to those categorized in the normal weight category; while children in the high weight category had lower odds 0.92 (0.88, 0.96). Females had higher odds 1.13 (1.07, 1.19) than males having adjusted for all other factors. Children in 0 to 28 days and 5 to 12 years age bands had lower odds (0.60 (0.45, 0.81), and 0.76 (0.73, 0.81) respectively) than those in the 1 to 4 months age band. Asian ethnicity had higher odds than the whites (with odds ratios of 1.22 (1.14, 1.29)). The risk factors, odds ratios, upper and lower confidence intervals can be found in Supplementary Table, Figure 2, Figure 3, and, Figure 4.

## Discussion

Children who were of low weight, female, or of Asian ethnic backgrounds had higher odds of adverse events following oral antibiotic prescriptions compared to their respective reference groups having adjusted for age, sex, ethnic group, deprivation quintiles, and weight category. Conversely, children categorized as high weight and children in 0 to 28 days and 5 to 12 years age groups demonstrated lower odds of experiencing adverse events. Similarly, those of low weight, smaller children (aged up-to 28 days or between one to eleven months), of Asian ethnicity, or residing in deprivation quintile 1 were found to have an increased odds of an emergency hospital admission within 5 days of the initial oral antibiotic prescribed. This was analogous to the result from investigating the repeat primary care prescription of oral antibiotics within 14 days of the initial oral antibiotic as children who were of Asian ethnicity, or female were found to have higher odds of this subset of adverse event. The reason for the observed trend is unknown and requires further investigation, ideally in a more ethnically diverse population with a more equal representation of the various age bands.

Our findings align with Bielicki et al.'s assertion that weight, in addition to age bands, is a crucial variable in antibiotic prescription for children (8). Specifically, our results indicate that children classified as low weight for their sex and age band exhibit elevated odds of adverse events, consistent with existing literature (31). Conversely, our observation that high weight category children have lower odds of adverse events compared to those of normal weight provides further support to this notion. Taken together, these findings underscore the importance of considering weight alongside age when prescribing oral antibiotics to children, offering a potential avenue to mitigate adverse events in this population.

Studies have shown that babies of Asian (Indian, Pakistani, Bangladeshi, Chinese, and other Asian ethnic groups) ethnicity tend to have lower body weights in comparison to those of Caucasian ancestry (32,33). This observation may suggest that the increased odds of general adverse events

among minority ethnic groups could be attributed, at least in part, to the lower birth weight prevalent in these populations (34). Children of other ethnicity show a tendency towards very high odds (OR 1.84 (1.53, 2.19)) of adverse events. However, the prevalence of this ethnic group in Wales is small (0.86%) and results in a wide confidence interval so the likely odds ratio is inconclusive and would require further investigation.

Sex also appears to be associated with general adverse event outcome in children prescribed with oral antibiotics; with our result suggesting that females have higher odds than males to experience a general adverse event. Given that boys tend to have a higher weight trajectory than girls (35); and, there is no difference in dosage based on sex, the observed increase in odds is likely linked to the weight difference between the sexes. This would further emphasize the need to prioritize weight measurement when prescribing oral antibiotics to children.

**Strengths and limitations**

This study was carried out by linking routinely collected data for the whole population of Wales over a period of 10 years. It provides a valuable resource to help inform policy aimed at improving paediatric health outcomes and preventing the incidences of adverse events. Important patient demographics such as sex, deprivation quintiles, age group, and weight have been investigated to help healthcare professionals improve individualized care for children in need of oral antibiotics.

Two major limitations were identified in this study. Firstly, a formal causality assessment was not conducted (36). A significant challenge in pharmacovigilance is accurately pinpointing the root cause of adverse reactions to specific drugs (37). Despite implementing rigorous measures to establish a clear link between observed adverse reactions and the prescribed oral antibiotic, the absence of formal causality assessment limits the strength of our conclusions. Secondly, the study suffered from inadequate representation of minority ethnic groups in Wales (38), which hindered a comprehensive

assessment of ethnicity's impact on the measured outcome. Addressing these limitations in future research endeavors is crucial to enhance the robustness and generalizability of findings.

This study lays the groundwork for understanding the importance of weight measurement in the prescription of oral antibiotics. While a detailed exploration of the correlation between risk factors and adverse events necessitates focusing on specific classes of antibiotics and their indications, future research examining individual oral antibiotics can offer further insights to inform healthcare policies and enhance patient care.

**Conclusion**

Our study sheds light on the significant role of weight as a crucial variable in determining adverse events following oral antibiotic prescriptions in children. Our findings highlight that children who are of low weight, female, or, of certain minority ethnic backgrounds are at heightened risk of adverse events. Conversely, children categorized as high weight and older children demonstrate lower odds of experiencing adverse events. These results underscore the importance of considering weight alongside other demographic factors when prescribing oral antibiotics to children in primary care. By prioritizing weight measurement, healthcare providers can better tailor antibiotic prescriptions, potentially mitigating adverse drug reactions and improving outcomes for pediatric patients.

This finding does not overlook the fact that weight may serve as a proxy for various underlying conditions and factors that can predispose children to adverse outcomes following oral antibiotic prescriptions. While weight itself may not be the direct issue, it signifies potential links with factors such as malnutrition, intrauterine growth restriction (IUGR), neglect, prematurity, immunocompromise, and other health conditions. By disregarding weight and dosing based solely on averages, we overlook the complexities of individual health profiles and miss opportunities to tailor treatments accordingly. Weight, as a measure of growth and development, is integral to monitoring overall health status. Our study underscores the importance of recognizing weight as more than just a number—it represents a critical aspect of a child's health that warrants careful consideration in antibiotic prescription practices to optimize outcomes and mitigate adverse events.

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**List of Abbreviations**

GP: General practice.

BNFC: British National Formulary for Children.

NCCHD: National Community Child Health Database.

ALF: Anonymised Linkage Field.

SAIL: Secure Anonymised Information Linkage.

WLGP: Welsh Longitudinal General Practice Dataset.

PEDW: Patient Episode Dataset for Wales

WDSD: Welsh Demographic Service Dataset

WIMD: Welsh Index of Multiple Deprivation

LWC: Low Weight Category

NWC: Normal Weight Category

HWC: High Weight Category

BNF: British National Formulary

ADDE: Annual District Death Extract

EDDS: Emergency Department Datasets

DB2 SQL: Structured Query Language developed by IBM

CI: Confidence Interval

aOR: Adjusted Odds Ratio

IGRP: Independent Information Governance Review Panel

WHO: World Health Organization

**Figure, Tables, and, Appendices Caption**

**Figures:**

One figure was provided with the manuscript:

1. Flow chart showing inclusion and exclusions from WLGP, NCCHD.
2. Forest plot of odds ratio of combined adverse events after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.
3. Forest plot of odds ratio of repeat antibiotics prescription after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.
4. Forest plot of odds ratio of emergency hospital admission after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.

**Tables:**

Two tables were provided with the manuscript:

1. Table 1: Demographic data for study cohort. LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups
2. Supplementary Table: Table showing the odds ratios of the risk factors for the respective adverse events (95% CI). LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other

Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups. Reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, Weight categories: normal weigh category.

**Appendices:**

Five supplementary documents were provided with the manuscript:

1. Appendix 1: Read codes for the oral antibiotics
2. Appendix 2: Risk factors for adverse events in children prescribed oral antibiotics in the GP
3. Appendix 3: Read Codes for records of adverse events in the GP
4. Appendix 4: Adverse events data source
5. Appendix 5: Information on sensitivity group

**Competing Interests**

The authors declare that they have no competing interests.

**Ethics Approval**

All access to SAIL datasets for research purposes is subject to Independent Information Governance Review Panel (IGRP) approval which involves a panel that considers ethical implications. Due to the anonymity of the data which is specifically collated by SAIL for research purposes, no additional ethical approval of this research was required.

**Contributorship Statement**

Ayodele Vincent Opatola serves as the guarantor for the integrity of the work as a whole.

Contributorship:

- Ayodele Vincent Opatola: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing, Visualization.
- Micheal Seaborne: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Writing – Review & Editing.
- Jon Kennedy: Conceptualization, Methodology, Software, Validation, Resources, Writing – Review & Editing.
- Hamish Laing: Investigation, Writing – Review & Editing.
- Rhiannon K Owen: Methodology, Formal Analysis, Writing – Review & Editing.
- Dyfrig Hughes: Investigation, Writing – Review & Editing.
- Robert Bracchi: Investigation, Writing – Review & Editing.
- David Tuthill: Investigation, Writing – Review & Editing.
- Sinead Brophy: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Data Curation, Writing – Review & Editing, Supervision, Project Administration, Funding Acquisition.

**Data Sharing Statement**

The data is held in the Secure Anonymised Information Linkage Databank (Data Science Building, Swansea University, Singleton Park, SA28PP) TRE (Trusted Research Environments) and is available through application. The data is restricted and requires review by Information Governance Review Panel (IGRP); they provide independent guidance and advice on Information Governance policies, procedures and processes for SAIL Databank. All necessary information can be found in the following link: https://saildatabank.com/contact/.

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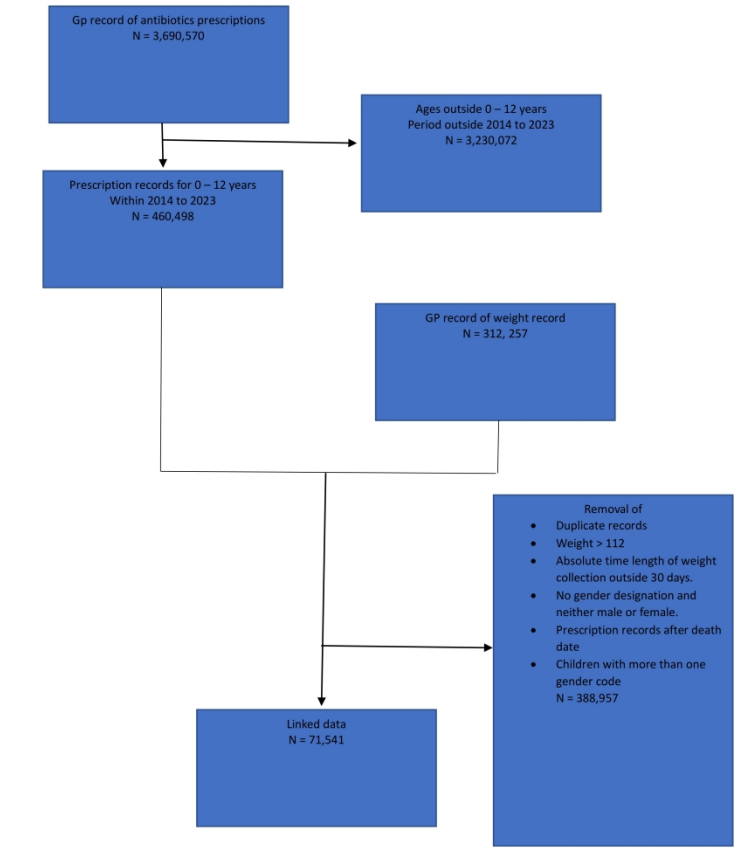
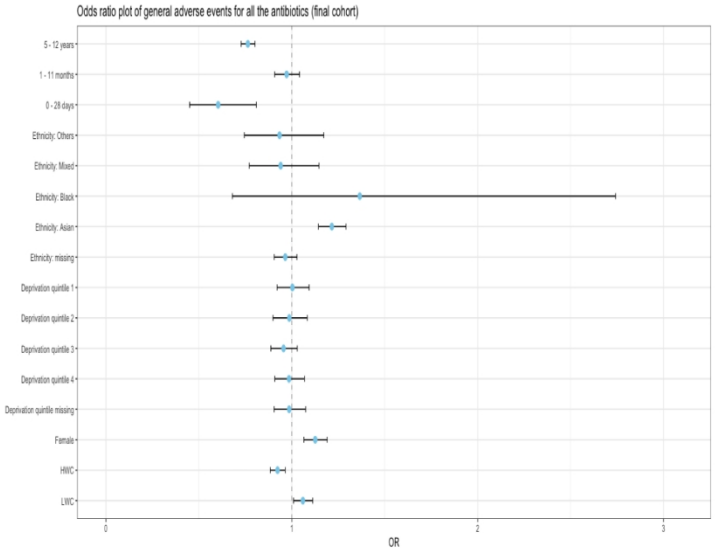



*Figure 1: Flow chart showing inclusion and exclusions from WLGP.*

Flow chart showing inclusion and exclusions from WLGP.

1093x1547mm (96 x 96 DPI)

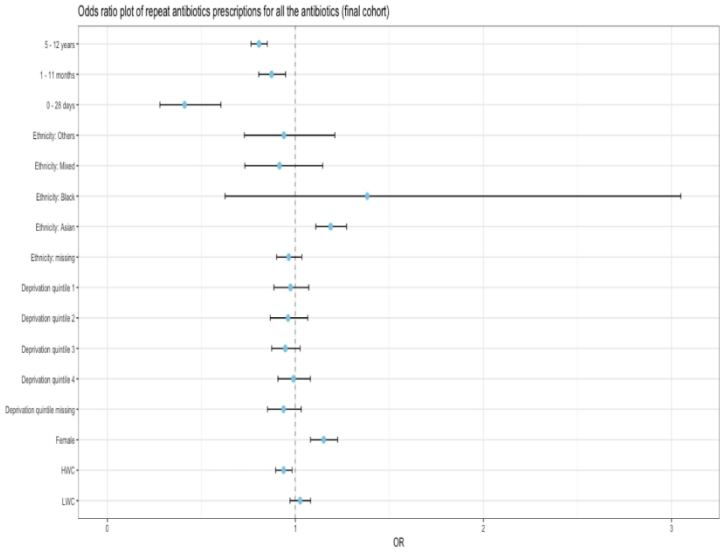
*Figure 2: Forest plot of odds ratio of combined adverse events after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.*




Forest plot of odds ratio of combined adverse events after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.

1093x1547mm (96 x 96 DPI)

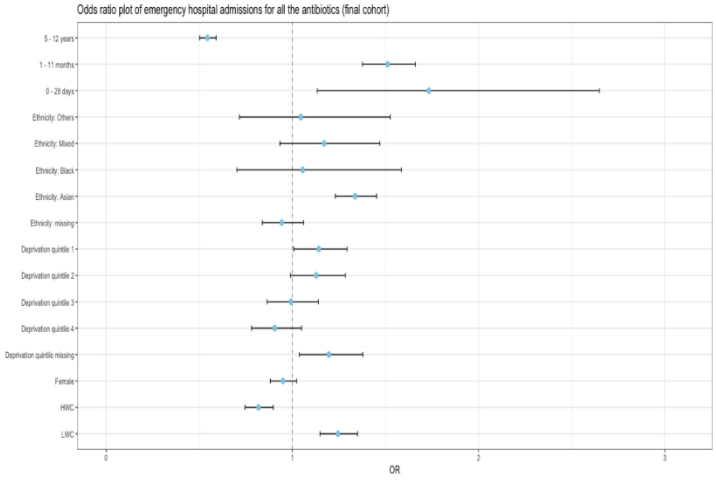
*Figure 3: Forest plot of odds ratio of repeat antibiotics prescription after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.*




Forest plot of odds ratio of repeat antibiotics prescription after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.

1093x1547mm (96 x 96 DPI)

*Figure 4: Forest plot of odds ratio of emergency hospital admission after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.*




Forest plot of odds ratio of emergency hospital admission after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.

1093x1547mm (96 x 96 DPI)

**APPENDIX 1:** Read codes for the oral antibiotics

| Read codes | Description |
|---|---|
| e15.. | PHENOXYMETHYLPENICILLIN |
| e151. | PHENOXYMETHYLPENICILLIN 250mg capsules |
| e152. | PHENOXYMETHYLPENICILLIN 125mg capsules |
| e153. | PHENOXYMETHYLPENICILLIN 250mg tablets |
| e154. | PHENOXYMETHYLPENICILLIN 62.5mg/5mL syrup |
| e155. | PHENOXYMETHYLPENICILLIN 125mg/5mL syrup |
| e156. | PHENOXYMETHYLPENICILLIN granules 125mg/sachet |
| e157. | PHENOXYMETHYLPENICILLIN 250mg/5mL syrup |
| e158. | *APSIN VK 250mg tablets |
| e159. | *APSIN VK 125mg/5mL syrup |
| e15A. | PHENOXYMETHYLPENICILLIN 125mg tablets |
| e15B. | *RIMAPEN 250mg tablets |
| e15a. | APSIN VK 250mg/5mL syrup |
| e15b. | *CRYSTAPEN V 125mg/5mL syrup |
| e15c. | *CRYSTAPEN V 250mg/5mL syrup |
| e15d. | *DISTAQUAINE V-K 125mg tablets |
| e15e. | *DISTAQUAINE V-K 250mg tablets |
| e15f. | DISTAQUAINE V-K 62.5mg/5mL syrup |
| e15g. | DISTAQUAINE V-K 125mg/5mL syrup |
| e15h. | *DISTAQUAINE 250mg/5mL syrup |
| e15i. | *ECONOCIL VK 250mg capsules |
| e15j. | *ECONOCIL VK 125mg tablets |
| e15k. | *ECONOCIL VK 250mg tablets |
| e15l. | *STABILLIN V-K 250mg tablets |
| e15m. | STABILLIN V-K 62.5mg/5mL syrup |
| e15n. | *STABILLIN V-K 125mg/5mL syrup |
| e15o. | *STABILLIN V-K 250mg/5mL syrup |
| e15p. | *V-CIL-K 250mg capsules |
| e15q. | *V-CIL-K 125mg tablets |
| e15r. | *V-CIL-K 250mg tablets |
| e15s. | V-CIL-K PAEDIATRIC 62.5mg/5mL syrup |
| e15t. | V-CIL-K PAEDIATRIC 125mg/5mL syrup |
| e15u. | *V-CIL-K 250mg/5mL syrup |
| e15v. | *TENKICIN 250mg tablets |
| e15w. | PHENOXYMETHYLPENICILLIN 125mg/5mL s/f oral solution |
| e15x. | PHENOXYMETHYLPENICILLIN 250mg/5mL s/f oral solution |
| e221. | FLUCLOXACILLIN 250mg capsules |
| e222. | FLUCLOXACILLIN 500mg capsules |
| e223. | FLOXAPEN 250mg capsules |
| e224. | FLOXAPEN 500mg capsules |
| e225. | FLOXAPEN 125mg/5mL syrup |
| e226. | FLOXAPEN FORTE 250mg/5mL syrup |
| e22A. | FLUCLOXIN 125mg/5mL oral suspension |
| e22B. | FLUCLOXACILLIN 250mg/5mL oral suspension |
| e22C. | FLUCLOXACILLIN 125mg/5mL s/f oral solution |
| e22D. | FLUCLOXACILLIN 250mg/5mL s/f oral solution |
| e22a. | *LADROPEN 250mg capsules |
| e22b. | *LADROPEN 500mg capsules |
| e22c. | *STAFOXIL 250mg capsules |

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|---|---|
| e22d. | *STAFOXIL 500mg capsules |
| e22e. | *STAPHLIPEN 250mg capsules |
| e22f. | *STAPHLIPEN 500mg capsules |
| e22j. | FLUCLOXACILLIN 125mg/5mL syrup |
| e22k. | FLUCLOXACILLIN 250mg/5mL syrup |
| e22l. | *FLUCLOMIX 250mg capsules |
| e22m. | FLUCLOMIX 500mg capsules |
| e22n. | LADROPEN 125mg/5mL suspension 100mL |
| e22t. | *GALFLOXIN 250mg capsules |
| e22u. | *GALFLOXIN 500mg capsules |
| e22v. | FLUCLOXACILLIN 125mg/5mL oral suspension |
| e22w. | *ZOXIN 250 capsules |
| e22x. | *ZOXIN 500 capsules |
| e22y. | *FLUCLOXIN 250mg capsules |
| e22z. | *FLUCLOXIN 500mg capsules |
| e311. | AMOXICILLIN 250mg capsules |
| e312. | AMOXICILLIN 500mg capsules |
| e313. | *AMOXIDIN 250mg capsules |
| e314. | *AMOXIDIN 500mg capsules |
| e315. | AMOXIL 250mg capsules |
| e316. | AMOXIL 500mg capsules |
| e317. | AMOXIL 500mg dispersible tablets |
| e318. | *AMOXIL 125mg/5mL syrup |
| e319. | *AMOXIL SF 125mg/5mL syrup |
| e31A. | *AMIX 125mg/5mL suspension |
| e31B. | *AMIX 250mg/5mL suspension |
| e31C. | *AMRIT 125mg/5mL suspension |
| e31D. | *AMRIT 250mg/5mL suspension |
| e31E. | *AMRIT 250mg capsules |
| e31F. | *AMRIT 500mg capsules |
| e31G. | *AMOPEN 250mg capsules |
| e31H. | *AMOPEN 500mg capsules |
| e31I. | *AMOPEN 125mg/5mL suspension |
| e31J. | *AMOPEN 250mg/5mL suspension |
| e31K. | FLEMOXIN SOLUTAB 375mg dispersible tablets |
| e31L. | FLEMOXIN SOLUTAB 750mg dispersible tablets |
| e31M. | AMOXIL FIZTAB 125mg chewable tablets |
| e31N. | AMOXIL FIZTAB 250mg chewable tablets |
| e31O. | AMOXIL FIZTAB 500mg chewable tablets |
| e31P. | AUGMENTIN 250/62 in 5mL suspension |
| e31Q. | CO-AMOXICLAV 125/31mg in 5mL suspension |
| e31R. | *AMOXYMED 250mg capsules |
| e31S. | *AMOXYMED 125mg/5mL syrup |
| e31T. | AUGMENTIN 625mg tablets |
| e31U. | CO-AMOXICLAV 625mg tablets |
| e31V. | ALMODAN 125mg/5mL sugar free syrup |
| e31W. | ALMODAN 250mg/5mL sugar free syrup |
| e31X. | CO-AMOXICLAV 400/57mg in 5mL sugar free suspension |
| e31Y. | AUGMENTIN-DUO 400/57 in 5mL sugar free suspension |
| e31a. | *AMOXIL SF 250mg/5mL syrup |
| e31b. | AMOXIL 125mg/1.25mL paediatric suspension |
| e31c. | *AMOXIL SF 750mg sachets |

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|---|---|
| e31d. | *AMOXIL SF 3g sachets |
| e31h. | AUGMENTIN 375mg tablets |
| e31i. | AUGMENTIN 375mg dispersible tablets |
| e31j. | AUGMENTIN JUNIOR 125/62 in 5mL suspension |
| e31k. | AUGMENTIN 125/31 in 5mL paediatric suspension |
| e31n. | *ALMODAN 250mg capsules |
| e31o. | *ALMODAN 500mg capsules |
| e31p. | *ALMODAN 125mg/5mL syrup |
| e31q. | *ALMODAN 250mg/5mL syrup |
| e31t. | CO-AMOXICLAV 375mg tablets |
| e31u. | CO-AMOXICLAV 375mg dispersible tablets |
| e31v. | CO-AMOXICLAV 125mg/5mL suspension |
| e31w. | CO-AMOXICLAV 125mg/mL suspension |
| e31z. | CO-AMOXICLAV 250/62 in 5mL suspension |
| e321. | AMPICILLIN 250mg capsules |
| e322. | AMPICILLIN 500mg capsules |
| e323. | AMPICILLIN 125mg/5mL mixture |
| e324. | AMPICILLIN 250mg/5mL mixture |
| e325. | *AMFIPEN 250mg capsules |
| e326. | *AMFIPEN 500mg capsules |
| e327. | *AMFIPEN 125mg/5mL syrup |
| e328. | *AMFIPEN 250mg/5mL syrup |
| e329. | *AMFIPEN 250mg injection |
| e32A. | *RIMACILLIN 250mg capsules |
| e32B. | *RIMACILLIN 500mg capsules |
| e32C. | *RIMACILLIN 125mg/5mL syrup |
| e32D. | *RIMACILLIN 250mg/5mL syrup |
| e32E. | *AMPICILLIN 250mg injection |
| e32F. | AMPICILLIN 500mg injection |
| e32G. | AMPICILLIN 125mg/1.25mL paediatric suspension |
| e32H. | AMPICILLIN 125mg/5mL sugar free suspension |
| e32J. | AMPICILLIN 250mg/5mL sugar free suspension |
| e32K. | Ampicillin 125mg/5mL oral suspension |
| e32b. | *AMPILAR 250mg capsules |
| e32c. | *AMPILAR 500mg capsules |
| e32d. | *AMPILAR 125mg/5mL syrup |
| e32e. | *AMPILAR 250mg/5mL syrup |
| e32f. | *BRITCIN 250mg capsules |
| e32g. | *BRITCIN 500mg capsules |
| e32h. | PENBRITIN 250mg capsules |
| e32i. | PENBRITIN 500mg capsules |
| e32j. | *PENBRITIN 125mg tablets |
| e32k. | PENBRITIN 125mg/5mL syrup |
| e32l. | PENBRITIN 250mg/5mL syrup |
| e32m. | PENBRITIN 100mg/mL paediatric suspension |
| e32p. | *VIDOPEN 250mg capsules |
| e32q. | *VIDOPEN 500mg capsules |
| e32r. | *VIDOPEN 125mg/5mL syrup |
| e32s. | *VIDOPEN 250mg/5mL syrup |
| e32v. | *AMPITRIN 250mg capsules |
| e32w. | *AMPITRIN 500mg capsules |
| e32x. | AMPITRIN 125mg/5mL oral suspension |
| e32y. | AMPITRIN 250mg/5mL oral suspension |
| e32z. | *AMPICILLIN 125mg tablets |

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|---|---|
| e334. | *FLU-AMP 250/250mg capsules |
| e335. | MAGNAPEN 500mg capsules |
| e336. | *MAGNAPEN 250mg/5mL syrup |
| e339. | CO-FLUAMPICIL 250mg/250mg capsules |
| e33a. | CO-FLUAMPICIL 125/125mg syrup |
| e33h. | *UNASYN 375mg tablets |
| e33i. | *SULTAMICILLIN 375mg tablets |
| e3A.. | AMOXICILLIN [2] |
| e3A1. | *RESPILLIN 250mg capsules |
| e3A2. | *RESPILLIN 500mg capsules |
| e3A3. | RESPILLIN 125mg/5mL oral suspension |
| e3A4. | RESPILLIN 250mg/5mL oral suspension |
| e3A5. | RESPILLIN 125mg/5mL sugar free suspension |
| e3A6. | RESPILLIN 250mg/5mL sugar free suspension |
| e3A7. | *AMICLAV 250mg/125mg tablets |
| e3A8. | *RANCLAV 375mg tablets |
| e3A9. | *RANCLAV 625mg tablets |
| e3AA. | RANCLAV 125mg/31mg sugar free suspension |
| e3AB. | RANCLAV 250mg/62mg sugar free suspension |
| e3z.. | AMOXICILLIN [GENERIC ADDITIONS] |
| e3z1. | *AMORAM 250mg capsules |
| e3z2. | *AMORAM 500mg capsules |
| e3z3. | *AMORAM 125mg/5mL suspension |
| e3z4. | *AMORAM 250mg/5mL suspension |
| e3z5. | AMIX 250mg capsules |
| e3z6. | AMIX 500mg capsules |
| e3z7. | *GALENAMOX 250mg capsules |
| e3z8. | *GALENAMOX 500mg capsules |
| e3z9. | GALENAMOX 125mg/5mL suspension |
| e3zA. | GALENAMOX TP 250mg capsules |
| e3zB. | GALENAMOX TP 500mg capsules |
| e3zC. | *ZOXYCIL 250 capsules |
| e3zD. | *ZOXYCIL 500 capsules |
| e3zE. | AMOXICILLIN 125mg/sachet sugar free powder |
| e3zF. | AMOXIDENT 250mg capsules |
| e3zG. | AMOXIDENT 500mg capsules |
| e3za. | GALENAMOX 250mg/5mL suspension |
| e3zb. | GALENAMOX 125mg/5mL sugar free suspension |
| e3zc. | GALENAMOX 250mg/5mL sugar free suspension |
| e3zf. | *RIMOXALLIN 125mg/5mL syrup |
| e3zg. | *RIMOXALLIN 250mg capsules |
| e3zh. | *RIMOXALLIN 500mg capsules |
| e3zj. | *RIMOXALLIN 250mg/5mL syrup |
| e3zk. | AMOXICILLIN 125mg/5mL sugar free suspension |
| e3zl. | AMOXYCILLIN 500mg dispersible tablets |
| e3zm. | AMOXICILLIN 125mg/5mL syrup |
| e3zn. | AMOXICILLIN 250mg/5mL syrup |
| e3zo. | AMOXICILLIN 125mg/1.25mL paediatric suspension |
| e3zp. | AMOXYCILLIN powder 750mg/sachet |
| e3zq. | AMOXICILLIN powder 3g/sachet |
| e3zu. | AMOXICILLIN 250mg/5mL sugar free suspension |
| e3zv. | AMOXYCILLIN 125mg s/f chewable tablets |
| e3zw. | AMOXYCILLIN 250mg s/f chewable tablets |
| e3zx. | AMOXYCILLIN 500mg s/f chewable tablets |

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|---|---|
| e3zy. | AMOXYCILLIN 375mg s/f dispersible tablets |
| e3zz. | AMOXYCILLIN 750mg s/f dispersible tablets |
| e52.. | PIVMECILLINAM HYDROCHLORIDE |
| e521. | SELEXID 200mg tablets |
| e522. | SELEXID 100mg/sachet suspension |
| e52v. | PIVMECILLINAM 100mg/sachet suspension |
| e52w. | PIVMECILLINAM HYDROCHLORIDE 200mg tablets |
| e69.. | CEFALEXIN |
| e691. | CEFALEXIN 250mg capsules |
| e692. | CEFALEXIN 500mg capsules |
| e693. | CEFALEXIN 250mg tablets |
| e694. | CEFALEXIN 500mg tablets |
| e695. | CEFALEXIN 125mg/5mL mixture |
| e696. | CEFALEXIN 250mg/5mL mixture |
| e697. | CEFALEXIN 500mg/5mL syrup |
| e698. | CEPOREX 250mg capsules |
| e699. | CEPOREX 500mg capsules |
| e69A. | *TENKOREX 250mg capsules |
| e69B. | *TENKOREX 500mg capsules |
| e69C. | *TENKOREX 125mg/5mL suspension |
| e69D. | *TENKOREX 250mg/5mL suspension |
| e69E. | *TENKOREX 500mg tablets |
| e69F. | *KIFLONE 500mg tablets |
| e69G. | *KIFLONE 250mg capsules |
| e69H. | *KIFLONE 500mg capsules |
| e69J. | *KIFLONE 125mg/5mL syrup |
| e69K. | *KIFLONE 250mg/5mL syrup |
| e69a. | CEPOREX 250mg tablets |
| e69b. | CEPOREX 500mg tablets |
| e69c. | CEPOREX 125mg/1.25mL paediatric drops |
| e69d. | *CEPOREX 125mg/5mL suspension |
| e69e. | *CEPOREX 250mg/5mL suspension |
| e69f. | CEPOREX 125mg/5mL syrup |
| e69g. | CEPOREX 250mg/5mL syrup |
| e69h. | CEPOREX 500mg/5mL syrup |
| e69i. | KEFLEX 250mg capsules |
| e69j. | KEFLEX 500mg capsules |
| e69k. | KEFLEX 250mg tablets |
| e69l. | KEFLEX 500mg tablets |
| e69m. | KEFLEX 125mg/5mL suspension |
| e69n. | KEFLEX 250mg/5mL suspension |
| e69o. | KEFLEX-C 125mg chewable tablets |
| e69p. | KEFLEX-C 250mg chewable tablets |
| e69q. | *CEPOREX 1g tablets |
| e69v. | CEFALEXIN 125mg/5mL syrup |
| e69w. | CEFALEXIN 250mg/5mL syrup |
| e69x. | *CEPHALEXIN 1g tablets |
| e69y. | CEPHALEXIN 125mg/1.25mL paediatric drops |
| e61.. | CEFACLOR |
| e611. | *DISTACLOR 250mg capsules |
| e612. | DISTACLOR 125mg/5mL suspension |
| e613. | DISTACLOR 250mg/5mL suspension |
| e614. | CEFACLOR 250mg capsules |
| e615. | CEFACLOR 125mg/5mL suspension |

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|---|---|
| e616. | CEFACLOR 250mg/5mL suspension |
| e617. | DISTACLOR 500mg capsules |
| e618. | CEFACLOR 500mg capsules |
| e619. | DISTACLOR MR 375mg m/r tablets |
| e61A. | KEFTID 250mg capsules |
| e61B. | KEFTID 500mg capsules |
| e61C. | CEFACLOR 125mg/5mL sugar free suspension |
| e61D. | CEFACLOR 250mg/5mL sugar free suspension |
| e61E. | KEFTID 125mg/5mL sugar free suspension |
| e61F. | KEFTID 250mg/5mL sugar free suspension |
| e61G. | BACTICLOR MR 375mg m/r tablets |
| e61a. | CEFACLOR 375mg m/r tablets |
| e61b. | DISTACLOR MR 500mg m/r tablets |
| e61c. | *CEFACLOR 500mg m/r tablets |
| e62.. | CEFADROXIL |
| e621. | *BAXAN 500mg capsules |
| e622. | *BAXAN 125mg/5mL suspension |
| e623. | *BAXAN 250mg/5mL suspension |
| e624. | *BAXAN 500mg/5mL suspension |
| e625. | CEFADROXIL 125mg/5mL suspension |
| e626. | CEFADROXIL 250mg/5mL suspension |
| e627. | CEFADROXIL 500mg capsules |
| e62w. | *CEFADROXIL 500mg capsules |
| e62x. | *CEFADROXIL 500mg capsules |
| e62z. | CEFADROXIL 500mg/5mL suspension |
| e684. | ZINNAT 125mg tablets |
| e685. | ZINNAT 250mg tablets |
| e686. | CEFUROXIME 125mg tablets |
| e687. | CEFUROXIME 250mg tablets |
| e689. | ZINNAT 125mg/5mL suspension |
| e68a. | CEFUROXIME 125mg/5mL suspension |
| e68b. | ZINNAT 125mg/sachet suspension |
| e68c. | CEFUROXIME 125mg/sach for suspension |
| e6h.. | CEFIXIME |
| e6h1. | CEFIXIME 200mg tablets |
| e6h2. | CEFIXIME 100mg/5mL suspension |
| e6h3. | SUPRAX 200mg tablets |
| e6h4. | SUPRAX 100mg/5mL paediatric suspension 37.5mL |
| e6h5. | SUPRAX 100mg/5mL paediatric suspension 75mL |
| e6h6. | SUPRAX 100mg/5mL paediatric suspension 50mL |
| e6h7. | SUPRAX 100mg/5mL paediatric suspension 100mL |
| e911. | ERYTHROMYCIN 250mg e/c tablets |
| e912. | ERYTHROMYCIN 500mg tablets |
| e913. | ERYTHROMYCIN STEARATE 250mg tablets |
| e914. | ERYTHROMYCIN STEARATE 500mg tablets |
| e915. | ARPIMYCIN 125mg/5mL sugar free suspension |
| e916. | ARPIMYCIN 250mg/5mL sugar free suspension |
| e917. | ARPIMYCIN 500mg/5mL sugar free suspension |
| e918. | *ERYCEN 250mg tablets |
| e919. | *ERYCEN 500mg tablets |
| e91A. | ERYTHROPED FORTE granules 500mg/sachet |
| e91B. | ERYTHROPED P.I. granules 125mg/sachet |
| e91C. | ERYTHROPED P.I. 125mg/5mL sugar free suspension 140mL |

| | |
|---|---|
| e91D. | ERYTHROPED 250mg/5mL sugar free suspension 140mL |
| e91E. | ERYTHROMYCIN 125mg/5mL sugar free suspension |
| e91F. | ERYTHROMYCIN 250mg/5mL sugar free suspension |
| e91G. | *ROMMIX-125 suspension |
| e91H. | *ROMMIX-250 tablets |
| e91I. | KERYMAX 250mg e/c granules in capsules |
| e91J. | *ROMMIX-500 tablets |
| e91L. | *ERYTHROMYCIN 250mg capsules |
| e91M. | ERYTHROMYCIN 125mg/sachet granules |
| e91N. | ERYTHROMYCIN 250mg/sachet granules |
| e91P. | ERYTHROMYCIN 500mg/sachet granules |
| e91Q. | ERYTHROMYCIN 1g/sachet granules |
| e91R. | ERYTHROMYCIN 500mg/5mL sugar free suspension |
| e91S. | TILORYTH 250mg e/c granules in capsules |
| e91T. | ERYMIN 250mg/5mL sugar free suspension |
| e91U. | ARPIMYCIN 125mg/5mL suspension |
| e91V. | ARPIMYCIN 250mg/5mL suspension |
| e91W. | ARPIMYCIN 500mg/5mL suspension |
| e91X. | ERYTHROMYCIN 250mg e/c granules in capsules |
| e91Y. | ERYTHROPED FORTE SF 500mg/5mL sugar free suspension |
| e91Z. | PRIMACINE 125mg/5mL suspension 100mL |
| e91a. | ERYMAX 250mg e/c granules in capsules |
| e91b. | ERYTHROCIN 250mg tablets |
| e91c. | ERYTHROCIN 500mg tablets |
| e91e. | *ERYTHROLAR 250mg tablets |
| e91f. | *ERYTHROLAR 500mg tablets |
| e91g. | ERYTHROLAR 250mg/5mL suspension |
| e91h. | *ERYTHROMID 250mg tablets |
| e91i. | *ERYTHROMID DS 500mg tablets |
| e91j. | ERYTHROPED P.I. 125mg/5mL suspension |
| e91k. | ERYTHROPED 250mg/5mL suspension 140mL |
| e91l. | ERYTHROPED 250mg/sachet sugar free granules |
| e91m. | ERYTHROPED FORTE 500mg/5mL suspension |
| e91n. | ERYTHROPED A 500mg tablets |
| e91o. | *ILOSONE 250mg capsules |
| e91p. | *ILOSONE 500mg tablets |
| e91q. | *ILOSONE 125mg/5mL suspension |
| e91r. | ILOSONE FORTE 250mg/5mL suspension |
| e91s. | *ILOTYCIN 250mg tablets |
| e91t. | RETCIN 250mg tablets |
| e91u. | ERYTHROMYCIN 125mg/5mL suspension |
| e91v. | ERYTHROMYCIN 250mg/5mL suspension |
| e91w. | ERYTHROMYCIN 500mg/5mL suspension |
| e91x. | ERYTHROPED A 1g/sachet granules |
| e91y. | ERYMAX SPRINKLE 125mg capsules |
| e91z. | ERYTHROPED 250mg/sachet granules |
| e921. | CLARITHROMYCIN 250mg tablets |
| e922. | KLARICID 250mg tablets 14CP |
| e923. | CLARITHROMYCIN 125mg/5mL paediatric suspension |
| e924. | KLARICID 125mg/5mL paediatric suspension |
| e927. | CLARITHROMYCIN 500mg tablets |
| e928. | KLARICID 500mg tablets |

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|---|---|
| e929. | CLARITHROMYCIN 500mg m/r tablets |
| e92A. | KLARICID XL 500mg m/r tablets |
| e92B. | CLARITHROMYCIN 250mg/sachet granules |
| e92C. | KLARICID adult 250mg/sachet granules |
| e92D. | CLARITHROMYCIN 250mg/5mL paediatric suspension |
| e92E. | KLARICID 250mg/5mL paediatric suspension |
| e92F. | CLARITHROMYCIN 125mg granules straw |
| e92G. | *CLAROSIP 125mg granules straw |
| e92H. | CLARITHROMYCIN 187.5mg granules straw |
| e92I. | CLAROSIP 187.5mg granules straw |
| e92J. | CLARITHROMYCIN 250mg granules straw |
| e92K. | CLAROSIP 250mg granules straw |
| e92L. | XETININ XL 500mg m/r/ tablets |
| e92M. | FEBZIN XL 500mg m/r tablets |
| e92N. | MYCIFOR XL 500mg m/r tablets |
| e931. | AZITHROMYCIN 250mg capsules |
| e932. | AZITHROMYCIN 40mg/mL suspension |
| e933. | ZITHROMAX 250mg capsules |
| e934. | ZITHROMAX 40mg/mL suspension 15mL |
| e935. | ZITHROMAX 40mg/mL suspension 22.5mL |
| e936. | ZITHROMAX 40mg/mL suspension 30mL |
| e937. | AZITHROMYCIN 500mg tablets |
| e938. | *ZITHROMAX 500mg tablets |
| e939. | CLAMELLE AZITHROMYCIN 500mg tablets |
| e95.. | ERYTHROMYCIN [2] |
| e951. | PRIMACINE 125mg/5mL suspension 140mL |
| e952. | PRIMACINE 250mg/5mL suspension 100mL |
| e953. | PRIMACINE 250mg/5mL suspension 140mL |
| e954. | PRIMACINE 500mg/5mL suspension 100mL |
| e955. | PRIMACINE 500mg/5mL suspension 140mL |
| ea11. | DALACIN C 75mg capsules |
| ea12. | DALACIN C 150mg capsules |
| ea13. | DALACIN C 75mg/5mL paediatric suspension |
| ea1v. | CLINDAMYCIN 75mg capsules |
| ea1w. | CLINDAMYCIN 150mg capsules |
| ea1x. | *CLINDAMYCIN 75mg/5mL syrup |
| ec11. | CO-TRIMOXAZOLE 480mg tablets |
| ec12. | CO-TRIMOXAZOLE 480mg dispersible tablets |
| ec13. | CO-TRIMOXAZOLE 960mg tablets |
| ec14. | CO-TRIMOXAZOLE 960mg dispersible tablets |
| ec15. | CO-TRIMOXAZOLE 120mg tablets |
| ec16. | CO-TRIMOXAZOLE 480mg/5mL mixture |
| ec17. | CO-TRIMOXAZOLE 240mg/5mL mixture |
| ec1A. | CO-TRIMOXAZOLE 240mg/5mL sugar free suspension |
| ec1B. | CO_TRIMOXAZOLE 480mg/5mL suspension |
| ec21. | *BACTRIM 480mg tablets |
| ec22. | BACTRIM 480mg dispersible tablets |
| ec23. | BACTRIM 960mg double strength tablets |
| ec24. | BACTRIM PAEDIATRIC 120mg tablets |
| ec25. | *BACTRIM 480mg/5mL suspension |
| ec26. | BACTRIM 240mg/5mL paediatric syrup |
| ec29. | CHEMOTRIM 240mg/5mL suspension |

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|---|---|
| ec2a. | *COMOX 480mg tablets |
| ec2b. | COMOX 480mg dispersible tablets |
| ec2c. | *COMOX FORTE 960mg tablets |
| ec2d. | COMOX 240mg/5mL paediatric suspension |
| ec2e. | FECTRIM STANDARD 480mg dispersible tablets |
| ec2f. | FECTRIM FORTE 960mg dispersible tablets |
| ec2g. | FECTRIM 120mg paediatric tablets |
| ec2h. | *LARATRIM 480mg tablets |
| ec2i. | *LARATRIM FORTE 960mg tablets |
| ec2j. | *LARATRIM 480mg/5mL suspension |
| ec2k. | LARATRIM 240mg/5mL paediatric suspension |
| ec2l. | SEPTRIN 480mg tablets |
| ec2m. | SEPTRIN 480mg dispersible tablets |
| ec2n. | SEPTRIN FORTE 960mg tablets |
| ec2o. | SEPTRIN PAEDIATRIC 120mg dispersible tablets |
| ec2p. | SEPTRIN 480mg/5mL adult suspension |
| ec2q. | SEPTRIN 240mg/5mL paediatric suspension |
| ec2t. | *COMIXCO 80/400 tablets |
| ec2u. | *COMIXCO 160/800 tablets |
| ec2v. | COMIXCO 40/200/5mL paediatric suspension |
| ec2w. | COMIXCO 80/400 dispersible tablets |
| ecc1. | TRIMETHOPRIM 100mg tablets |
| ecc2. | TRIMETHOPRIM 200mg tablets |
| ecc3. | *TRIMETHOPRIM 300mg tablets |
| ecc4. | TRIMETHOPRIM 50mg/5mL sugar free suspension |
| ecc6. | *IPRAL 100mg tablets |
| ecc7. | *IPRAL 200mg tablets |
| ecc8. | IPRAL SF 50mg/5mL paediatric suspension |
| ecc9. | *MONOTRIM 100mg tablets |
| ecca. | *MONOTRIM 200mg tablets |
| eccb. | MONOTRIM 50mg/5mL sugar free suspension |
| eccd. | *SYRAPRIM 100mg tablets |
| ecce. | *SYRAPRIM 300mg tablets |
| eccf. | *SYRAPRIM 100mg/5mL injection |
| eccg. | TIEMPE 100mg tablets |
| ecch. | TIEMPE 200mg tablets |
| ecci. | *TRIMOGAL 100mg tablets |
| eccj. | *TRIMOGAL 200mg tablets |
| ecck. | *TRIMOPAN 100mg tablets |
| eccl. | *TRIMOPAN 200mg tablets |
| eccm. | TRIMOPAN 50mg/5mL sugar free suspension |
| eccn. | *TRIPRIMIX 200mg tablets |
| ef11. | METRONIDAZOLE 200mg tablets |
| ef12. | METRONIDAZOLE 400mg tablets |
| ef1A. | METRONIDAZOLE 200mg/5mL suspension |
| ef1D. | METRONIDAZOLE 500mg tablets |
| ef1c. | FLAGYL 200mg tablets |
| ef1d. | FLAGYL 400mg tablets |
| ef1g. | FLAGYL S suspension 100mL |
| ef1l. | *METROLYL 200mg tablets |
| ef1m. | *METROLYL 400mg tablets |
| ef1r. | *NIDAZOL 200mg tablets |
| ef1s. | VAGINYL 200mg tablets |
| ef1t. | VAGINYL 400mg tablets |

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|---|---|
| ef1u. | *ZADSTAT 200mg tablets |
| eg1.. | NITROFURANTOIN |
| eg11. | NITROFURANTOIN 50mg tablets |
| eg12. | NITROFURANTOIN 100mg tablets |
| eg13. | FURADANTIN 50mg tablets |
| eg14. | FURADANTIN 100mg tablets |
| eg15. | FURADANTIN 25mg/5mL sugar free suspension |
| eg16. | MACRODANTIN 50mg capsules |
| eg17. | MACRODANTIN 100mg capsules |
| eg18. | URANTOIN 50mg tablets |
| eg19. | URANTOIN 100mg tablets |
| eg1A. | MACROBID 100mg m/r capsules |
| eg1B. | GENFURA 50mg tablets |
| eg1C. | GENFURA 100mg tablets |
| eg1w. | NITROFURANTOIN 100mg m/r capsules |
| eg1x. | NITROFURANTOIN 25mg/5mL sugar free suspension |
| eg1y. | NITROFURANTOIN 50mg capsules |
| eg1z. | NITROFURANTOIN 100mg capsules |
| eg61. | CIPROXIN 250mg tablets |
| eg64. | CIPROXIN 500mg tablets |
| eg65. | CIPROXIN 750mg tablets |
| eg67. | CIPROFLOXACIN 100mg tablets |
| eg68. | *CIPROXIN 100mg tablets |
| eg69. | CIPROFLOXACIN 5g/100mL oral suspension |
| eg6A. | CIPROXIN 5g/100mL oral suspension |
| eg6v. | CIPROFLOXACIN 750mg tablets |
| eg6w. | CIPROFLOXACIN 500mg tablets |
| eg6x. | CIPROFLOXACIN 250mg tablets |

**APPENDIX 2:** Risk factors for adverse events in children prescribed oral antibiotics in the GP

| Risk factors | Variable from routine data | source |
|---|---|---|
| Deprivation quintile | Welsh index of multiple deprivation 2014 overall index quartile. | Welsh Demographic Service Dataset (WDSD) |
| Ethnicity | Ethnic group description | Patient Episode Dataset for Wales (PEDW), National Community Child Health Database (NCCHD) |
| Sex | Gender codes | Welsh Longitudinal General Practice Dataset (WLGP) – Welsh Primary Care |
| Weight | Patient weight values within 30 days of oral antibiotics prescription date | WLGP |
| Age band | Patient age at oral antibiotics prescription date (prescription date – Week of Birth (WOB)) | WLGP |

Cohort selection (inclusion and exclusion criteria)

- Children born in Wales.
- Study population include children (aged 0 to 12 years) with a GP oral antibiotics prescription record (WLGP dataset)
- Weight record in WLGP.
- Weight record was within 30 days before or after oral antibiotics prescription.

Datasets used: WDSD, WLGP, PEDW, NCCHD.

**Appendix 3**: Read Codes for records of adverse events in the GP

| read codes | description |
|---|---|
| SL05. | Cephalosporin group poisoning - |
| SL050 | Cefalexin poisoning |
| SL051 | Cephaloglycin poisoning |
| SL052 | Cephaloridine poisoning |
| SL053 | Cephalothin poisoning |
| SL052 | Cephalosporin poisoning NOS |
| TJ05z | Adverse reaction to cephalosporin NOS |
| T105. | Adverse reaction to cephalosporin group |
| TJ050 | Adverse reaction to cefacior |
| TJ051 | Adverse reaction to cefadroxil |
| TJ052 | Adverse reaction to cefotaxime |
| TJ053 | Adverse reaction to cefoxitin |
| TJ054 | Adverse reaction to cefsulodin sodium |
| TJ055 | Adverse reaction to ceftazidime |
| TJ056 | Adverse reaction to ceftizoxime |
| TJ057 | Adverse reaction to cephalexin |
| TJ058 | Adverse reaction to cephalothin |
| 1J059 | Adverse reaction to cephamandole |
| TJ05A | Adverse reaction to cephazolin |
| TJ05B | Adverse reaction to cephradine |
| TJ05z | Adverse reaction to cephalosporin NOS |
| U6001 | [X] Adverse reaction to cephalosporin NOS |
| Xa5ru | Macrolide allergy |
| Xa5rv | Erythromycin allergy |
| Xa5rw | Clarithromycin allergy |
| Xa5rx | Azithromycin allergy |
| Xa6Pw | Macrolide overdose |
| Xa6Px | Erythromycin overdose |
| Xa6Q1 | Azithromycin overdose |
| Xa6Q5 | Clarithromycin overdose |
| Xa5TR | Macrolide adverse reaction |
| Xa5TS | Erythromycin adverse reaction |
| Xa5TT | Clarithromycin adverse reaction |
| Xa5TU | Azithromycin adverse reaction |
| TJ03z | Adverse reaction to macrolide NOS |
| XM1Fr | Adverse reaction to macrolide group |
| TJ03. | Adverse reaction to erythromycin and other macrolides |
| TJ030 | Adverse reaction to erythromycin |
| TJ031 | Adverse reaction to oleandomycin |
| TJ032 | Adverse reaction to spiramycin |
| XE1oI | Erythromycin and macrolide poisoning |
| SL03z | Erythromycin or macrolide poisoning NOS |
| TJ03. | Adverse reaction to erythromycin and other macrolides |
| U6003 | [X]Macrolides causing adverse effects in therapeutic use |

| | |
|---|---|
| Xa5s3 | Nitrofurantoin allergy |
| 14LI. | H/O: nitrofurantoin allergy |
| Xa6QP | Nitrofuran derivative overdose |
| Xa5Ta | Nitrofurantoin adverse reaction |
| Xa56l | Accidental nitrofuran derivative poisoning |
| Xa56m | Intentional nitrofuran derivative poisoning |
| Xa56n | Nitrofuran derivative poisoning of undetermined intent |
| TJ1z2 | Adverse reaction to nitrofurantoin |
| Xa6QQ | Accidental nitrofuran derivative overdose |
| Xa6QR | Intentional nitrofuran derivative overdose |
| Xa56l | Accidental nitrofuran derivative poisoning |
| Xa56m | Intentional nitrofuran derivative poisoning |
| Xa6QS | Nitrofuran derivative overdose of undetermined intent |
| Xa56n | Nitrofuran derivative poisoning of undetermined intent |
| Xa5tS | Nitroimidazole allergy |
| Xa5tT | Metronidazole allergy |
| Xa5tV | Nimorazole allergy |
| Xa5Uz | Nitroimidazole adverse reaction |
| Xa5V0 | Metronidazole adverse reaction |
| Xa5V1 | Tinidazole adverse reaction |
| Xa5V2 | Nimorazole adverse reaction |
| SL00. | Penicillin poisoning |
| SL000 | Ampicillin poisoning |
| SL001 | Cloxacillin poisoning |
| SL002 | Carbenicillin poisoning |
| SL003 | Penicillin G poisoning |
| SL00z | Penicillin poisoning NOS |
| SL003 | Penicillin G poisoning |
| SL340 | Penicillinase poisoning |
| e1... | PENICILLINASE SENS PENICILLINS |
| e11.. | BENZYLPENICILLIN(PENICILLIN G) |
| e12.. | *BENETHAMINE PENICILLIN |
| e13.. | *BENZATHINE PENICILLIN |
| e14.. | *PHENETHICILLIN |
| e15.. | PHENOXYMETHYLPENICILLIN |
| e16.. | PROCAINE PENICILLIN |
| TJ00. | Adverse reaction to penicillins |
| TJ000 | Adverse reaction to natural penicillins |
| TJ001 | Adverse reaction to cloxacillin |
| TJ002 | Adverse reaction to flucloxacillin |
| TJ003 | Adverse reaction to amoxycillin |
| TJ004 | Adverse reaction to ampicillin |
| TJ005 | Adverse reaction to bacampicillin |
| TJ006 | Adverse reaction to ciclacillin |
| TJ007 | Adverse reaction to mezlocillin |
| TJ008 | Adverse reaction to pivampicillin |
| TJ009 | Adverse reaction to talampicillin |
| TJ009 | Adverse reaction to talampicillin |
| TJ00A | Adverse reaction to azlocillin |
| TJ00B | Adverse reaction to carbenicillin |

| | |
|---|---|
| TJ00C | Adverse reaction to carfecillin sodium |
| TJ00D | Adverse reaction to piperacillin |
| TJ00E | Adverse reaction to ticarcillin |
| TJ00F | Adverse reaction to mecillinam |
| TJ00G | Adverse reaction to pivmecillinam |
| TJ00z | Adverse reaction to penicillin NOS |
| U6000 | [X]Penicillins causing adverse effects in therapeutic use |
| Xa5s2 | Trimethoprim allergy |
| Xa6QL | Trimethoprim overdose |
| Xa6QM | Accidental trimethoprim overdose |
| Xa6QN | Intentional trimethoprim overdose |
| Xa6QO | Trimethoprim overdose of undetermined intent |
| Xa56h | Trimethoprim poisoning |
| Xa56i | Accidental trimethoprim poisoning |
| Xa56j | Intentional trimethoprim poisoning |
| Xa56k | Trimethoprim poisoning of undetermined intent |
| 14LE. | H/O: trimethoprim allergy |
| Xa5TZ | Trimethoprim adverse reaction |
| TJ0yC | Adverse reaction to trimethoprim |
| Xa6QM | Accidental trimethoprim overdose |
| Xa6QN | Intentional trimethoprim overdose |
| Xa56j | Intentional trimethoprim poisoning |
| Xa6QO | Trimethoprim overdose of undetermined intent |
| Xa56k | Trimethoprim poisoning of undetermined intent |

**APPENDIX 4:** Adverse events data source

| Adverse events | Variable from routine data | source |
|---|---|---|
| Patient death within 5 days | Death date | Annual District Death Extract (ADDE) |
| Repeat GP antibiotic prescription within 14 days | Event date, antibiotics codes | Welsh Longitudinal General Practice Dataset (WLGP) |
| Non-elective hospital/emergency admission within 5 days of initial prescription | Admission date | Emergency Department Dataset (EDDS), Patient Episode Dataset for Wales (PEDW) |
| GP record of toxicity, poisoning, overdose, allergy or hypersensitivity within 14 days | Event date, event code | WLGP |

These records merged (row-bind) to the main dataset and arranged chronologically to detect the adverse outcomes.

Datasets used: ADDE, WLGP, and, PEDW.

APPENDIX 5: Information on the sensitivity group

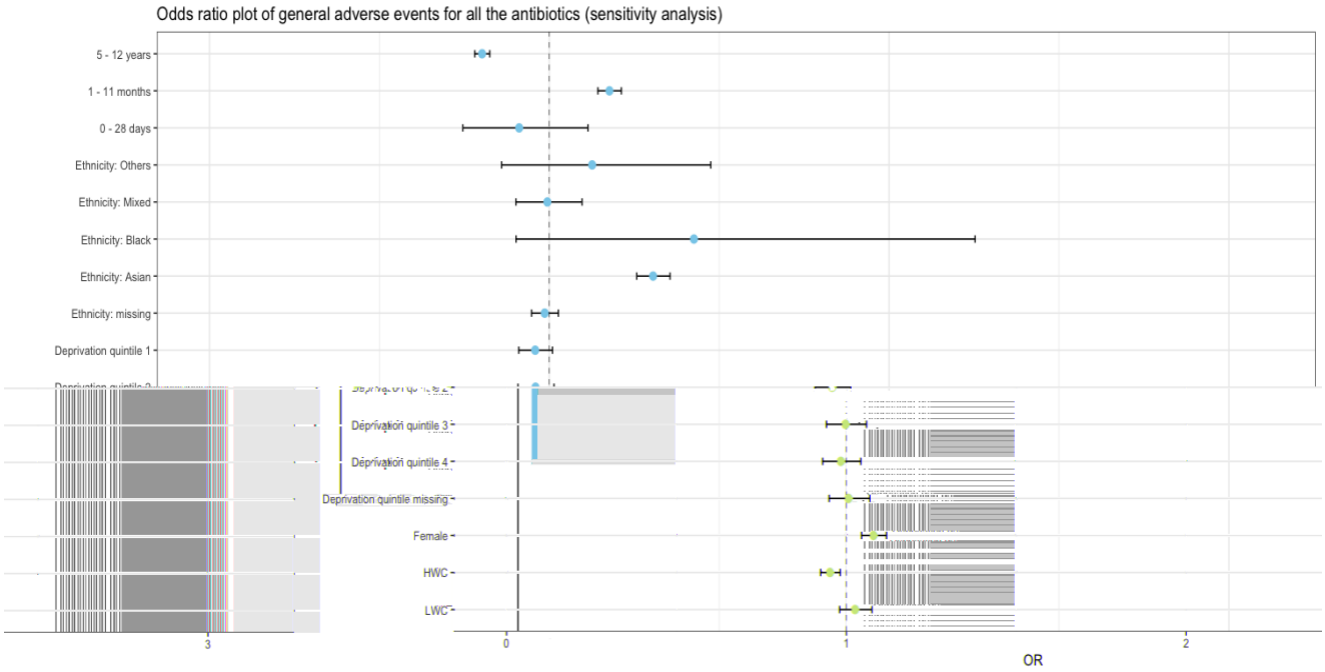
*Table 1: Characteristics of the sensitivity group*

| | Final cohort (71,541) | | sensitivity group (310,432) | |
|---|---|---|---|---|
| Sex | | | | |
| Male | 36,762 | 50.72% | 155,847 | 50.20% |
| Female | 34,779 | 49.28% | 154,585 | 49.80% |

*Table 2: adjusted odds ratio for an adverse drug event*

| variables | OR | Lower CI | Upper CI | P values |
|---|---|---|---|---|
| Weight category | | | | |
| HWC | 0.95 | 0.92 | 0.98 | 0.265 |
| LWC | 1.03 | 0.98 | 1.08 | 0.0000 |
| NWC | - | - | - | - |
| Sex | | | | |
| Female | 1.08 | 1.04 | 1.12 | 0.000 |
| Male | - | - | - | - |
| Ethnicity | | | | |
| Asian | 1.31 | 1.26 | 1.36 | 0.000 |
| Black | 1.43 | 0.90 | 2.25 | 0.129 |
| Mixed | 0.99 | 0.90 | 1.10 | 0.908 |
| Missing | 0.99 | 0.95 | 1.03 | 0.504 |
| Other ethnicities | 1.13 | 0.86 | 1.48 | 0.389 |
| White | - | - | - | - |
| Deprivation quintile | | | | |
| 1 | 0.96 | 0.91 | 1.01 | 0.108 |
| 2 | 0.96 | 0.91 | 1.01 | 0.141 |
| 3 | 1.00 | 0.94 | 1.06 | 0.961 |
| 4 | 0.99 | 0.93 | 1.04 | 0.000 |
| Missing | 1.01 | 0.95 | 1.07 | 0.809 |
| Age band | | | | |
| 0 - 28 days | 0.91 | 0.75 | 1.11 | 0.364 |
| 1 - 11 months | 1.18 | 1.14 | 1.21 | 0.000 |
| 0 – 4 years | - | - | - | - |
| 5 - 12 years | 0.80 | 0.78 | 0.85 | 0.000 |

*Figure 1: Forest plot of odds ratio of combined adverse events after initial oral antibiotics prescriptions. the x value of 1 denotes no difference in odds ratio between the reference group and the group being compared. reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, weight category: normal weight category.*



| Variables | General adverse events (combined) | | | | Repeat antibiotics | | | | Hospital/emergency admissions | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | Lower CI | Upper CI | P values | OR | Lower CI | Upper CI | P values | OR | Lower CI | Upper CI | P values |
| Weight categories | | | | | | | | | | | | |
| LWC | 1.06 | 1.01 | 1.11 | 0.019 | 1.03 | 0.97 | 1.08 | 0.361 | 1.25 | 1.15 | 1.35 | 0.000 |
| NWC | - | - | - | - | - | - | - | - | - | - | - | - |
| HWC | 0.92 | 0.88 | 0.96 | 0.001 | 0.94 | 0.90 | 0.98 | 0.007 | 0.82 | 0.75 | 0.90 | 0.000 |
| Sex | | | | | | | | | | | | |
| Female | 1.13 | 1.07 | 1.19 | 0.000 | 1.15 | 1.08 | 1.22 | 0.000 | 0.95 | 0.88 | 1.02 | 0.171 |
| Male | - | - | - | - | - | - | - | - | - | - | - | - |
| Ethnic groups | | | | | | | | | | | | |
| Asian | 1.22 | 1.14 | 1.29 | 0.000 | 1.19 | 1.11 | 1.27 | 0.000 | 1.34 | 1.23 | 1.45 | 0.000 |
| Black | 1.37 | 0.68 | 2.74 | 0.381 | 1.38 | 0.63 | 3.05 | 0.423 | 1.06 | 0.70 | 1.59 | 0.797 |
| Mixed | 0.94 | 0.77 | 1.15 | 0.541 | 0.92 | 0.73 | 1.15 | 0.441 | 1.17 | 0.93 | 1.47 | 0.174 |
| Missing | 0.97 | 0.91 | 1.03 | 0.266 | 0.97 | 0.90 | 1.03 | 0.311 | 0.94 | 0.84 | 1.06 | 0.321 |
| Other ethnicities | 0.93 | 0.75 | 1.17 | 0.557 | 0.94 | 0.73 | 1.21 | 0.626 | 1.05 | 0.72 | 1.53 | 0.820 |
| Whites | - | - | - | - | - | - | - | - | - | - | - | - |
| Deprivation quintiles | | | | | | | | | | | | |
| 1 | 1.00 | 0.93 | 1.09 | 0.941 | 0.97 | 0.89 | 1.07 | 0.589 | 1.14 | 1.01 | 1.29 | 0.038 |
| 2 | 0.99 | 0.90 | 1.08 | 0.775 | 0.96 | 0.87 | 1.07 | 0.455 | 1.13 | 0.99 | 1.29 | 0.072 |
| 3 | 0.96 | 0.89 | 1.03 | 0.230 | 0.95 | 0.87 | 1.02 | 0.178 | 0.99 | 0.86 | 1.14 | 0.909 |
| 4 | 0.99 | 0.91 | 1.07 | 0.714 | 0.99 | 0.91 | 1.08 | 0.821 | 0.91 | 0.78 | 1.05 | 0.188 |
| 5 | - | - | - | - | - | - | - | - | - | - | - | - |
| Missing | 0.99 | 0.91 | 1.07 | 0.746 | 0.93 | 0.85 | 1.03 | 0.183 | 1.20 | 1.04 | 1.38 | 0.013 |
| Age bands | | | | | | | | | | | | |
| 0 - 28 days | 0.60 | 0.45 | 0.81 | 0.001 | 0.41 | 0.28 | 0.60 | 0.000 | 1.73 | 1.13 | 2.65 | 0.011 |
| 1 - 11 months | 0.97 | 0.91 | 1.04 | 0.422 | 0.87 | 0.81 | 0.95 | 0.001 | 1.52 | 1.38 | 1.66 | 0.000 |
| 0 - 4 years | - | - | - | - | - | - | - | - | - | - | - | - |
| 5 - 12 years | 0.76 | 0.73 | 0.81 | 0.000 | 0.81 | 0.77 | 0.85 | 0.000 | 0.54 | 0.50 | 0.59 | 0.000 |

*Supplementary Table: Table showing the odds ratios of the risk factors for the respective adverse events (95% CI). LWC: Low Weight Category; NWC: Normal Weight Category; HWC: High Weight Category; Asian: Indian, Pakistani, Bangladeshi, Chinese, Any other Asian ethnic groups; Black: African, Caribbean, Any other black background; Mixed: White and Black Caribbean, White and Black African, White and Asian, Any other Mixed background; White: Any White Background (including Welsh, English, Scottish, Northern Irish, Irish, British), Gypsy, other White background; Other ethnicities: Arab and any other ethnic groups. Reference groups are -- age band: 1-4 years, ethnicity: white, sex: male, Weight categories: normal weigh category.*