**Introduction**

**Background**

**What do you believe in**

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.

**Objectives**

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.

**Methods**

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](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\Appendix\\appendix 3.docx) (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 1](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\figures\\figure 1.docx).

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](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\Appendix\\appendix 4.docx). 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 25th percentile), Normal Weight Category (NWC grouped by sex and age group; with weights above the 25th percentile and less than the 75th percentile) and, High Weight Category (HWC grouped by sex and age group; with weights equal or greater than the 75th 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).

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](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\Appendix\\appendix 1.docx)). The data source used to generate these adverse events can be found in [Appendix 5](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\Appendix\\appendix 5.docx).

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 the excluded group can be found in [Appendix 2](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\Appendix\\appendix 2.docx). 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 (27), tidyverse (28), lubridate (29), and caret (30).

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 (31)

**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](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\tables\\table 1.docx).

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](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\tables\\table 2.docx). The forest plots of the general adverse events, repeat GP oral antibiotics prescribing within 14 days after the initial prescription and hospital/emergency admission within 5 days of the initial prescription can be found in [Figure 2](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\figures\\Figure 2.docx), [Figure 3](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\figures\\Figure 3.docx), and [Figure 4](C:\\Users\\S.Brophy\\AppData\\Local\\Temp\\587bc44a-4c6e-489a-bcde-b6a0af1ac12c_final project (2).zip.12c\\final project\\figures\\Figure 4.docx) respectively

**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 (32). 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 (33,34). 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 (35). 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 (36,37).

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 (38); 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 (39). A significant challenge in pharmacovigilance is accurately pinpointing the root cause of adverse reactions to specific drugs (40). 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 (41), 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.